Medicines Information Services

Information on drug therapy
Information on any aspect of drug therapy can be obtained from Regional and District Medicines Information Services. Details regarding the local services provided within your region can be obtained by telephoning the following numbers.

England

Birmingham: (0121) 424 7298
Bristol: (0117) 342 6655
Ipswich: (01473) 704 431
Leeds: (0113) 206 5377
Leicester: (0116) 258 6491
Liverpool: (0151) 794 8113/7, or (0151) 794 8118
London:
  - Guy’s Hospital (020) 7188 8750, or (020) 7188 3849, or (020) 7188 3855
  - Northwick Park Hospital (020) 8869 2761, or (020) 8869 3973
Newcastle: (0191) 282 4631
Southampton: (023) 8120 6908/9

Wales

Cardiff: (029) 2074 2979, or (029) 2074 2251

Scotland

Aberdeen: (01224) 552 316
Dundee: (01382) 632 351, or (01382) 660 111 Extn 32351
Edinburgh: (0131) 242 2920
Glasgow: (0141) 211 4407

Northern Ireland

Belfast: (028) 9504 0558

Republic of Ireland

Dublin: (01) 473 0589, or (01) 453 7941 Extn 2348

United Kingdom Medicines Information (UKMI) website
www.sps.nhs.uk/

Manufacturers

Telephone numbers and email addresses of manufacturers listed in BNF Publications are shown in the Index of manufacturers p. 1621

UK Teratology Information Service

Information on drug and chemical exposures in pregnancy.
Tel: 0344 892 0909
www.uktis.org

UK Drugs in Lactation Advisory Service (UKDILAS)

Information on the compatibility of drugs with breastfeeding.
Tel: (0116) 258 6491, or (0121) 424 7298
Email: ukdilas.enquiries@nhs.net
www.sps.nhs.uk/ukdilas

Medicines in Dentistry Specialist Advisory Service

Information on drug therapy relating to dental treatment.
Liverpool: (0151) 794 8206

Driver and Vehicle Licensing Agency (DVLA)

Information on the national medical guidelines of fitness to drive is available from:
www.gov.uk/government/publications/at-a-glance

Medicines for Children Information Leaflets

Medicines information for parents and carers.
www.medicinesforchildren.org.uk

Patient Information Lines

NHS Urgent Care Services 111

Poisons Information Services

UK National Poisons Information Service (for healthcare professionals only)
Tel: 0344 892 0111
www.toxbase.org

Sport

Information regarding the use of medicines in sport is available from UK Anti-Doping:
www.ukad.org.uk
Tel: (020) 7842 3450
ukad@ukad.org.uk

UK Anti-Doping
Fleetbank House
2-6 Salisbury Square
London EC4Y 8AE

Information about the prohibited status of specific medicines based on the current World Anti-Doping Agency Prohibited List is available from Global Drug Reference Online: www.globaldro.com/UK/search

Travel Immunisation

Up-to-date information on travel immunisation requirements may be obtained from:

National Travel Health Network and Centre (for healthcare professionals only) 0845 602 6712 Monday and Friday: 9–11 a.m. and 1–2 p.m. Tuesday to Thursday: 9–11 a.m. and 1–3:30 p.m.
travelhealthpro.org.uk/T

Travel Medicine Team, Health Protection Scotland (0141) 300 1100 (2–4 p.m. weekdays)
www.travax.nhs.uk (for registered users of the NHS website Travax only)

Welsh Government Switchboard English language 0300 0603300 (9 a.m.–5:30 p.m. weekdays only)
Welsh Government Switchboard Yr laith Gymraeg 0300 0604400 (9 a.m.–5:30 p.m. weekdays only)

Department of Health and Social Services (Belfast) (028) 9052 2118 (weekdays)

List of Registered Medical Practitioners

Details on whether doctors are registered and hold a licence to practise medicine in the UK can be obtained from the General Medical Council.
Tel: (0161) 923 6602
www.gmc-uk.org/register
Since 1949 the British National Formulary (BNF) has been the UK's most trusted and authoritative healthcare resource, helping to ensure the safe and effective use of medicines at the point of care.

Now, as part of our anniversary celebrations, we want to showcase the rigorous editorial process that goes into creating the content that you rely on for your everyday practice. We will also go behind the scenes at the BNF in our ‘A day in the life’ articles. To find out more visit bnf.org

We really appreciate the support you have given the BNF for our first 70 years. If you have a story to tell about how the BNF has been pivotal in your healthcare journey, we would love to hear about it on social media, just use hashtag #BNF70years

Find out more about the BNF’s first 70 years at bnf.org
Access the BNF your way

The British National Formulary (BNF) and BNF for Children are updated monthly online via MedicinesComplete, ensuring healthcare professionals always have the latest medicines information.

**ONLINE**

BNF on MedicinesComplete
Access BNF and BNF for Children on MedicinesComplete and receive the very latest drug information through monthly online updates.

FormularyComplete
Create, edit and manage your own local formulary content built upon the trusted prescribing advice of the BNF and BNF for Children.

BNF on Evidence Search
Search the BNF and BNF for Children alongside other authoritative clinical and non-clinical evidence and best practice at www.evidence.nhs.uk from NICE.

**PRINT**

Eligible healthcare professionals will now receive one print copy a year – the September issue – to supplement online access. If you are entitled to an NHS copy please refer to page ii for full details on distribution, call 01268 495 609 or email BNF@wilmingtonhealthcare.com.

**PRINT SUBSCRIPTION**

BNF subscription – Take advantage of our print subscription option. We will send you the new BNF as soon as the book is published. One or two year packages (including or excluding BNF for Children) are available. Discounted pricing is also available on bulk sales.

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BNF eBook – Available as an ePDF. See www.pharmpress.com/bnf.
BNF on MedicinesComplete – Now mobile responsive.

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For enquiries about the BNF or BNF for Children in print, contact direct@macmillan.co.uk
Tel: +44 (0) 1256 302 699
For enquiries concerning MedicinesComplete, FormularyComplete, or bulk orders of the print edition, contact pharmpress-support@rpharms.com
Tel: +44 (0) 20 7572 2266

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For pricing information please visit the website at www.pharmpress.com/bnf
For international sales contact your local sales agent. Contact details at www.pharmpress.com/Information-Help/Bookseller-contacts/agents
Stay up to date - sign up to the BNF eNewsletter at www.bnf.org/newsletter

www.getintopharma.com
The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society. It is published under the authority of a Joint Formulary Committee which comprises representatives of the two professional bodies, the UK Health Departments, the Medicines and Healthcare products Regulatory Agency, and a national guideline producer. The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the Group includes representatives of the British Dental Association and a representative from the UK Health Departments. The Nurse Prescribers’ Advisory Group advises on the content relevant to nurses and includes representatives from different parts of the nursing community and from the UK Health Departments.

The BNF aims to provide prescribers, pharmacists, and other healthcare professionals with sound up-to-date information about the use of medicines.

The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified. Little or no information is included on medicines promoted for purchase by the public.

Information on drugs is drawn from the manufacturers’ product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies. Advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources. The BNF also takes account of authoritative national guidelines and emerging safety concerns. In addition, the editorial team receives advice on all therapeutic areas from expert clinicians; this ensures that the BNF’s recommendations are relevant to practice.

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. Similarly, little or no information is included on medicines for very rare conditions. BNF for Children should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services, see Medicines Information Services (see inside front cover).

It is important to use the most recent BNF information for making clinical decisions. The print edition of the BNF is updated in March and September each year. Monthly updates are provided online via Medicines Complete and the NHS Evidence portal. The more important changes are listed under Changes; changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies.

The BNF Publications website (www.bnf.org) includes additional information of relevance to healthcare professionals. Other digital formats of the BNF—including versions for mobile devices and integration into local formularies—are also available.
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www.getintopharma.com
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BNF Staff

BNF DIRECTOR
Karen Baxter BSc, MSc, MRPharmS

SENIOR EDITORIAL STAFF
Kiri Aikman BPharm (NZ), PGDipClinPharm (NZ), APharmS
Rebecca Bloom BPharm (NZ)
Alison Brayfield BPharm, MRPharmS
Robert Buckingham BSc, SRPharmS
Catherine Cadart BPharm (AU), BA(Hons), GradDipHospPharm (AU), MRPharmS
Mahinaz Harrison BPharm, DipPharmPract, IP, MRPharmS

EDITORIAL STAFF
Lucía Camañas Sáez MPharm (ESP), PGDipClinPharm, PGCertPsychTherap, MRPharmS
Jacky Chan BPharm(Hons) (NZ), PGDipClinPharm (NZ)
Kiran Cheema MPharm
Kathleen Eager BPharm
Hannah Giles BPharm (NZ)
Holly Hayne BSc (Pharmacology) (NZ), BPharm (NZ)
Sue Ho BPharm (AU), MRPharmS
Stephanie Jones MPharm, MSc (Genomic Medicine), MRPharmS
Elizabeth King MAppPharmT
Marta Leon-Alonso MPharm (ESP), MRPh (ESP), MSc ClinPharm, MRPharmS
David Lipanovic BPharm (NZ), PGCertClinPharm (NZ)
Jean MacKershan BSc, PgDip
John Martin BPharm, PhD, MRPharmS
Angela McFarlane BSc, DipClinPharm
Deirdre McGuirk BComm, MPharm, MRPharmS

SUPPORT STAFF
Matt Bradbury BSc(Hons)
Darren Chan BSc, MSc
Lauren Cheetham BA(Hons)
Filsane Haji BSc, MSc
Hannah Kitt BSc(Hons)

Rebecca Luckhurst BSc, MSc
Alexander McPhail MPharm, PGDipClinPharm
Claire McSherry BPharm (NZ), PGCertClinPharm (NZ)
Claire Preston BPharm, PGDipMedMan, MRPharmS
Kate Towers BPharm (AU), GCDipPharm (AU)
Anna McLachlan BPharm (NZ), PGCertClinPharm (NZ)
Liliana Moreira Vilas Boas MPharm(PT), PGDipHPS(PT), PGCertHSDM(PT), PGCertGPF, MRPharmS
Merusha Naidoo BPharm (NZ), PGCertClinPharm (NZ)
Hana Numan BPharm (NZ), PGCertClinPharm (NZ)
Kere Odumah MPharm, PGCertClinPharm
Barbara Okpala MPharm, PGDipHospPharm
Catherine Pitt MPharm, PGDipClinPharm, MRPharmS
Stephanie Powell MBioSci
Rebekah Raymond BSc, DipPharmPrac, MRPharmS
Harpreet Sandhu MPharm, MRPharmS
Beejal Shah MPharm, PGDipClinPharm, IP, MRPharmS
Tadeh Tahmasi MPharm, MRPharmS
Hannah Tan BPharm (AU)
Jacob Warner BPharm (AU)
Julia Webb MPharm, PGCertPharmPrac
Hans Yu BPharm(Hons) (NZ), PGDipClinPharm (NZ)

Philip Lee BSc, PhD
Vicky Pollington BSc(Hons)
Carina Redig de Campos
Jannah Ryan BSc(Hons)
Nikolaos Tsimplis BSc, MRes
Joint Formulary Committee

CHAIR
Derek G. Waller
BSc, MB BS, DM, FRCP

COMMITTEE MEMBERS
Andy Burman
CMgr, FCMI, FRSA, FIAM

Daniel Burrage
BSc, MB BS, MSc, MRCP

Jo Lyn Chooi
BMedSc, BM BS, FRCA

Carmel M. Darcy
BSc, MSc, IP, MPSNI, MRPharmS

Andrew Evans
BPharm, MPh, DipClinPharm, MRPharmS

Sue Faulding
BPharm, MSc, FRPharmS

Tracy Hall
BSc, MSc, Cert N, Dip N, RGN, DN, NIP, QN

Brian Hawkins
BSc, PhD, MRPharmS, FFRPS, IP

Lynn Haygarth
BPharm, MEd, FFRPS, FRPharmS, FCMHP

Simon Hurding
MB, ChB, MRCGP

Sandee Kapur
BSc(Hons), MB BS, MRCGP(Dist)

W. Moira Kinnear
BSc, MSc, MRPharmS

Mark P. Lythgoe
MB BS, MRPharmS

Louise Picton
BSc, DipCommPharm, MSc, MRPharmS

Bernadette Rae
Pg Cert Ed, Fellow HEA, MSc Nursing, Pg CertANP, BSc(Hons), Grad Cert NMP, RGN

Muhammad Magdi Yaqoob
MD, FRCP

Dental Advisory Group

CHAIR
Sarah Manton
BDS, FDSRCS Ed, FHEA, PhD, FDFTEd

COMMITTEE MEMBERS
Rebecca Bloor
BPharm (NZ)

Andrew K. Brewer
BSc, BchD, MFDS (Glas)

Alexander Crighton
BDS, MB, ChB, FDS, OM

Hannah Giles
BPharm (NZ)

Michelle Moffat
BDS MFDS RCS Ed, M Paed Dent RCPS, FDS (Paed Dent) RCS Ed

Barbara Okpala
MPharm, PgDipHospPharm

Wendy Thompson
BSc(Hons), BDS(Hons), MJDF

Kate Towers
BPharm (AU), GClinPharm (AU)

SECRETARY
Arianne J. Matlin
MA, MSci, PhD

ADVICE ON DENTAL PRACTICE
The British Dental Association has contributed to the advice on medicines for dental practice through its representatives on the Dental Advisory Group.

Nurse Prescribers’ Advisory Group

CHAIR
Molly Courtenay
PhD, MSc, Cert Ed, BSc, RGN

COMMITTEE MEMBERS
Penny M. Franklin
RN, RCN, RSCPHN(HV), MA, PGCE

Matt Griffiths
BA(Hons), FAETC, RGN, Cert A&E, NISP, PHECC

Tracy Hall
BSc, MSc, RGN, DN, Dip N, Cert N

Penny Harrison
BSc(Hons)

Julie MacAngus
BSc(Hons), RGN, RM, PGCE

Joan Myers
MSc, BSc, RGN, RSCN, Dip DN

Fiona Peniston-Bird
BSc(Hons), NIP, RHV, RGN

Kathy Radley
BSc, RGN

Kate Towers
BPharm (AU), GClinPharm (AU)
How BNF Publications are constructed

Overview
The BNF is an independent professional publication that addresses the day-to-day prescribing information needs of healthcare professionals. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately.

Hundreds of changes are made between print editions, and are published monthly in a number of digital formats. The most clinically significant updates are listed under Changes p. xvi.

The BNF is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information. Validation of information follows a standardised process, reviewing emerging evidence, best-practice guidelines, and advice from a network of clinical experts. Where the evidence base is weak, further validation is undertaken through a process of peer review. The process and its governance are outlined in greater detail in the sections that follow.

Joint Formulary Committee
The Joint Formulary Committee (JFC) is responsible for the content of the BNF. The JFC includes pharmacy, medical, nursing and lay representatives; there are also representatives from the Medicines and Healthcare products Regulatory Agency (MHRA), the UK Health Departments, and a national guideline producer.
The JFC decides on matters of policy and reviews amendments to the BNF in the light of new evidence and expert advice.

Dental Advisory Group
The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the group includes representatives from the British Dental Association and a representative from the UK Health Departments.

Nurse Prescribers’ Advisory Group
The Nurse Prescribers’ Advisory Group oversees the list of drugs approved for inclusion in the Nurse Prescribers’ Formulary; the group includes representatives from a range of nursing disciplines and stakeholder organisations.

Expert advisers
The BNF uses about 60 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with clinical content. The role of these expert advisers is to review existing text and to comment on amendments drafted by the clinical writers. These clinical experts help to ensure that the BNF remains reliable by:

- commenting on the relevance of the text in the context of best clinical practice in the UK;
- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breastfeeding, children, the elderly, palliative care, and the emergency treatment of poisoning.

In addition to consulting with regular advisers, the BNF calls on other clinical specialists for specific developments when particular expertise is required.

The BNF works closely with a number of expert bodies that produce clinical guidelines. Drafts or pre-publication copies of guidelines are often received for comment and assimilation into the BNF.

Editorial team
BNF clinical writers have all worked as pharmacists or possess a pharmacy degree and a further, relevant post-graduate qualification, and have a sound understanding of how drugs are used in clinical practice. As a team, the clinical writers are responsible for editing, maintaining, and updating BNF content. They follow a systematic prioritisation process in response to updates to the evidence base in order to ensure the most clinically important topics are reviewed as quickly as possible. In parallel the team of clinical writers undertakes a process of rolling revalidation, aiming to review all of the content in the BNF over a 3- to 4-year period.

Amendments to the text are drafted when the clinical writers are satisfied that any new information is reliable and relevant. A set of standard criteria define when content is referred to expert advisers, the Joint Formulary Committee or other advisory groups, or submitted for peer review.

Clinical writers prepare the text for publication and undertake a number of validation checks on the knowledge at various stages of the production process.

Sources of BNF information
The BNF uses a variety of sources for its information; the main ones are shown below.

Summaries of product characteristics
The BNF reviews summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are the principal source of product information and are carefully processed. Such processing involves:

- verifying the approved names of all relevant ingredients including ‘non-active’ ingredients (the BNF is committed to using approved names and descriptions as laid down by the Human Medicine Regulations 2012);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breastfeeding;
- incorporating the information into the BNF using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by a second clinical writer before submitting to a content manager; changes relating to doses receive a further check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs.

Much of this processing is applicable to the following sources as well.

Literature
Clinical writers monitor core medical and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in the BNF and the paper is noted, the new information is assessed for reliability (using tools based on SIGN methodology) and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Joint Formulary Committee. The BNF enjoys a close working relationship with a number of national information providers.

In addition to the routine process, which is used to identify ‘triggers’ for changing the content, systematic literature searches are used to identify the best quality evidence available to inform an update. Clinical writers receive training in critical appraisal, literature evaluation, and search strategies.

Consensus guidelines
The advice in the BNF is checked against consensus guidelines produced by expert bodies. The quality of the guidelines is assessed using adapted versions of the AGREE II tool. A number of bodies make drafts or pre-publication copies of the guidelines available to the BNF; it is therefore impossible to ensure that a consistent message is disseminated. The BNF routinely processes guidelines from the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

Reference sources
Textbooks and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNF team works closely with the editorial team that produces Martindale: The Complete Drug Reference. The BNF has access to Martindale information resources and each team
keeps the other informed of significant developments and shifts in the trends of drug usage.

Peer review
Although every effort is made to identify the most robust data available, inevitably there are areas where the evidence base is weak or contradictory. While the BNF has the valuable support of expert advisers and the Joint Formulary Committee, the recommendations made may be subject to a further level of scrutiny through peer review to ensure they reflect best practice.

Content for peer review is posted on bnf.org and interested parties are notified via a number of channels, including the BNF e-newsletter.

Statutory information
The BNF routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescriptions only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that the BNF complies with the relevant sections of the Human Medicines Regulations 2012.

The BNF maintains close links with the Home Office (in relation to controlled drug regulations) and the Medicines and Healthcare products Regulatory Agency (including the British Pharmacopoeia Commission). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug are issued by the UK health departments are processed as a matter of routine.

Relevant professional statements issued by the Royal Pharmaceutical Society are included in the BNF as are guidelines from bodies such as the Royal College of General Practitioners.

Medicines and devices
NHS Prescription Services (from the NHS Business Services Authority) provides non-clinical, categorical information (including prices) on the medicines and devices included in the BNF.

Comments from readers
Readers of the BNF are invited to send in comments. Numerous letters and emails are received by the BNF team. Such feedback helps to ensure that the BNF provides practical and clinically relevant information. Many changes in the presentation and scope of the BNF have resulted from comments sent in by users.

Comments from industry
Close scrutiny of BNF by the manufacturers provides an additional check and allows them an opportunity to raise issues about BNF’s presentation of the role of various drugs; this is yet another check on the balance of BNF’s advice. All comments are looked at with care and, where necessary, additional information and expert advice are sought.

Market research
Market research is conducted at regular intervals to gather feedback on specific areas of development.

Assessing the evidence
From January 2016, recommendations made in BNF publications have been evidence graded to reflect the strength of the recommendation. The addition of evidence grading is to support clinical decision making based on the best available evidence.

The BNF aims to revalidate all content over a rolling 3- to 4-year period and evidence grading will be applied to recommendations as content goes through the revalidation process. Therefore, initially, only a small number of recommendations will have been graded.

Grading system
The BNF has adopted a five level grading system from A to E, based on the former SIGN grading system. This grade is displayed next to the recommendation within the text.

Evidence used to make a recommendation is assessed for validity using standardised methodology tools based on AGREE II and assigned a level of evidence. The recommendation is then given a grade that is extrapolated from the level of evidence, and an assessment of the body of evidence and its applicability.

Evidence assigned a level 1- or 2- score has an unacceptable level of bias or confounding and is not used to form recommendations.

Levels of evidence
- **Level 1++**
  - High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
- **Level 1+**
  - Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
- **Level 1-**
  - Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
- **Level 2++**
  - High quality systematic reviews of case control or cohort studies; or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
- **Level 2+**
  - Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
- **Level 2-**
  - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
- **Level 3**
  - Non-analytic studies, e.g. case reports, case series.
- **Level 4**
  - Expert advice or clinical experience from respected authorities.

Grades of recommendation
- **Grade A: High strength**
  - NICE-accredited guidelines; or guidelines that pass AGREE II assessment; or at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1++, directly applicable to the target population, and demonstrating overall consistency of results.
- **Grade B: Moderate strength**
  - A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
- **Grade C: Low strength**
  - A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+.
- **Grade D: Very low strength**
  - Evidence level 3; or extrapolated evidence from studies rated as 2+; or tertiary reference source created by a transparent, defined methodology, where the basis for recommendation is clear.
- **Grade E: Practice point**
  - Evidence level 4.
How to use BNF Publications in print

How to use the BNF
This edition of the BNF continues to display the fundamental change to the structure of the content that was first shown in BNF 70. The changes were made to bring consistency and clarity to BNF content, and to the way that the content is arranged within print and digital products, increasing the ease with which information can be found.

For reference, the most notable changes to the structure of the content include:

- Drug monographs – where possible, all information that relates to a single drug is contained within its drug monograph, moving information previously contained in the prescribing notes. Drug monographs have also changed structurally: additional sections have been added, ensuring greater regularity around where information is located within the publication.
- Drug class monographs – where substantial amounts of information are common to all drugs within a drug class (e.g. macrolides p. 536), a drug class monograph has been created to contain the common information.
- Medicinal forms – categorical information about marketed medicines, such as price and pack size, continues to be sourced directly from the Dictionary of Medicines and Devices provided by the NHS Business Services Authority. However, clinical information curated by the BNF team has been clearly separated from the categorical pricing and pack size information and is included in the relevant section of the drug monograph.
- Section numbering – the BNF section numbering has been removed. This section numbering tied the content to a rigid structure and enforced the retention of defunct classifications, such as mercurial diuretics, and hindered the relocation of drugs where therapeutic use had altered. It also caused constraints between the BNF and BNF for Children, where drugs had different therapeutic uses in children.
- Appendix 4 – the content has been moved to individual drug monographs. The introductory notes have been replaced with a new guidance section, Guidance on intravenous infusions p. 16.

Introduction
In order to achieve the safe, effective, and appropriate use of medicines, healthcare professionals must be able to use the BNF effectively, and keep up to date with significant changes in the BNF that are relevant to their clinical practice. This How to Use the BNF is key in reinforcing the details of the new structure of the BNF to all healthcare professionals involved with prescribing, monitoring, supplying, and administering medicines, as well as supporting the learning of students training to join these professions.

Structure of the BNF
This BNF edition continues to broadly follows the high-level structure of earlier editions of the BNF (i.e. those published before BNF 70):

Front matter, comprising information on how to use the BNF, the significant content changes in each edition, and guidance on various prescribing matters (e.g. prescription writing, the use of intravenous drugs, particular considerations for special patient populations).

Chapters, containing drug monographs describing the uses, doses, safety issues and other considerations involved in the use of drugs; drug class monographs; and treatment summaries, covering guidance on the selection of drugs. Monographs and treatment summaries are divided into chapters based on specific aspects of medical care, such as Chapter 5, Infections, or Chapter 16, Emergency treatment of poisoning; or drug use related to a particular system of the body, such as Chapter 2, Cardiovascular.

Within each chapter, content is organised alphabetically by therapeutic use (e.g. Airways disease, obstructive), with the treatment summaries first, (e.g. asthma), followed by the monographs of the drugs used to manage the conditions discussed in the treatment summary. Within each therapeutic use, the drugs are organised alphabetically by classification (e.g. Antimuscarinics, Beta 2-agonist bronchodilators) and then alphabetically within each classification (e.g. Aclidinium bromide, Glycopyrronium bromide, Ipratropium bromide).

Appendices, covering interactions, borderline substances, cautionary and advisory labels, and woundcare.

Back matter, covering the lists of medicines approved by the NHS for Dental and Nurse Practitioner prescribing, proprietary and specials manufacturers’ contact details, and the index. Yellow cards are also included, to facilitate the reporting of adverse events, as well as quick reference guides for life support and key drug doses in medical emergencies, for ease of access.

Navigating the BNF
The contents page provides the high-level layout of information within the BNF; and in addition, each chapter begins with a small contents section, describing the therapeutic uses covered within that chapter. Once in a chapter, location is guided by the side of the page showing the chapter number (the thumbnail), alongside the chapter title. The top of the page includes the therapeutic use (the running head) alongside the page number.

Once on a page, visual cues aid navigation: treatment summary information is in black type, with therapeutic use titles similarly styled in black, whereas the use of colour indicates drug-related information, including drug classification titles, drug class monographs, and drug monographs.

Although navigation is possible by browsing, primarily access to the information is via the index, which covers the titles of drug class monographs, drug monographs, and treatment summaries. The index also includes the names of branded medicines and other topics of relevance, such as abbreviations, guidance sections, tables, and images.

Content types
Treatment summaries
Treatment summaries are of three main types;

- an overview of delivering a drug to a particular body system (e.g. Skin conditions, management p. 1220)
- a comparison between a group or groups of drugs (e.g. beta-adrenoceptor blockers (systemic) p. 147)
- an overview of the drug management or prophylaxis of common conditions intended to facilitate rapid appraisal of options (e.g. Hypertension p. 140, or Malaria, prophylaxis p. 607).

In order to select safe and effective medicines for individual patients, information in the treatment summaries must be used in conjunction with other prescribing details about the drugs and knowledge of the patient’s medical and drug history.

Monographs
Overview
In earlier editions (i.e. before BNF 70), a systemically administered drug with indications for use in different body systems was split across the chapters relating to those body systems. So, for example, codeine phosphate p. 454 was found in chapter 1, for its antimotility effects and chapter 4 for its analgesic effects. However, the monograph in
chapter 1 contained only the dose and some selected safety precautions.

Now, all of the information for the systemic use of a drug is contained within one monograph, so codeine phosphate p. 454 is now included in chapter 4. This carries the advantage of providing all of the information in one place, so the user does not need to flick back and forth across several pages to find all of the relevant information for that drug. Cross references are included in chapter 1, where the management of diarrhoea is discussed, to the drug monograph to assist navigation.

Where drugs have systemic and local uses, for example, chloramphenicol p. 568, L173, L196, and the considerations around drug use are markedly different according to the route of administration, the monograph is split, as with earlier editions, into the relevant chapters.

This means that the majority of drugs are still placed in the same chapters and sections as earlier editions, and although there may be some variation in order, all of the relevant information will be easier to locate.

One of the most significant changes to the monograph structure is the increased granularity, with a move from around 9 sections to over 20 sections; sections are only included when relevant information has been identified. The following information describes these sections and their uses in more detail.

**Nomenclature**

Monograph titles follow the convention of recommended international non-proprietary names (rINNs), or, in the absence of a rINN, British Approved Names. Relevant synonyms are included below the title and, in some instances a brief description of the drug action is included. Over future editions these drug action statements will be rolled out for all drugs.

In some monographs, immediately below the nomenclature or drug action, there are a number of cross references or flags used to signpost the user to any additional information they need to consider about a drug. This is most common for drugs formulated in combinations, where users will be signposted to the monographs for the individual ingredients (e.g. senna with ispaghula husk p. 63) or for drugs that are related to a drug class monograph (see Drug class monographs, below).

**Indication and dose**

User feedback has highlighted that one of the main uses of the BNF is identifying indications and doses of drugs. Therefore, indication and dose information has been promoted to the top of the monograph and highlighted by a coloured panel to aid quick reference.

The indication and dose section is more highly structured than in earlier editions, giving greater clarity around which doses should be used for which indications and by which route. In addition, if the dose varies with a specific preparation or formulation, that dosing information has been moved out of the preparations section and in to the indication and dose panel, under a heading of the preparation name.

Doses are either expressed in terms of a definite frequency (e.g. 1 g 4 times daily) or in the total daily dose format (e.g. 6 g daily in 3 divided doses); the total daily dose should be divided into individual doses (in the second example, the patient should receive 2 g 3 times daily).

Doses for specific patient groups (e.g. the elderly) may be included if they are different to the standard dose. Doses for children can be identified by the relevant age range and may vary according to their age or body-weight.

In earlier editions of the BNF, age ranges and weight ranges overlapped. For clarity and to aid selection of the correct dose, wherever possible these age and weight ranges now do not overlap. When interpreting age ranges it is important to understand that a patient is considered to be 64 up until the point of their 65th birthday, meaning that an age range of adult 18 to 64 is applicable to a patient from the day of their 18th birthday until the day before their 65th birthday. All age ranges should be interpreted in this way. Similarly, when interpreting weight ranges, it should be understood that a weight of up to 30 kg is applicable to a patient up to, but not including, the point that they tip the scales at 30 kg and a weight range of 35 to 60 kg is applicable to a patient as soon as they tip the scales at 35 kg right up until, but not including, the point that they tip the scales at 60 kg. All weight ranges should be interpreted in this way.

In all circumstances, it is important to consider the patient in question and their physical condition, and select the dose most appropriate for the individual.

**Other information relevant to Indication and dose**

The dose panel also contains, where known, an indication of pharmacokinetic considerations that may affect the choice of dose, and dose equivalence information, which may aid the selection of dose when switching between drugs or preparations.

The BNF includes unlicensed use of medicines when the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience. When the BNF recommends an unlicensed medicine or the ‘off-label’ use of a licensed medicine, this is shown below the indication and dose panel in the unlicensed use section.

**Minimising harm and drug safety**

The drug chosen to treat a particular condition should minimise the patient’s susceptibility to adverse effects and, where co-morbidities exist, have minimal detrimental effects on the patient’s other diseases. To achieve this, the Contra-indications, Cautions and Side-effects of the relevant drug should be reviewed.

The information under Cautions can be used to assess the risks of using a drug in a patient who has co-morbidities that are also included in the Cautions for that drug—i.e. a safer alternative cannot be found, the drug may be prescribed while monitoring the patient for adverse-effects or deterioration in the co-morbidity. Contra-indications are far more restrictive than Cautions and mean that the drug should be avoided in a patient with a condition that is contra-indicated.

The impact that potential side-effects may have on a patient’s quality of life should also be assessed. For instance, in a patient who has difficulty sleeping, it may be preferable to avoid a drug that frequently causes insomnia.

Therefore, indication and advice section in the BNF, delineated by a coloured outline box, highlights important safety concerns, often those raised by regulatory authorities or guideline producers. Safety warnings issued by the Commission on Human Medicines (CHM) or Medicines and Healthcare products Regulatory Agency (MHRA) are found here.

Drug selection should aim to minimise drug interactions. If it is necessary to prescribe a potentially serious combination of drugs, patients should be monitored appropriately. The mechanisms underlying drug interactions are explained in Appendix 1, followed by details of drug interactions.

**Use of drugs in specific patient populations**

Drug selection should aim to minimise the potential for drug accumulation, adverse drug reactions, and exacerbation of pre-existing hepatic or renal disease. If it is necessary to prescribe drugs whose effect is altered by hepatic or renal disease, appropriate drug dose adjustments should be made, and patients should be monitored adequately. The general principles for prescribing are outlined under Prescribing in hepatic impairment p. 19, and Prescribing in renal impairment p. 19. Information about drugs that should be avoided or used with caution in hepatic disease or renal
Typical layout of a monograph and associated medicinal forms

1. **Class Monographs and drug monographs**
   In most cases, all information that relates to an individual drug is contained in its drug monograph and there is no symbol. Class monographs have been created where substantial amounts of information are common to all drugs within a drug class, these are indicated by a flag symbol in a circle.

   Drug monographs with a corresponding class monograph are indicated by a tab with a flag symbol:

   Class monograph

   The page number of the corresponding class monograph is indicated within the tab. For further information, see How to use BNF Publications.

2. **Drug classifications**
   Used to inform users of the class of a drug and to assist in finding other drugs of the same class. May be based on pharmacological class (e.g. opioids) but can also be associated with the use of the drug (e.g. cough suppressants).

3. **Review date**
   The date of last review of the content.

4. **Specific preparation name**
   If the dose varies with a specific preparation or formulation it appears under a heading of the preparation name.

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**CLASSIFICATION**

**Drug monograph**

(Synonym) another name by which a drug may be known

- **DRUG ACTION** how a drug exerts its effect in the body

- **INDICATIONS AND DOSE**
  Indications are the clinical reasons a drug is used. The dose of a drug will often depend on the indications

  **Indication**
  - **ROUTE**

  **Age groups**: [Child/Adult/Elderly]

  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS** dosing information when used concurrently with other drugs

  **DOSES AT EXTREMES OF BODY-WEIGHT** dosing information for patients who are overweight or underweight

  **DOSE EQUIVALENCE AND CONVERSION** information around the bioequivalence between formulations of the same drug, or equivalent doses of drugs that are members of the same class

  **PHARMACOKINETICS** how the body affects a drug (absorption, distribution, metabolism, and excretion)

  **POTENCY** a measure of drug activity expressed in terms of the concentration required to produce an effect of given intensity

- **UNLICENSED USE** describes the use of medicines outside the terms of their UK licence (off-label use), or use of medicines that have no licence for use in the UK

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**IMPORTANT SAFETY INFORMATION**

Information produced and disseminated by drug regulators often highlights serious risks associated with the use of a drug, and may include advice that is mandatory

- **CONTRA-INDICATIONS** circumstances when a drug should be avoided
- **CAUTIONS** details of precautions required
- **INTERACTIONS** when one drug changes the effects of another drug; the mechanisms underlying drug interactions are explained in Appendix 1
- **SIDE-EFFECTS** listed in order of frequency, where known, and arranged alphabetically
- **ALLERGY AND CROSS-SENSITIVITY** for drugs that carry an increased risk of hypersensitivity reactions
- **CONCEPTION AND CONTRACEPTION** potential for a drug to have harmful effects on an unborn child when prescribing for a woman of childbearing age or for a man trying to father a child; information on the effect of drugs on the efficacy of latex condoms or diaphragms

www.getintopharma.com
- **PREGNANCY** advice on the use of a drug during pregnancy
- **BREAST FEEDING** advice on the use of a drug during breast feeding
- **HEPATIC IMPAIRMENT** advice on the use of a drug in hepatic impairment
- **RENAL IMPAIRMENT** advice on the use of a drug in renal impairment
- **PRE-TREATMENT SCREENING** covers one off tests required to assess the suitability of a patient for a particular drug
- **MONITORING REQUIREMENTS** specifies any special monitoring requirements, including information on monitoring the plasma concentration of drugs with a narrow therapeutic index
- **EFFECTS ON LABORATORY TESTS** for drugs that can interfere with the accuracy of seemingly unrelated laboratory tests
- **TREATMENT CESSIONATION** specifies whether further monitoring or precautions are advised when the drug is withdrawn
- **DIRECTIONS FOR ADMINISTRATION** practical information on the preparation of intravenous drug infusions; general advice relevant to other routes of administration
- **PRESCRIBING AND DISPENSING INFORMATION** practical information around how a drug can be prescribed and dispensed including details of when brand prescribing is necessary
- **HANDLING AND STORAGE** includes information on drugs that can cause adverse effects to those who handle them before they are taken by, or administered to, a patient; advice on storage conditions
- **PATIENT AND CARER ADVICE** for drugs with a special need for counselling
- **PROFESSION SPECIFIC INFORMATION** provides details of the restrictions certain professions such as dental practitioners or nurse prescribers need to be aware of when prescribing on the NHS
- **NATIONAL FUNDING/ACCESS DECISIONS** details of NICE Technology Appraisals, SMC advice and AWMSG advice
- **LESS SUITABLE FOR PRESCRIBING** preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing
- **EXCEPTION TO LEGAL CATEGORY** advice and information on drugs which may be sold without a prescription under specific conditions

### Evidence grading
Evidence grading to reflect the strengths of recommendations will be applied as content goes through the revalidation process. A five level evidence grading system based on the former SIGN grading system has been adopted. The grades A, B, C, D, E are displayed next to the recommendations within the text, and are preceded by the symbol: 🌟

For further information, see How BNF Publications are constructed

### Legal categories
Legal categories 🍀 This symbol has been placed against those preparations that are available only on a prescription issued by an appropriate practitioner. For more detailed information see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition)

<table>
<thead>
<tr>
<th>Legal category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P ☢️</td>
<td>These symbols indicate that the preparations are subject to the prescription requirements of the Misuse of Drugs Act</td>
</tr>
</tbody>
</table>

For regulations governing prescriptions for such preparations, see Controlled Drugs and Drug Dependence

Not all monographs include all possible sections; sections are only included when relevant information has been identified

### Medicinal forms
**Form**

- **CAUTIONARY AND ADVISORY LABELS** if applicable
- **EXCIPIENTS** clinically important but not comprehensive [consult manufacturer information for full details]
- **ELECTROLYTES** if clinically significant quantities occur

#### Preparation name (Manufacturer/Non-proprietary)
- **Drug name and strength pack sizes** 🍀 Prices

#### Combinations available
This indicates a combination preparation is available and a cross reference page number is provided to locate this preparation
impairment can be found in drug monographs under Hepatic impairment and Renal impairment (e.g. fluconazole p. 595). Similarly, drug selection should aim to minimise harm to the fetus, nursing infant, and mother. The infant should be monitored for potential side-effects of drugs used by the mother during pregnancy or breast-feeding. The general principles for prescribing are outlined under Prescribing in pregnancy p. 23 and Prescribing in breast-feeding p. 23. The Treatment Summaries provide guidance on the drug treatment of common conditions that can occur during pregnancy and breast-feeding (e.g. Asthma, acute p. 240).

Information about the use of specific drugs during pregnancy and breast-feeding can be found in their drug monographs under Pregnancy, and Breast-feeding (e.g. fluconazole p. 595).

A section, Conception and contraception, containing information around considerations for females of childbearing potential or men who might father a child (e.g. isotretinoin p. 1270) has been included.

Administration and monitoring
When selecting the most appropriate drug, it may be necessary to screen the patient for certain genetic markers or metabolic states. This information is included within a section called Pre-treatment screening (e.g. abacavir p. 647). This section covers one-off tests required to assess the suitability of a patient for a particular drug.

Once the drug has been selected, it needs to be given in the most appropriate manner. A Directions for administration section contains the information about intravenous administration previously located in Appendix 4. This provides practical information on the preparation of intravenous drug infusions, including compatibility of drugs with standard intravenous infusion fluids, method of dilution or reconstitution, and administration rates. In addition, general advice relevant to other routes of administration is provided within this section (e.g. fentanyl p. 458).

After selecting and administering the most appropriate drug by the most appropriate route, patients should be monitored to ensure they are achieving the expected benefits from drug treatment without any unwanted side-effects. The Monitoring section specifies any special monitoring requirements, including information on monitoring the plasma concentration of drugs with a narrow therapeutic index (e.g. theophylline p. 274). Monitoring may, in certain cases, be affected by the impact of a drug on laboratory tests (e.g. hydroxocobalamin p. 1026), and this information is included in Effects on laboratory tests.

In some cases, when a drug is withdrawn, further monitoring or precautions may be advised (e.g. clonidine hydrochloride p. 145): these are covered under Treatment cessation.

Choice and supply
The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (see Taking Medicines to Best Effect). Taking the time to explain to the patient (and carers) the rationale and the potential adverse effects of treatment may improve adherence. For some medicines there is a special need for counselling (e.g. appropriate posture during administration of doxycycline p. 564); this is shown in Patient and carer advice.

Other information contained in the latter half of the monograph also helps prescribers and those dispensing medicines choose medicinal forms (by indicating information such as flavour or when branded products may not be interchangeable (e.g. diltiazem hydrochloride p. 157), assess the suitability of a drug for prescribing, understand the NHS funding status for a drug (e.g. sildenafil p. 813), or assess when a patient may be able to purchase a drug without prescription (e.g. loperamide hydrochloride p. 66).

Medicinal forms
In the BNF, preparations follow immediately after the monograph for the drug that is their main ingredient. In earlier editions, when a particular preparation had safety information, dose advice or other clinical information specific to the product, it was contained within the preparations section. This information has been moved to the relevant section in the main body of the monograph under a heading of the name of the specific medicinal form (e.g. peppermint oil p. 48).

The medicinal forms (formerly preparations) section provides information on the type of formulation (e.g. tablet), the amount of active drug in a solid dosage form, and the concentration of active drug in a liquid dosage form. The legal status is shown for prescription-only medicines and controlled drugs, as well as pharmacy medicines and medicines on the general sales list. Practitioners are reminded, by a statement under the heading of “Medicinal Forms” that not all products containing a specific drug ingredient may be similarly licensed. To be clear on the precise licensing status of specific medicinal forms, practitioners should check the product literature for the particular product being prescribed or dispensed.

Details of all medicinal forms available on the dm+d for each drug in BNF Publications appears online on MedicineComplete. In print editions, due to space constraints, only certain branded products are included in detail. Where medicinal forms are listed they should not be inferred as equivalent to the other brands listed under the same form heading. For example, all the products listed under a heading of “Modified release capsule” will be available as modified release capsules, however, the brands listed under that form heading may have different release profiles, the available strengths may vary and/or the products may have different licensing information. As with earlier editions of the BNF, practitioners must ensure that the particular product being prescribed or dispensed is appropriate.

As medicinal forms are derived from dm+d data, some drugs may appear under names derived from that data; this may vary slightly from those in previous BNF versions, e.g. sodium acid phosphate, is now sodium dihydrogen phosphate anhydrous.

Patients should be prescribed a preparation that complements their daily routine, and that provides the right dose of drug for the right indication and route of administration. When dispensing liquid preparations, a sugar-free preparation should always be used in preference to one containing sugar. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries.

In earlier editions, the BNF only included excipients and electrolyte information for proprietary medicines. This information is now covered at the level of the dose form (e.g. tablet). It is not possible to keep abreast of all the generic-products available on the UK market, and so this information serves as a reminder to the healthcare professional that, if the presence of a particular excipient is of concern, they should check the product literature for the particular product being prescribed or dispensed.

Cautionary and advisory labels that pharmacists are recommended to add when dispensing are included in the medicinal forms section. Details of these labels can be found in Appendix 3, Guidance for cautionary and advisory labels p. 1588. As these labels have now been applied at the level of the dose form, a full list of medicinal products with their relevant labels would be extensive. This list has therefore been removed, but the information is retained within the monograph.

In the case of compound preparations, the prescribing information for all constituents should be taken into account.
Prices in the BNF

Basic NHS net prices are given in the BNF to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective prescribing must, however, take into account other factors (such as dose frequency and duration of treatment) that affect the total cost. The use of more expensive drugs is justified if it will result in better treatment of the patient, or a reduction of the length of an illness, or the time spent in hospital.

Prices are regularly updated using the Drug Tariff and proprietary price information published by the NHS dictionary of medicines and devices (dm+d, www.nhsbsa.nhs.uk/edications-and-devices-dmd). The weekly updated dm+d data (including prices) can be accessed using the dm+d browser of the NHS Business Services Authority (apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do). Prices have been calculated from the net cost used in pricing NHS prescriptions and generally reflect whole dispensing packs. Prices for extemporaneously prepared preparations are not provided in the BNF as prices vary between different manufacturers. In Appendix 4, prices stated are per dressing or bandage.

BNF prices are not suitable for quoting to patients seeking private prescriptions or contemplating over-the-counter purchases because they do not take into account VAT, professional fees, and other overheads.

A fuller explanation of costs to the NHS may be obtained from the Drug Tariff. Separate drug tariffs are applicable to England and Wales (www.ppa.org.uk/ppa/edit intro.htm), Scotland (www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/), and Northern Ireland (www.hscbusiness.hscni.net/services/2034.htm); prices in the different tariffs may vary.

Drug class monographs

In earlier editions of the BNF, information relating to a class of drugs sharing the same properties (e.g. tetracyclines p. 564), was contained within the prescribing notes. In the updated structure, drug class monographs have been created to contain the common information; this ensures such information is easier to find, and has a more regularised structure.

For consistency and ease of use, the class monograph follows the same structure as a drug monograph. Class monographs are indicated by the presence of a flag (e.g. beta-adrenoceptor blockers (systemic) p. 147). If a drug monograph has a corresponding class monograph, that needs to be considered in tandem, in order to understand the full information about a drug, the monograph is also indicated by a flag (e.g. metoprolol tartrate p. 154). Within this flag, the page number of the drug class monograph is provided (e.g. 1234), to help navigate the user to this information. This is particularly useful where occasionally, due to differences in therapeutic use, the drug monograph may not directly follow the drug class monograph (e.g. sotalol hydrochloride p. 108).

Evidence grading

The BNF has adopted a five level evidence grading system (see How BNF Publications are constructed p. vii). Recommendations that are evidence graded can be identified by a symbol appearing immediately before the recommendation. The evidence grade is displayed at the end of the recommendation.

Other content

Nutrition

Appendix 2, Borderline substances p. 1556, includes tables of ACBS-approved enteral feeds and nutritional supplements based on their energy and protein content. There are separate tables for specialised formulae for specific clinical conditions. Classified sections on foods for special diets and nutritional supplements for metabolic diseases are also included.

Wound dressings

A table on wound dressings in Appendix 4, Wound management products and elasticated garments p. 1591, allows an appropriate dressing to be selected based on the appearance and condition of the wound. Further information about the dressing can be found by following the cross-reference to the relevant classified section in the Appendix.

Advanced wound contact dressings have been classified in order of increasing absorbency.

Other useful information

Finding significant changes in the BNF

- Changes, provides a list of significant changes, dose changes, classification changes, new names, and new preparations that have been incorporated into the BNF, as well as a list of preparations that have been discontinued and removed from the BNF. Changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies. So many changes are made for each update of the BNF, that not all of them can be accommodated in the Changes section. We encourage healthcare professionals to regularly review the prescribing information on drugs that they encounter frequently;

- Changes to the Dental Practitioners’ Formulary, are located at the end of the Dental List;

- E-newsletter, the BNF & BNFC e-newsletter service is available free of charge. It alerts healthcare professionals to details of significant changes in the clinical content of these publications and to the way that this information is delivered. Newsletters also review clinical case studies, provide tips on using these publications effectively, and highlight forthcoming changes to the publications. To sign up for e-newsletters go to www.bnf.org.

- An e-learning programme developed in collaboration with the Centre for Pharmacy Postgraduate Education (CPPE), enables pharmacists to identify and assess how significant changes in the BNF affect their clinical practice. The module can be found at www.cppe.ac.uk.

Using other sources for medicines information

The BNF is designed as a digest for rapid reference. Less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. BNF for Children should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services.

www.getintopharma.com
Changes

Monthly updates are provided online via Medicines Complete and the NHS Evidence portal. The changes listed below are cumulative (from one print edition to the next).

Significant changes

Significant changes that appear in the print edition of BNF 79 (September 2019 — March 2020):

- Abemaciclib p. 967 with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [NICe guidance].
- Alemtuzumab p. 857 (Lemtrada®): restriction of use due to serious safety concerns [MHRA/CHM advice].
- Attention deficit hyperactivity disorder p. 346: updated guidance on management.
- Belimumab p. 845 (Benlysta®): increased risk of serious psychiatric events seen in clinical trials [MHRA/CHM advice].
- Benralizumab p. 266 for treating severe eosinophilic asthma [NICe guidance].
- Breast cancer p. 942: updated guidance on management.
- Brentuximab vedotin p. 664 for treating CD30-positive cutaneous T-cell lymphoma [NICe guidance].
- Brigatinib p. 971 for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [NICe guidance].
- Carbimazole p. 771: increased risk of congenital malformations; strengthened advice on contraception [MHRA/CHM advice].
- Carbimazole p. 771: risk of acute pancreatitis [MHRA/CHM advice].
- Certolizumab pegol p. 1111 for treating moderate to severe plaque psoriasis [NICe guidance].
- Chronic heart failure p. 191: updated guidance on management.
- Controlled drugs and drug dependence p. 8: reclassification of gabapentin p. 315 and pregabalin p. 324 as Class C and Schedule 3 Controlled Drugs.
- Daratumumab p. 866 with bortezomib p. 964 and dexamethasone p. 675 for previously treated multiple myeloma [NICe guidance].
- Elvitegravir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1 [MHRA/CHM advice] (see elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide p. 649 and elvitegravir with cobicistat, emtricitabine and tenofovir disoproxil p. 650).
- Emollients (see Emollient and barrier preparations p. 1221): new information about risk of severe and fatal burns with paraffin-containing and paraffin-free emollients [MHRA/CHM advice].
- Encorafenib p. 578 and binimetinib p. 969 for unresectable or metastatic BRAF V600 mutation-positive melanoma [NICe guidance].
- Epilepsy p. 305: inclusion of guidance for the management of Dravet syndrome and Lennox-Gastaut syndrome.
- Ertugliflozin p. 707 as monotherapy or with metformin for treating type 2 diabetes [NICe guidance].
- Fluoroquinolone antibiotics (ciprofloxacin p. 558, levofloxacin p. 559, moxifloxacin p. 560, ofloxacin p. 561): new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects [MHRA/CHM advice].
- Gabapentin p. 315 (Neurontin®) and risk of abuse and dependence: new scheduling requirements from 1 April [MHRA/CHM advice].
- Gemtuzumab ozogamicin p. 869 for untreated acute myeloid leukaemia [NICe guidance].
- Heavy menstrual bleeding p. 753: updated recommendations for the use of ulipristal acetate.
- Hydrocortisone p. 1216: muco-adhesive buccal tablets: should not be used off-label for adrenal insufficiency in children due to serious risks [MHRA/CHM advice].
- Ipilimumab p. 871 (Yervoy®): reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation [MHRA/CHM advice].
- Irinotecan hydrochloride p. 926, liposomal formulations (Onyxide®): reports of serious and fatal thromboembolic events [MHRA/CHM advice].
- Lenvatinib p. 987 for untreated advanced hepatocellular carcinoma [NICe guidance].
- Liposomal daunorubicin with cytarabine p. 900 for untreated acute myeloid leukaemia [NICe guidance].
- Methotrexate p. 913: updated recommendations for conception and contraception.
- Nivolumab p. 873 for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [NICe guidance].
- Olaratumab p. 876 (Lartrano®): no new patients to be prescribed due to study showing no clinical benefit [MHRA/CHM advice].
- Pembrolizumab p. 878 for adjuvant treatment of resected melanoma with high risk of recurrence [NICe guidance].
- Pembrolizumab p. 878 with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [NICe guidance].
- Pertuzumab p. 880 for adjuvant treatment of HER2-positive early stage breast cancer [NICe guidance].
- Pregabalin p. 324 (Lyrica®) and risk of abuse and dependence: new scheduling requirements from 1 April [MHRA/CHM advice].
- Prescribing in pregnancy p. 23: Medicines with teratogenic potential, what is effective contraception and how often is pregnancy testing needed? [MHRA/CHM advice].
- Quinolones p. 557: new MHRA/CHM advice on restrictions and precautions for use of fluoroquinolone antibiotics.
- Regorafenib p. 996 for previously treated advanced hepatocellular carcinoma [NICe guidance].
- Renal and ureteric stones p. 788: new guidance on management.
- Respiratory system infections, antibacterial therapy p. 515: new guidance for acute exacerbations of Bronchiectasis (non-cystic fibrosis).
Respiratory system infections, antibacterial therapy p. 515: updated guidance for acute exacerbations of Chronic obstructive pulmonary disease.

Respiratory system infections, antibacterial therapy p. 515: new guidance on management of Cough, acute.

SGLT2 inhibitors (canagliflozin p. 702, dapagliflozin p. 704, empagliflozin p. 706, ertugliflozin p. 707): reports of Fournier’s gangrene (necrotising fasciitis of the genitalia or perineum) [MHRA/CHM advice].

Smoking cessation p. 497: updated guidance.

Tapentadol p. 471 (Palexia®): risk of seizures and reports of serotonin syndrome when co-administered with other medicines [MHRA/CHM advice].

Tildrakizumab p. 1260 for treating moderate to severe plaque psoriasis [NICE guidance].

Tofacitinib p. 1105 for moderately to severely active ulcerative colitis [NICE guidance].

Tofacitinib p. 1105 (Xeljanz®): increased risk of pulmonary embolism and mortality in rheumatoid arthritis patients receiving 10 mg twice daily in a clinical trial [MHRA/CHM advice].


Valproate medicines and serious harms in pregnancy: new Annual Risk Acknowledgement Form and clinical guidance from professional bodies to support compliance with the Pregnancy Prevention Programme [MHRA/CHM advice] (see sodium valproate p. 327 and valproic acid p. 354).

Valproate medicines (see sodium valproate p. 327 and valproic acid p. 354): are you in acting in compliance with the pregnancy prevention measures? [MHRA/CHM advice].

Vandetanib p. 1003 for treating medullary thyroid cancer [NICE guidance].

Venetoclax p. 1007 with rituximab p. 882 for previously treated chronic lymphocytic leukaemia [NICE guidance].

Yellow fever vaccine, live p. 1327 (Stamaril®) and fatal adverse reactions: extreme caution needed in people who may be immunosuppressed [MHRA/CHM advice].

Yellow fever vaccine, live p. 1327 (Stamaril®) and fatal adverse reactions: extreme caution needed in those aged 60 years and older [MHRA/CHM advice] (BNF only).


Dose changes
Changes in dose statements that appear in the print edition of BNF 78 (September 2019 — March 2020):

- Adalimumab p. 1108 [maintenance dosing updated].
- Alirocumab p. 206 [dosing options for primary hypercholesterolaemia or mixed dyslipidaemia].
- Anthrax vaccine p. 1312 [dosing schedule updated].
- Imipenem with cilastatin p. 522 [dosing recommendation in renal impairment updated].
- Japanese encephalitis vaccine p. 1323 [dosing schedule updated].
- Malarone® (atovaquone with proguanil hydrochloride p. 615) [update to weight range for prophylaxis of falciparum malaria].
- Oseltamivir p. 662 [duration of treatment in immunocompromised patients].
- Pembrolizumab p. 878 [dose for non-small cell lung cancer (following prior chemotherapy) and melanoma].
- Rivaroxaban p. 128 [clarification of dosing options for prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism].
- Secukinumab p. 1100 [dosing for psoriatic arthritis].

New preparations
New preparations that appear in the print edition of BNF 78 (September 2019 — March 2020):

- Alunbrig® [brigatinib p. 971].
- Brafton® [encorafenib p. 978].
- Bavidal® [buprenorphine p. 447].
- Cidofovir p. 637.
- Delstrigo® [lamivudine with tenofovir disoproxil and doravirine p. 653].
- Diacomit® [stiripentol p. 330].
- Erleada® [apalutamide p. 946].
- Fortacin® [lidocaine with prilocaine p. 1354].
- Ilumetri® [tildrakizumab p. 1260].
- Intrarosa® [prasterone p. 833].
- Mektovi® [binimetinib p. 969].
- Namuscla® [mexiletine p. 1126].
- Ozempic® [semaglutide p. 701].
- Pifeltro® [doravirine p. 644].
- Prevyvis® [fetzimide p. 639].
- Steglatro® [ertugliflozin p. 707].
- Suliqua® [insulin glargine with lixisenatide p. 718].
- Symkevi® [tezacaftor with ivacaftor p. 295].
- Tegsedi® [notersen p. 408].
- Testavan® [testosterone p. 768].
- Verzenios® [abemaciclib p. 967].
Guidance on prescribing

General guidance
Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered. It is important to discuss treatment options carefully with the patient to ensure that the patient is content to take the medicine as prescribed. In particular, the patient should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, the patient should be advised of this.

Prescribing competency framework
The Royal Pharmaceutical Society has published a Prescribing Competency Framework that includes a common set of competencies that form the basis for prescribing, regardless of professional background. The competencies have been developed to help healthcare professionals to be safe and effective prescribers, with the aim of supporting patients to get the best outcomes from their medicines. It is available at www.rpharms.com/resources/frameworks/prescribers-competency-framework.

Multimorbidity
The presence of two or more long-term health conditions in a patient (multimorbidity) is associated with reduced quality of life, higher mortality, higher rates of adverse drug reactions, greater use of the health service, and a higher treatment burden (due to polypharmacy or multiple appointments). Treatment decisions in these patients should involve consideration of the patient’s needs, preferences for treatment, health priorities, and lifestyle with the aim of improving quality of life by reducing treatment burden, adverse events, and unplanned or uncoordinated care.

Prescribers should consider the risks and benefits of treatments recommended for patients with multimorbidity from guidance for single health conditions; evidence for these recommendations is commonly drawn from patients without multimorbidity or who are taking fewer prescribed regular medicines.

Treatments intended to relieve symptoms should be reviewed for effectiveness, including reducing or stopping the treatment and monitoring the effects. Alternatively, non-pharmacological treatments may be offered or treatments of limited benefit can be considered for discontinuation. The management of risk factors for future disease can be a major treatment burden for patients with multimorbidity and is not always appropriate.

Deprescribing
Deprescribing is the process of discontinuing or reducing the dose of medicines, supervised by a healthcare professional, with the aim of managing polypharmacy and improving outcomes. Deprescribing requires careful counselling and shared decision-making with patients, and is considered part of routine clinical care.

Taking medicines to best effect
Difficulties in adherence to drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

- patients’ perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear;
- physical difficulty in taking medicines (e.g. swallowing the medicine, handling small tablets, or opening medicine containers);
- unattractive formulation (e.g. unpleasant taste);
- complicated regimen.

The prescriber and the patient should agree on the health outcomes that the patient wishes to achieve and the strategy for achieving them (‘concordance’). The prescriber should be sensitive to religious, cultural, and personal beliefs that can affect a patient’s acceptance of medicines.

Taking the time to explain to the patient (and relatives) the rationale and the potential adverse effects of treatment may improve adherence. Reinforcement and elaboration of the physician’s instructions by the pharmacist and other members of the healthcare team also helps. Advising the patient of the possibility of alternative treatments may encourage the patient to seek advice rather than merely abandon unacceptable treatment.

Simplifying the drug regimen may help: the need for frequent administration may reduce adherence, although there appears to be little difference in adherence between once-daily and twice-daily administration. Combination products reduce the number of drugs taken but at the expense of the ability to titrate individual doses.

Advanced Pharmacy Services
Advanced Services are provided as part of the NHS Community Pharmacy Contractual Framework, and include services such as the New Medicines Service and Medicines Use Review service. These services are provided by accredited community pharmacists, with the aim of targeting specific patients to help manage their medicines more effectively, improve adherence, and reduce medicines wastage.

New Medicines Service
The New Medicines Service (NMS) provides education and support to patients who are newly prescribed a medicine to manage a long-term condition. The service is split into three stages: patient engagement, intervention and follow-up. As of 2018, this service is available for patients living in England who have either been prescribed a new medicine for one of the following conditions – asthma, chronic obstructive pulmonary disease (COPD), type 2 diabetes, or hypertension, or have been prescribed a new antplatelet or anticoagulant. Patients can be offered the service by the prescriber nominal, or opportunistically by the community pharmacy. For further information, see: psnc.org.uk/services-commissioning/advanced-services/nms/.

Medicines Use Review
The Medicines Use Review (MUR) service consists of structured adherence-centred reviews with patients on multiple medicines, particularly those receiving medicines for long-term conditions. The service is undertaken periodically, or when there is a need to make an adherence-focused intervention due to a problem identified while providing the dispensing service. The pharmacist providing the service is required to ensure that at least 70% of all MURs undertaken in a year are for patients who fall into one or more of the national target groups. The national target groups for MURs in England are:

- patients taking high-risk medicines (NSAIDs, anticoagulants (including low molecular weight heparin), antplatelets, or diuretics);
- patients recently discharged from hospital who have had changes made to their medicines;
patients prescribed certain respiratory medicines;
- patients with, or at risk of cardiovascular disease, and are regularly prescribed at least four medicines.

For further information, see: pscn.org.uk/services-commissioning/advanced-services/murs/.

Wales, Northern Ireland, and Scotland have variations on this service, including different national target groups.

In Wales, see www.cwpales.org.uk/Contract-support-and-it/Advanced-Services/Medicines-Use-review-MUR.aspx

In Northern Ireland, see www.hscbusiness.hscni.net/services/2427.htm.

In Scotland, see www.communitypharmacyscotland.org.uk/nhs-care-services/services/chronic-medication-service/.

Biological medicines

Biological medicines are medicines that are made by or derived from a biological source using biotechnology processes, such as recombinant DNA technology. The size and complexity of biological medicines, as well as the way they are produced, may result in a degree of natural variability in molecules of the same active substance, particularly in different batches of the medicine. This variation is maintained within strict acceptable limits. Examples of biological medicines include insulins and monoclonal antibodies.

Biological medicines must be prescribed by brand name and the brand name specified on the prescription should be dispensed in order to avoid inadvertent switching. Automatic substitution of brands at the point of dispensing is not appropriate for biological medicines.

Biosimilar medicines

A biosimilar medicine is a biological medicine that is highly similar and clinically equivalent (in terms of quality, safety, and efficacy) to an existing biological medicine that has already been authorised in the European Union (known as the reference biological medicine or originator medicine). The active substance of a biosimilar medicine is similar, but not identical, to the originator biological medicine. Once the patent for a biological medicine has expired, a biosimilar medicine may be authorised by the European Medicines Agency (EMA). A biosimilar medicine is not the same as a generic medicine, which contains a simpler molecular structure that is identical to the originator medicine.

Therapeutic equivalence

Biosimilar medicines should be considered to be therapeutically equivalent to the originator biological medicine within their authorised indications. Biosimilar medicines are usually licensed for all the indications of the originator biological medicine, but this depends on the evidence submitted to the EMA for authorisation and must be scientifically justified on the basis of demonstrated or extrapolated equivalence.

Prescribing and dispensing

The choice of whether to prescribe a biosimilar medicine or the originator biological medicine rests with the clinician in consultation with the patient.

Safety monitoring

Biosimilar medicines are subject to a black triangle status (▼) at the time of initial authorisation.

It is important to report suspected adverse reactions using the Yellow Card Scheme (see Adverse reactions to drugs p. 12). For all biological medicines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine.

UK Medicines Information centres have developed a validated tool to determine potential safety issues associated with all new medicines. These ‘in-use product safety assessment reports’ will be published for new biosimilar medicines as they become available, see www.sps.nhs.uk/home/medicines/.

National funding/access decisions

The Department of Health has confirmed that, in England, NICE can decide to apply the same remit, and the resulting technology appraisal guidance, to relevant biosimilar medicines which appear on the market subsequent to their originator biological medicine. In other circumstances, where a review of the evidence for a particular biosimilar medicine is necessary, NICE will consider producing an evidence summary (see Evidence summary: new medicines, www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines).

National information


In Northern Ireland, see niformulary.hscni.net/ManagedEntry/bios/Pages/default.aspx.

In Scotland, see www.scottishmedicines.org.uk/About_SMC/Policy_statements/Biosimilar_Medicines.

In Wales, see www.wales.nhs.uk/sites/documents/814/Biosimilar_4abIUHPositionStatement%5BNov2015%5D.pdf.

Availability

The following drugs are available as a biosimilar medicine:

- Adalimumab p. 1108
- Bevacizumab p. 862
- Enoxaparin sodium p. 132
- Epoetin alfa p. 1014
- Epoetin zeta p. 1016
- Etanercept p. 1113
- Filgrastim p. 1029
- Follitropin alfa p. 745
- Infliximab p. 1116
- Insulin glargine p. 718
- Insulin lispro p. 714
- Rituximab p. 882
- Somatropin p. 748
- Teriparatide p. 734
- Trastuzumab p. 885

Complementary and alternative medicine

An increasing amount of information on complementary and alternative medicine is becoming available. The scope of the BNF is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John’s wort). Further information on herbal medicines is available at www.mhra.gov.uk.

Abbreviation of titles

In general, titles of drugs and preparations should be written in full. Unofficial abbreviations should not be used as they may be misinterpreted.

Non-proprietary titles

Where non-proprietary (‘generic’) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where there is a demonstrable difference in clinical effect between each manufacturer’s version of the formulation, making it important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should not be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations.

Titles used as headings for monographs may be used freely in the United Kingdom but in other countries may be subject to restriction.

www.getintopharma.com
Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia, or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Human Medicines Regulations 2012.

**Proprietary titles**
Names followed by the symbol® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

**Marketing authorisation and BNF advice**
In general the doses, indications, cautions, contra-indications, and side-effects in the BNF reflect those in the manufacturers’ data sheets or Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). The BNF does not generally include proprietary medicines that are not supported by a valid Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, the BNF reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisations. Unlicensed products can be obtained from ‘special-order’ manufacturers or specialist importing companies.

Where an unlicensed drug is included in the BNF, this is indicated in square brackets after the entry. When the BNF suggests a use (or route) that is outside the licensed indication of a product (‘off-label’ use), this too is indicated. Unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults.

**Prescribing unlicensed medicines**
Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber’s professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines, and also inform the patient or the patient’s carer that the prescribed medicine is unlicensed.

**Oral syringes**
An oral syringe is supplied when oral liquid medicines are prescribed in doses other than multiples of 5 mL. The oral syringe is marked in 0.5 mL divisions from 1 to 5 mL to measure doses of less than 5 mL (other sizes of oral syringe may also be available). It is provided with an adaptor and an instruction leaflet. The 5–mL spoon is used for doses of 5 mL (or multiples thereof).

**Important** To avoid inadvertent intravenous administration of oral liquid medicines, only an appropriate oral or enteral syringe should be used to measure an oral liquid medicine (if a medicine spoon or graduated measure cannot be used); these syringes should not be compatible with intravenous or other parenteral devices. Oral or enteral syringes should be clearly labelled ‘Oral’ or ‘Enteral’ in a large font size; it is the healthcare practitioner’s responsibility to label the syringe with this information if the manufacturer has not done so.

**Excipients**
Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as ‘sugar-free’ in the BNF. Preparations containing hydrogenated glucose syrup, mannnitol, maltitol, sorbitol, or xylitol are also marked ‘sugar-free’ since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where information on the presence of aspartame, gluten, sulfites, tartrazine, arachis (peanut) oil or sesame oil is available, this is indicated in the BNF against the relevant preparation.

Information is provided on selected excipients in skin preparations, in vaccines, and on selected preparations and excipients in eye drops and injections.

The presence of benzyl alcohol and polyoxyl castor oil (polyethoxylated castor oil) in injections is indicated in the BNF. Benzyl alcohol has been associated with a fatal toxic syndrome in preterm neonates, and therefore, parenteral preparations containing the preservative should not be used in neonates. Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions.

The presence of propylene glycol in oral or parenteral medicines is indicated in the BNF; it can cause adverse effects if its elimination is impaired, e.g. in renal failure, in neonates and young children, and in slow metabolisers of the substance. It may interact with disulfiram p. 495 and metronidazole p. 542.

The lactose content in most medicines is too small to cause problems in most lactose-intolerant patients. However in severe lactose intolerance, the lactose content should be determined before prescribing. The amount of lactose varies according to manufacturer, product, formulation, and strength.

**Important** In the absence of information on excipients in the BNF and in the product literature (available at www.medicines.org.uk/emc), contact the manufacturer (see Index of Manufacturers) if it is essential to check details.

**Extemporaneous preparation**
A product should be dispensed extemporaneously only when no product with a marketing authorisation is available. The BP direction that a preparation must be freshly prepared indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25°C.

The term water used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation (Water for injections).

**Drugs and driving**
Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

A new offence of driving, attempting to drive, or being in charge of a vehicle, with certain specified controlled drugs in excess of specified limits, came into force on 2nd March 2015. This offence is an addition to the existing rules on drug impaired driving and fitness to drive, and applies to two groups of drugs—commonly abused drugs, including amphetamines, cannabis, cocaine, and ketamine p. 1345, and drugs used mainly for medical reasons, such as opioids and benzodiazepines. Anyone found to have any of the drugs...
(including related drugs, for example, apomorphine hydrochloride p. 418) above specified limits in their blood will be guilty of an offence, whether their driving was impaired or not. This also includes prescribed drugs which metabolise to those included in the offence, for example, selegiline hydrochloride p. 428. However, the legislation provides a statutory “medical defence” for patients taking drugs for medical reasons in accordance with instructions, if their driving was not impaired—it continues to be an offence to drive if actually impaired. Patients should therefore be advised to continue taking their medicines as prescribed, and when driving, to carry suitable evidence that the drug was prescribed, or sold, to treat a medical or dental problem, and that it was taken according to the instructions given by the prescriber, or information provided with the medicine (e.g. a repeat prescription form or the medicine’s patient information leaflet). Further information is available from the Department for Transport at www.gov.uk/government/collections/drug-driving.

Patents
In the BNF, certain drugs have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

Health and safety
When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Substances such as corticosteroids, some antimicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

Safety in the home
Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable child-resistant container unless:

- the medicine is in an original pack or patient pack such as to make this inadvisable;
- the patient will have difficulty in opening a child-resistant container;
- a specific request is made that the product shall not be dispensed in a child-resistant container;
- no suitable child-resistant container exists for a particular liquid preparation.

All patients should be advised to dispose of unwanted medicines by returning them to a supplier for destruction.

Labelling of prescribed medicines
There is a legal requirement for the following to appear on the label of any prescribed medicine:

- name of the patient;
- name and address of the supplying pharmacy;
- date of dispensing;
- name of the medicine;
- directions for use of the medicine;
- precautions relating to the use of the medicine.

The Royal Pharmaceutical Society recommends that the following also appears on the label:

- the words ‘Keep out of the sight and reach of children’;
- where applicable, the words ‘Use this medicine only on your skin’.

A pharmacist can exercise professional skill and judgement to amend or include more appropriate wording for the name of the medicine, the directions for use, or the precautions relating to the use of the medicine.

Non-proprietary names of compound preparations
Non-proprietary names of compound preparations which appear in the BNF are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients.

Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misinterpreted.

Special care should be taken to avoid errors when prescribing compound preparations; in particular the hyphen in the prefix ‘co-’ should be retained.

Special care should also be taken to avoid creating generic names for modified-release preparations where the use of these names could lead to confusion between formulations with different lengths of action.

EEA and Swiss prescriptions
Pharmacists can dispense prescriptions issued by doctors and dentists from the European Economic Area (EEA) or Switzerland (except prescriptions for controlled drugs in Schedules 1, 2, or 3, or for drugs without a UK marketing authorisation). Prescriptions should be written in ink or otherwise so as to be indelible, should be dated, should state the name of the patient, should state the address of the prescriber, should contain particulars indicating whether the prescriber is a doctor or dentist, and should be signed by the prescriber.

Security and validity of prescriptions
The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions. In particular, prescription forms should:

- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

Patient group direction (PGD)
In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine (including some Controlled Drugs in specific circumstances) by certain classes of healthcare professionals; the Direction is signed by a doctor (or dentist) and by a pharmacist. Further information on Patient Group Directions is available in Health Service Circular HSC 2000/026 (England), HSL (2001) 7 (Scotland), and WHC (2000) 116 (Wales); see also the Human Medicines Regulations 2012.

NICE, Scottish Medicines Consortium and All Wales Medicines Strategy Group
Advice issued by the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) is included in the BNF when relevant. Details of the advice together with updates can be obtained from: www.nice.org.uk, www.scottishmedicines.org.uk and www.awmsg.org.
Prescription writing

Shared care
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Requirements
Prescriptions should be written legibly in ink or otherwise so as to be indelible (it is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink), should be dated, should state the name and address of the patient, the address of the prescriber, an indication of the type of prescriber, and should be signed in ink by the prescriber (computer-generated facsimile signatures do not meet the legal requirement). The age and the date of birth of the patient should preferably be stated, and it is a legal requirement in the case of prescription-only medicines to state the age for children under 12 years. These recommendations are acceptable for prescription-only medicines. Prescriptions for controlled drugs have additional legal requirements.

Wherever appropriate the prescriber should state the current weight of the child to enable the dose prescribed to be calculated. Consideration should also be given to including the dose per unit mass e.g. mg/kg or the dose per m² body-surface area e.g. mg/m² where this would reduce error.

The following should be noted:

- The strength or quantity to be contained in capsules, lozenges, tablets etc. should be stated by the prescriber. In particular, strength of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).
- The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg. Quantities of 1 gram or more should be written as 1 g etc. Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g. Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg. When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL. Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.
- ‘Micrograms’ and ‘nanograms’ should not be abbreviated. Similarly ‘units’ should not be abbreviated.
- The term ‘millilitre’ (mL or mL) is used in medicine and pharmacy, and cubic centimetre, c.c., or cm³ should not be used. (The use of capital L in mL is a printing convention throughout the BNF; both ‘mL’ and ‘ml’ are recognised SI abbreviations).
- Dose and dose frequency should be stated; in the case of preparations to be taken ‘as required’ a minimum dose interval should be specified. Care should be taken to ensure children receive the correct dose of the active drug. Therefore, the dose should normally be stated in terms of the mass of the active drug (e.g. ‘125 mg 3 times daily’); terms such as ‘5 mL’ or ‘1 tablet’ should be avoided except for compound preparations. When doses other than multiples of 5 mL are prescribed for oral liquid preparations the dose-volume will be provided by means of an oral syringe, (except for preparations intended to be measured with a pipette). Suitable quantities:
  - Elixirs, Linctuses, and Paediatric Mixtures (5-mL dose), 50, 100, or 150 mL
  - Adult Mixtures (10 mL dose), 200 or 300 mL
  - Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer’s pack)
  - Eye Lotions, Gargles, and Mouthwashes, 200 mL
  - The names of drugs and preparations should be written clearly and not abbreviated, using approved titles only; avoid creating generic titles for modified-release preparations.
  - The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated. When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.

- Although directions should preferably be in English without abbreviation, it is recognised that some Latin abbreviations are used.

Sample prescription

Prescribing by dentists
Until new prescribing arrangements are in place for NHS prescriptions, dentists should use form FP10D (GP14 in Scotland, WP10D in Wales) to prescribe only those items listed in the Dental Practitioners’ Formulary. The Human Medicines Regulations 2012 does not set any limitations upon the number and variety of substances which the dentist may administer to patients in the surgery or may order by private prescription—provided the relevant legal requirements are observed the dentist may use or order whatever is required for the clinical situation. There is no statutory requirement for the dentist to communicate with a patient’s medical practitioner when prescribing for dental use. There are, however, occasions when this would be in the patient’s interest and such communication is to be encouraged. For legal requirements relating to prescriptions
of Controlled Drugs, see Controlled drugs and drug dependence p. 8.

Computer-issued prescriptions
For computer-issued prescriptions the following advice, based on the recommendations of the Joint GP Information Technology Committee, should also be noted:

1. The computer must print out the date, the patient’s surname, one forename, other initials, and address, and may also print out the patient’s title and date of birth. The age of children under 12 years and of adults over 60 years must be printed in the box available; the age of children under 5 years should be printed in years and months. A facility may also exist to print out the age of patients between 12 and 60 years.

2. The doctor’s name must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor’s surgery address, reference number, and Primary Care Trust (PCT, Health Board in Scotland, Local Health Board in Wales) are also necessary. In addition, the surgery telephone number should be printed.

3. When prescriptions are to be signed by general practitioners, registrars, assistants, locums, or deputising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal.

4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and to ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checks are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.

5. The dictionary may contain information on the usual doses, formulations, and pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.

6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112). It must also be possible to prescribe by indicating the length of treatment required.

7. The BNF recommendations should be followed as listed above.

8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. For instructions such as ‘as directed’ and ‘when required’, the maximum daily dose should normally be specified.

9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.

10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should be in line with any warnings or advice in the BNF; numerical codes should not be used.

11. A mechanism (such as printing a series of nonspecific characters) should be incorporated to cancel out unused space, or wording such as ‘no more items on this prescription’ may be added after the last item. Otherwise the doctor should delete the space manually.

12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.

13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations must be made in the doctor’s own handwriting and countersigned; computer records should be updated to fully reflect any alteration. Prescriptions for drugs used for contraceptive purposes (but which are not promoted as contraceptives) may need to be marked in handwriting with the symbol ‘C’ (or endorsed in another way to indicate that the item is prescribed for contraceptive purposes).

14. Prescriptions for controlled drugs can be printed from the computer, but the prescriber’s signature must be handwritten (See Controlled Drugs and Drug Dependence; the prescriber may use a date stamp).

15. The strip of paper on the side of the FP10SS (GP10SS in Scotland, WP10SS in Wales) may be used for various purposes but care should be taken to avoid including confidential information. It may be advisable for the patient’s name to appear at the top, but this should be preceded by ‘confidential’.

16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.

17. Prescription forms that are reprinted or issued as a duplicate should be labelled clearly as such.
Emergency supply of medicines

Emergency supply requested by member of the public
Pharmacists are sometimes called upon by members of the public to make an emergency supply of medicines. The Human Medicines Regulations 2012 allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
   i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
   ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed for the person requesting it;
   iii) as to the dose that it would be appropriate for the person to take;

b) that no greater quantity shall be supplied than will provide 5 days’ treatment of phenobarbital p. 335, *phenobarbital sodium*, or Controlled Drugs in Schedules 4 or 5 (doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation) or 30 days’ treatment for other prescription-only medicines, except when the prescription-only medicine is:
   i) insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
   ii) an oral contraceptive when a full cycle may be supplied;
   iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;

c) that an entry shall be made by the pharmacist in the prescription book stating:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name and address of the patient;

d) that the container or package must be labelled to show:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name of the patient;
   iv) the name and address of the pharmacy;
   v) the words ‘Emergency supply’;
   vi) the words ‘Keep out of the reach of children’ (or similar warning);

e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital p. 335 or *phenobarbital sodium* for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition); (Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation).

Emergency supply requested by prescriber
Emergency supply of a prescription-only medicine may also be made at the request of a doctor, a dentist, a supplementary prescriber, a community practitioner nurse prescriber, a nurse, pharmacist, or optometrist independent prescriber, or a doctor or dentist from the European Economic Area or Switzerland, provided:

a) that the pharmacist is satisfied that the prescriber by reason of some emergency is unable to furnish a prescription immediately;

b) that the prescriber has undertaken to furnish a prescription within 72 hours;

c) that the medicine is supplied in accordance with the directions of the prescriber requesting it;

d) that the medicine is not a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital p. 335 or *phenobarbital sodium* for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition); (Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation).

e) that an entry shall be made in the prescription book stating:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name and address of the practitioner requesting the emergency supply;
   iv) the name and address of the patient;
   v) the date on the prescription;
   vi) when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society’s guidelines
1. The pharmacist should consider the medical consequences of not supplying a medicine in an emergency.
2. If the pharmacist is unable to make an emergency supply of a medicine the pharmacist should advise the patient how to obtain essential medical care.

For conditions that apply to supplies made at the request of a patient see *Medicines, Ethics and Practice*, London Pharmaceutical Press, (always consult latest edition).
Controlled drugs and drug dependence

Regulations and classification
The Misuse of Drugs Act, 1971 as amended prohibits certain activities in relation to ‘Controlled Drugs’, in particular their manufacture, supply, and possession (except where permitted by the 2001 Regulations or under licence from the Secretary of State). The penalties applicable to offences involving the different drugs are graded broadly according to the harmfulness attributable to a drug when it is misused and for this purpose the drugs are defined in the following three classes:


- **Class C** includes: certain drugs related to the amfetamines such as benzetamine and chlorphentermine, buprenorphine p. 447, mazindol, meperbamate, pemoline, pipradrol, most benzodiazepines, tramadol hydrochloride p. 471, zaleplon, zolpidem tartrate, zopiclone, and androgenic and anabolic steroids, clenbuterol, choric gonadotrophin (HCG), non-human choric gonadotrophin, somatotropin, somatrem, and somatropin p. 748. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements. Records in registers do not need to be kept (except in the case of Sativex®).

- **Schedule 3** includes the barbiturates (except secobarbital, now Schedule 2), buprenorphine p. 447, gabapentin p. 315, mazindol, meperbamate, midazolam p. 340, pentazocine, phentermine, pregabaline, temazepam p. 488, and tramadol hydrochloride p. 471. They are subject to the special prescription requirements. Safe custody requirements do apply, except for any 5,5 disubstituted barbituric acid (e.g. phenobarbital), gabapentin p. 315, mazindol, meperbamate, midazolam p. 340, pentazocine, phentermine, pregabaline, and tramadol hydrochloride p. 471, or any stereoisomeric form or salts of the above. Records in registers do not need to be kept (although there are requirements for the retention of invoices for 2 years).

- **Schedule 4** includes in Part I drugs that are subject to minimal control, such as benzodiazepines (except temazepam p. 488 and midazolam p. 340, which are in Schedule 3), non-benzodiazepine hypnotics (zaleplon, zolpidem tartrate, and zopiclone) and Sativex®. Part II includes androgenic and anabolic steroids, clenbuterol, choric gonadotrophin (HCG), non-human choric gonadotrophin, somatotropin, somatrem, and somatropin p. 748. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements. Records in registers do not need to be kept (except in the case of Sativex®).

- **Schedule 5** includes preparations of certain Controlled Drugs (such as codeine, pholcodine p. 296 or morphine p. 463) which due to their low strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years. Since the Responsible Pharmacist Regulations were published in 2008, standing operation procedures for the management of Controlled Drugs, are required in registered pharmacies.

The Misuse of Drugs (Safe Custody) Regulations 1973 as amended details the storage and safe custody requirements for Controlled Drugs.

The Misuse of Drugs Regulations 2001 (and subsequent amendments) defines the classes of person who are authorised to supply and possess Controlled Drugs while acting in their professional capacities and lays down the conditions under which these activities may be carried out. In the 2001 regulations, drugs are divided into five Schedules, each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

- **Schedule 1** includes drugs not used medicinally such as hallucinogenic drugs (e.g. LSD), ecstasy-type substances, raw opium, and cannabis. A Home Office licence is generally required for their production, possession, or supply. A Controlled Drug register must be used to record details of any Schedule 1 Controlled Drugs received or supplied by a pharmacy.

- **Schedule 2** includes opiates (e.g. diamorphine hydrochloride p. 456 (heroin), morphine p. 463, methadone hydrochloride p. 502, oxycodone hydrochloride p. 469, pethidine hydrochloride p. 470), major stimulants (e.g. amphetamine), quinilbarbitone (secobarbital), cocaine, ketamine p. 1345, and cannabin-based products for medicinal use in humans. Schedule 2 Controlled Drugs are subject to the full Controlled Drug requirements relating to prescriptions, safe custody (except for quinilbarbitone (secobarbital) and some liquid preparations), and the need to keep a Controlled Drug register, (unless exempted in Schedule 5). Possession, supply and procurement is authorised for pharmacists and other classes of persons named in the 2001 Regulations.

Prescriptions
Preparations in Schedules 1, 2, 3, 4 and 5 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are identified throughout the BNF and BNF for children using the following symbols:

- **01** for preparations in Schedule 1
- **02** for preparations in Schedule 2
- **03** for preparations in Schedule 3
- **04-1** for preparations in Schedule 4 (Part I)
- **04-2** for preparations in Schedule 4 (Part II)
- **05** for preparations in Schedule 5

The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance at www.gov.uk/dh).

**Prescription requirements** Prescriptions for Controlled Drugs that are subject to prescription requirements (all preparations in Schedules 2 and 3) must be indelible, must be signed by the prescriber, include the date on which they were signed, and specify the prescriber’s address (must be within the UK). A machine-written prescription is not acceptable.
acceptable, but the prescriber’s signature must be handwritten. Advanced electronic signatures can be accepted for Schedule 2 and 3 Controlled Drugs where the Electronic Prescribing Service (EPS) is used. All prescriptions for Controlled Drugs that are subject to the prescription requirements must always state:

- the name and address of the patient (use of a PO Box is not acceptable);
- in the case of a preparation, the form (the dosage form e.g. tablets must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name e.g. MST Continus, or whether only one form is available), and, where appropriate, the strength of the preparation (when more than one strength of a preparation exists the strength required must be specified); to avoid ambiguity, where a prescription requests multiple strengths of a medicine, each strength should be prescribed separately (i.e. separate dose, total quantity, etc);
- for liquids, the total volume in millilitres (in both words and figures) of the preparation to be supplied; for dosage units (tablets, capsules, ampoules), state the total number (in both words and figures) of dosage units to be supplied (e.g. 10 tablets of 10 mg rather than 100 mg total quantity);
- the dose, which must be clearly defined (i.e. the instruction ‘one as directed’ constitutes a dose but ‘as directed’ does not); it is not necessary that the dose is stated in both words and figures;
- the words ‘for dental treatment only’ if issued by a dentist.

A pharmacist is not allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist (e.g. name, date, signature and GPhC registration number). The prescription should be marked with the date of supply at the time the Controlled Drug supply is made.

The Department of Health and the Scottish Government have issued a strong recommendation that the maximum quantity of Schedule 2, 3 or 4 Controlled Drugs prescribed should not exceed 30 days; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient’s notes.

A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon (the prescriber may forward-date the prescription; the start date may also be specified in the body of the prescription). Schedule 5 prescriptions are valid for 6 months from the appropriate date.

Medicines that are not Controlled Drugs should not be prescribed on the same form as a Schedule 2 or 3 Controlled Drug.

See sample prescription:

![Sample Prescription]

Instalments and repeatable prescriptions

Prescriptions for Schedule 2 or 3 Controlled Drugs can be dispensed by instalments. An instalment prescription must have an instalment direction including both the dose and the instalment amount specified separately on the prescription, and it must also state the interval between each time the medicine can be supplied.

The first instalment must be dispensed within 28 days of the appropriate day (i.e. date of signing unless the prescriber indicates a date before which the Controlled Drug should not be dispensed) and the remainder should be dispensed in accordance with the instructions on the prescription. The prescription must be marked with the date of each supply.

The instalment direction is a legal requirement and needs to be complied with, however, for certain situations (e.g. if a pharmacy is closed on the day an instalment is due) the Home Office has approved specific wording which provides pharmacists some flexibility for supply. For details, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition) or see Home Office approved wording for instalment prescribing (Circular 027/2015), available at www.gov.uk/.

Repeatable prescriptions are prescriptions which contain a direction that they can be dispensed more than once (e.g. repeat × 3). Only Schedule 4 and 5 Controlled Drugs are permitted on repeatable prescriptions.

Private prescriptions

Private prescriptions for Controlled Drugs in Schedules 2 and 3 must be written on specially designated forms which are provided by local NHS England area teams in England (form FP10PCD), local NHS Health Boards in Scotland (form PPCD) and Wales (form W10PCD); in addition, prescriptions must specify the prescriber’s identification number (or a NHS prescriber code in Scotland).
Prescriptions to be supplied by a pharmacist in hospital are exempt from the requirements for private prescriptions.

**Dependence and misuse**

The most common drugs of addiction are crack cocaine and opioids, particularly diamorphine hydrochloride p. 456 (heroin). For arrangements for prescribing of diamorphine hydrochloride, dipipanone, or cocaine for addicts, see Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts below.

Along with traditional stimulants, such as amphetamine and cocaine, there has been an emerging use of methamphetamine and a range of psychoactive substances with stimulant, depressant or hallucinogenic properties such as lysergide (lysergic acid diethylamide, LSD), ketamine or gamma-hydroxybutyrate (sodium oxybate, GHB).

Benzodiazepines and z-drugs (i.e. zopiclone p. 490, zolpidem tartrate p. 490) have their own potential for misuse and dependence and are often taken in combination with opiates or stimulants.

Cannabis-based products for medicinal use are Schedule 2 Controlled Drugs and can be prescribed only by clinicians listed on the Specialist Register of the General Medical Council. Cannabis with no approved medicinal use is a Schedule 1 Controlled Drug and cannot be prescribed. It remains the most frequently used illicit drug by young people and dependence can develop in around 10% of users. Cannabis use can exacerbate depression and it may cause an acute short-lived toxic psychosis which resolves with cessation, however paranoid symptoms may persist in chronic users; withdrawal symptoms can occur in some users and these can contribute to sleep problems, agitation and risk of self-harm.

**Supervised consumption**

Supervised consumption is not a legal requirement under the 2001 Regulations. Nevertheless, when supervised consumption is directed on the prescription, the Department of Health recommends that any deviance from the prescriber’s intended method of supply should be documented and the justification for this recorded. Individuals prescribed opioid substitution therapy can take their daily dose under the supervision of a doctor, nurse, or pharmacist during the dose stabilisation phase (usually the first 3 months of treatment), after a relapse or period of instability, or if there is a significant increase in the dose of methadone. Supervised consumption should continue (in accordance with local protocols) until the prescriber is confident that the patient is compliant with their treatment. It is good practice for pharmacists to alert the prescriber when a patient has missed consecutive daily doses.

**Prescribing drugs likely to cause dependence or misuse**

The prescriber has three main responsibilities:

- To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious.
- To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics. The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a patient for the first time.
- To avoid being used as an unwitting source of supply for addicts and being vigilant to methods for obtaining medicines. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctor. Doctors should also remember that their own patients may be attempting to collect prescriptions from other prescribers, especially in hospitals. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring. Prescribers are responsible for the security of prescription forms once issued to them. The stealing and misuse of prescription forms could be minimised by the following precautions:

- records of serial numbers received and issued should be retained for at least three years;
- blank prescriptions should never be pre-signed;
- prescription forms should not be left unattended and should be locked in a secure drawer, cupboard, or carrying case when not in use;
- doctors’, dentists’ and surgery stamps should be kept in a secure location separate from the prescription forms;
- alterations are best avoided but if any are made and the prescription is to be used, best practice is for the prescriber to cross out the error, initial and date the error, then write the correct information;
- if an error made in a prescription cannot be corrected, best practice for the prescriber is to put a line through the script and write ‘spoiled’ on the form, or destroy the form and start writing a new prescription;
- prescribers and pharmacists dispensing drugs prone to abuse should ensure compliance with all relevant legal requirements specially when dealing with prescriptions for Controlled Drugs (see Prescription requirements and Installments above);
- at the time of dispensing, prescriptions should be stamped with the pharmacy stamp and endorsed by the pharmacist or pharmacy technician with what has been supplied; where loss or theft is suspected, the police should be informed immediately.

**Travelling abroad**

Prescribed drugs listed in Schedule 4 Part II (CD Anab) for self-administration and Schedule 5 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are not subject to export or import licensing. A personal import/export licence is required for patients travelling abroad with Schedules 2, 3, or Part I (CD Benz) and Part II (CD Anab) Controlled Drugs if, they are carrying more than 3 months’ supply or are travelling for 3 calendar months or more. A Home Office licence is required for any amount of a Schedule 1 Controlled Drug imported into the UK for personal use regardless of the duration of travel. Further details can be obtained at www.gov.uk/guidance/controlled-drugs-licences-fees-and-returns or from the Home Office by contacting DFLU.ie@homeoffice.gsi.gov.uk. In cases of emergency, telephone (020) 7035 6230.

Applications for obtaining a licence must be supported by a cover letter signed by the prescribing doctor or drug worker, which must confirm:

- the patient’s name and address;
- the travel itinerary;
- the names of the prescribed Controlled Drug(s), doses and total amounts to be carried.

Applications for licences should be sent to the Home Office, Drugs & Firearms Licensing Unit, Fry Building, 2 Marsham Street, London, SW1P 4DF. Alternatively, completed application forms can be emailed to DFLU.ie@homeoffice.gsi.gov.uk. A minimum of 10 days should be allowed for processing the application.

Patients travelling for less than 3 months or carrying less than 3 months supply of Controlled Drugs do not require a...
personal export/import licence, but are advised to carry a
cover letter signed by the prescribing doctor or drug worker.
Those travelling for more than 3 months are advised to make
arrangements to have their medication prescribed by a
practitioner in the country they are visiting.
Doctors who want to take Controlled Drugs abroad while
accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who
want to take Controlled Drugs abroad solely in case a family
emergency should arise.
Personal export/import licences do not have any legal status
outside the UK and are issued only to comply with the
Misuse of Drugs Act 2001 and to facilitate passage through
UK Customs and Excise control. For clearance in the country
to be visited it is necessary to approach that country’s
consulate in the UK.

Notification of patients receiving structured
drug treatment for substance dependence
In England, doctors should report cases where they are
providing structured drug treatment for substance
dependence to their local National Drug Treatment
Monitoring System (NDTMS) Team. General information
about NDTMS can be found at www.gov.uk/government/
collections/alcohol-and-drug-misuse-prevention-and-treatment-
guidance.
Enquiries about NDTMS, and how to submit data, should
initially be directed to:

- EvidenceApplicationteam@phe.gov.uk

In Scotland, doctors should report cases to the Substance
Drug Misuse Database. General information about the
Scottish Drug Misuse Database can be found in
www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/
Drugs-Misuse/Scottish-Drug-Misuse-Database/. Enquiries about
reporting can be directed to:

- nss.isdsubstancemisuse@nhs.net

In Northern Ireland, the Misuse of Drugs (Notification of
and Supply to Addicts) (Northern Ireland) Regulations 1973
require doctors to send particulars of persons whom they
consider to be addicted to certain Controlled Drugs to the
Chief Medical Officer of the Ministry of Health and Social
Services. The Northern Ireland contact is:
Public Health Information & Research Branch
Department of Health,
Annexe 2,
Castle Buildings,
Stormont,
Belfast
BT4 3SQ
Tel: 028 9052 2340
phirb@health-ni.gov.uk
Public Health Information & Research Branch also
maintains the Northern Ireland Drug Misuse Database
(NIDMD) which collects detailed information on those
presenting for treatment, on drugs misused and injecting
behaviour; participation is not a statutory requirement.
In Wales, doctors should report cases where they are
providing structured drug treatment for substance
dependence on the Welsh National Database for Substance
Misuse; enquiries should be directed to: substancemisuse-
queries@wales.nhs.uk.

Prescribing of diamorphine (heroin),
dipipanone, and cocaine for addicts
The Misuse of Drugs (Supply to Addicts) Regulations 1997
require that only medical practitioners who hold a special
licence issued by the Home Secretary (or Scottish
Government’s Chief Medical Officer) may prescribe,
administer, or supply diamorphine hydrochloride p. 456,
dipipanone, or cocaine for the treatment of drug addiction.
Medical prescribers, pharmacists independent prescribers,
Adverse reactions to drugs

Yellow card scheme
Any drug may produce unwanted or unexpected adverse reactions. Rapid detection and recording of adverse drug reactions is of vital importance so that unrecognised hazards are identified promptly and appropriate regulatory action is taken to ensure that medicines are used safely. Healthcare professionals and coroners are urged to report suspected adverse drug reactions directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available from the address below and are also bound in the inside back cover of the 

Yellow Card Scheme, an independent scheme monitors the safety of new medicines using a different approach. The Drug Safety Research Unit identifies patients who have been prescribed selected new medicines and collects data on clinical events in these patients. The data are submitted on a voluntary basis by general practitioners on green forms. More information about the scheme and the Unit’s educational material is available from www.dsrui.org.

Newer drugs and vaccines
Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice. The black triangle symbol identifies newly licensed medicines that require additional monitoring by the European Medicines Agency. Such medicines include new active substances, biosimilar medicines, and medicines that the European Medicines Agency consider require additional monitoring. The black triangle symbol also appears in the Patient Information Leaflets for relevant medicines, with a brief explanation of what it means. Products usually retain a black triangle for 5 years, but this can be extended if required.

Established drugs and vaccines
Healthcare professionals and coroners are asked to report all suspected reactions to established drugs (including over-the-counter, herbal, and unlicensed medicines and medicines used off-label) and vaccines that are serious, medically significant, or result in harm. Serious reactions include those that are fatal, life-threatening, disabling,
incapacitating, or which result in or prolong hospitalisation, or a congenital abnormality; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable comparison with other drugs of a similar class. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs. For established drugs there is no need to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants or constipation with opioids.

Medication errors
Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

Adverse reactions to medical devices
Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at: www.mhra.gov.uk.

Side-effects in the BNF
The BNF includes clinically relevant side-effects for most drugs; an exhaustive list is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Where causality has not been established, side-effects in the manufacturers’ literature may be omitted from the BNF. Recognising that hypersensitivity reactions (including anaphylactic and anaphylactoid reactions) can occur with virtually all drugs, this effect is not generally listed, unless the drug carries an increased risk of such reactions or specific management advice is provided by the manufacturer. Administration site reactions have been omitted from the BNF (e.g. pain at injection site). The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes). Drugs that are applied locally or topically carry a theoretical or low risk of systemic absorption and therefore systemic side-effects for these drugs are not listed in the BNF unless they are associated with a high risk to patient safety. Infections are a known complication of treatment with drugs that affect the immune system (e.g. corticosteroids or immunosuppressants); this side-effect is listed in the BNF as ‘increased risk of infection’. Symptoms of drug withdrawal reactions are not individually listed, but are collectively termed ‘withdrawal syndrome’. Side-effects are generally listed alphabetically in order of frequency. In the product literature the frequency of side-effects is generally described as follows:

<table>
<thead>
<tr>
<th>Description of the frequency of side-effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>greater than 1 in 10</td>
</tr>
<tr>
<td>Common</td>
<td>1 in 100 to 1 in 10</td>
</tr>
<tr>
<td>Uncommon [formerly ‘less commonly’ in BNF publications]</td>
<td>1 in 1000 to 1 in 1000</td>
</tr>
<tr>
<td>Rare</td>
<td>1 in 10 000 to 1 in 1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>less than 1 in 10 000</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>frequency is not defined by product literature or the side-effect has been reported from post-marketing surveillance data</td>
</tr>
</tbody>
</table>

For consistency, the terms used to describe side-effects are standardised using a defined vocabulary across all of the drug monographs in the BNF (e.g. postural hypotension is used for the term orthostatic hypotension).

Special problems
Delayed drug effects Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported directly to the MHRA through the Yellow Card Scheme.

The elderly Particular vigilance is required to identify adverse reactions in the elderly.

Congenital abnormalities When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

Children Particular vigilance is required to identify and report adverse reactions in children, including those resulting from the unlicensed use of medicines; all suspected reactions should be reported directly to the MHRA through the Yellow Card Scheme (see also Adverse Drug Reactions in Children).

Prevention of adverse reactions
Adverse reactions may be prevented as follows:

- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the patient had previous reactions to the drug or formulation;
- ask if the patient is already taking other drugs including self-medication drugs, health supplements, complementary and alternative therapies; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism, and therefore for the adverse effect of the drug; notably of isoniazid p. 587 and the tricyclic antidepressants;
- prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions;
- whenever possible use a familiar drug; with a new drug, be particularly alert for adverse reactions or unexpected events;
- consider if excipients (e.g. colouring agents) may be contributing to the adverse reaction. If the reaction is minor, a trial of an alternative formulation of the same drug may be considered before abandoning the drug;
- warn the patient if serious adverse reactions are liable to occur.
Drug allergy (suspected or confirmed)

Suspected drug allergy is any reaction caused by a drug with clinical features compatible with an immunological mechanism. All drugs have the potential to cause adverse drug reactions, but not all of these are allergic in nature. A reaction is more likely to be caused by drug allergy if:

- The reaction occurred while the patient was being treated with the drug, or
- The drug is known to cause this pattern of reaction, or
- The patient has had a similar reaction to the same drug or drug-class previously.

A suspected reaction is less likely to be caused by a drug allergy if there is a possible non-drug cause or if there are only symptoms present.

The following signs, allergic patterns and timing of onset can be used to help decide whether to suspect drug allergy:

### Immediate, rapidly-evolving reactions (onset usually less than 1 hour after drug exposure)
- Anaphylaxis, with erythema, urticaria or angioedema, and hypotension and/or bronchospasm. See also Antihistamines, allergen immunotherapy and allergic emergencies p. 277
- Urticaria or angioedema without systemic features
- Exacerbation of asthma e.g. with non-steroidal anti-inflammatory drugs (NSAIDs)

### Non-immediate reactions, without systemic involvement (onset usually 6–10 days after first drug exposure or 3 days after second exposure)
- Cutaneous reactions, e.g. widespread red macules and/or papules, or, fixed drug eruption (localised inflamed skin)
- Non-immediate reactions, with systemic involvement (onset may be variable, usually 3 days to 6 weeks after first drug exposure, depending on features, or 3 days after second exposure)
- Cutaneous reactions with systemic features, e.g. drug reaction with eosinophilia and systemic signs (DRESS) or drug hypersensitivity syndrome (DHS), characterised by widespread red macules, papules or erythema, fever, lymphadenopathy, liver dysfunction or eosinophilia
- Toxic epidermal necrolysis or Stevens–Johnson syndrome
- Acute generalised exanthematous pustulosis (AGEP)

### Suspected drug allergy information

Suspected drug allergy information should be clearly and accurately documented in clinical notes and prescriptions, and shared among all healthcare professionals. Patients should be given information about which drugs and drug-classes to avoid and encouraged to share their drug allergy status.

- If a drug allergy is suspected, consider stopping the suspected drug and advising the patient or carer to avoid this drug in future. Symptoms of the acute reaction should be treated, in hospital if severe. Patients presenting with a suspected anaphylactic reaction, or a severe or non-immediate cutaneous reaction, should be referred to a specialist drug allergy service. Patients presenting with a suspected drug allergic reaction or anaphylaxis to NSAIDs, and local and general anaesthetics may also need to be referred to a specialist drug allergy service, e.g. in cases of anaphylactoid reactions or to determine future treatment options. Patients presenting with a suspected drug allergic reaction or anaphylaxis associated with beta-lactam antibiotics should be referred to a specialist drug allergy service if their disease or condition can only be treated by a beta-lactam antibiotic or they are likely to need beta-lactam antibiotics frequently in the future (e.g. immunodeficient patients).
- For further information see Drug allergy: diagnosis and management. NICE Clinical Guideline 183 (September 2014) www.nice.org.uk/guidance/cg183.

### Oral side-effects of drugs

Drug-induced disorders of the mouth may be due to a local action on the mouth or to a systemic effect manifested by oral changes. In the latter case urgent referral to the patient’s medical practitioner may be necessary.

**Oral mucosa** Medicaments left in contact with or applied directly to the oral mucosa can lead to inflammation or ulceration; the possibility of allergy should also be borne in mind.

- Aspirin tablets p. 121 allowed to dissolve in the sulcus for the treatment of toothache can lead to a white patch followed by ulceration.
- Flavouring agents, particularly essential oils, may sensitise the skin, but mucosal swelling is not usually prominent.
- The oral mucosa is particularly vulnerable to ulceration in patients treated with cytotoxic drugs, e.g. methotrexate p. 913. Other drugs capable of causing oral ulceration include ACE inhibitors, gold, nicoaridil p. 212, NSAIDs, pancreatin p. 96, penicillamine p. 1097, proguanil hydrochloride p. 618, and protease inhibitors.

Erythema multiforme or Stevens–Johnson syndrome may follow the use of a wide range of drugs including antibacterials, antiretrovirals, sulfonamide derivatives, and anticonvulsants; the oral mucosa may be extensively ulcerated, with characteristic target lesions on the skin. Oral lesions of toxic epidermal necrolysis have been reported with a similar range of drugs.

- Lichenoid eruptions are associated with ACE inhibitors, NSAIDs, methyldopa p. 145, chloroquine p. 616, oral antidiabetics, thiazide diuretics, and gold.
- CANDIDIASIS can complicate treatment with antibacterials and immunosuppressants and is an occasional side-effect of corticosteroid inhalers.

**Teeth and jaw** Brown staining of the teeth frequently follows the use of chlorhexidine mouthwash, spray or gel p. 1211, but can readily be removed by polishing. Iron salts in liquid form can stain the enamel black. Superficial staining has been reported rarely with co-amoxiclav suspension p. 551. Intrinsic staining of the teeth is most commonly caused by tetracyclines. They will affect the teeth if given at any time from about the fourth month in utero until the age of twelve years; they are contra-indicated during pregnancy, in breastfeeding women, and in children under 12 years. All tetracyclines can cause permanent, unsightly staining in children, the colour varying from yellow to grey.

- Excessive ingestion of fluoride leads to dental fluorosis with mottling of the enamel and areas of hypoplasia or pitting; fluoride supplements occasionally cause mild mottling (white patches) if the dose is too large for the child’s age (taking into account the fluoride content of the local drinking water and of toothpaste).

The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget’s disease. All patients receiving bisphosphonates should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients with a cancer receiving bevacizumab p. 862 or sunitinib p. 999 may also be at risk of osteonecrosis of the jaw.

**Periodontium** Gingival overgrowth (gingival hyperplasia) is a side-effect of phenytoin p. 323 and sometimes of ciclosporin p. 838 or of nifedipine p. 162 (and some other calcium-channel blockers). Thrombocytopenia may be drug related and may cause bleeding at the gingival margins, which may be spontaneous or may follow mild trauma (such as toothbrushing).

**Salivary glands** The most common effect that drugs have on the salivary glands is to reduce flow (xerostomia). Patients with a persistently dry mouth may have poor oral hygiene;
they are at an increased risk of dental caries and oral infections (particularly candidiasis). Many drugs have been implicated in xerostomia, particularly antimuscarinics (anticholinergics), antidepressants (including tricyclic antidepressants, and selective serotonin re-uptake inhibitors), alpha-blockers, antihistamines, antipsychotics, baclofen p. 1128, bupropion hydrochloride p. 498, clonidine hydrochloride p. 145, 5HT1 agonists, opioids, and tizanidine p. 1129. Excessive use of diuretics can also result in xerostomia. Some drugs (e.g. clozapine p. 396, neostigmine p. 1125) can increase saliva production but this is rarely a problem unless the patient has associated difficulty in swallowing. Pain in the salivary glands has been reported with some antihypertensives (e.g. clonidine hydrochloride p. 145, methyldopa p. 145) and with vinca alkaloids. Swelling of the salivary glands can occur with iodides, antithyroid drugs, phenothiazines, and sulfonamides.

**Taste**

There can be decreased taste acuity or alteration in taste sensation. Many drugs are implicated, including amiodarone hydrochloride p. 105, calcitonin, ACE inhibitors, carbimazole p. 771, clarithromycin p. 538, gold, griseofulvin p. 601, lithium salts, metformin hydrochloride p. 692, metronidazole p. 542, penicillamine p. 1097, phenindione p. 140, propafenone hydrochloride p. 104, protease inhibitors, terbinafine p. 1234, and zopiclone p. 490.

**Defective medicines**

During the manufacture or distribution of a medicine an error or accident may occur whereby the finished product does not conform to its specification. While such a defect may impair the therapeutic effect of the product and could adversely affect the health of a patient, it should not be confused with an Adverse Drug Reaction where the product conforms to its specification. The Defective Medicines Report Centre assists with the investigation of problems arising from licensed medicinal products thought to be defective and co-ordinates any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency,
151 Buckingham Palace Road, London, SW1W 9SZ
Tel: (020) 3080 6574
dmrc@mhra.gsi.gov.uk
Guidance on intravenous infusions

Intravenous additives policies
A local policy on the addition of drugs to intravenous fluids should be drawn up by a multi-disciplinary team and issued as a document to the members of staff concerned. Centralised additive services are provided in a number of hospital pharmacy departments and should be used in preference to making additions on wards. The information that follows should be read in conjunction with local policy documents.

Guidelines
- Drugs should only be added to infusion containers when constant plasma concentrations are needed or when the administration of a more concentrated solution would be harmful.
- In general, only one drug should be added to any infusion container and the components should be compatible. Ready-prepared solutions should be used whenever possible. Drugs should not normally be added to blood products, mannitol, or sodium bicarbonate. Only specially formulated additives should be used with fat emulsions or amino-acid solutions.
- Solutions should be thoroughly mixed by shaking and checked for absence of particulate matter before use.
- Strict asepsis should be maintained throughout and in general the giving set should not be used for more than 24 hours (for drug admixtures).
- The infusion container should be labelled with the patient’s name, the name and quantity of additives, and the date and time of addition (and the new expiry date or time). Such additional labelling should not interfere with information on the manufacturer’s label that is still valid.
- It is good practice to examine intravenous infusions from time to time while they are running. If cloudiness, crystallisation, change of colour, or any other sign of interaction or contamination is observed the infusion should be discontinued.

Problems
Microbial contamination The accidental entry and subsequent growth of micro-organisms converts the infusion fluid pathway into a potential vehicle for infection with micro-organisms, particularly species of Candida, Enterobacter, and Klebsiella. Ready-prepared infusions containing the additional drugs, or infusions prepared by an additive service (when available) should therefore be used in preference to making extemporaneous additions to infusion containers on wards etc. However, when this is necessary strict aseptic procedure should be followed.

Incompatibility Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity, or other adverse effect. The solutions may become opalescent or precipitate or other chemical changes. Precipitation or other particle concentration changes, particularly species of bacteria or virus, may occur with loss of potency, increase in toxicity, or other chemical changes. Precipitation or other particle concentration changes, particularly species of bacteria or virus, may occur with loss of potency, increase in toxicity, or other chemical changes.

Common incompatibilities Precipitation reactions are numerous and varied and may occur as a result of pH, concentration changes, ‘salting-out’ effects, complexation or other chemical changes. Precipitation or other particle formation must be avoided since, apart from lack of control of dosage on administration, it may initiate or exacerbate adverse effects. This is particularly important in the case of drugs which have been implicated in either thrombophlebitis (e.g. diazepam) or in skin sloughing or necrosis caused by extravasation (e.g. sodium bicarbonate and certain cytotoxic drugs). It is also especially important to effect solution of colloidal drugs and to prevent their subsequent precipitation in order to avoid a pyrogenic reaction (e.g. amphotericin). It is considered undesirable to mix beta-lactam antibiotics, such as semi-synthetic penicillins and cephalosporins, with proteinaceous materials on the grounds that immunogenic and allergenic conjugates could be formed. A number of preparations undergo significant loss of potency when added singly or in combination to large volume infusions. Examples include ampicillin in infusions that contain glucose or lactates. The breakdown products of dacarbazine have been implicated in adverse effects.

Blood Because of the large number of incompatibilities, drugs should not normally be added to blood and blood products for infusion purposes. Examples of incompatibility with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextrans (rouleaux formation and interference with cross-matching), glucose (clumping of red cells), and oxytocin (inactivated). If the giving set is not changed after the administration of blood, but used for other infusion fluids, a fibrin clot may form which, apart from blocking the set, increases the likelihood of microbial growth.

Intravenous fat emulsions These may break down with coalescence of fat globules and separation of phases when additions such as antibacterials or electrolytes are made, thus increasing the possibility of embolism. Only specially formulated products such as Vitlipid N® may be added to appropriate intravenous fat emulsions.

Other infusions Infusions that frequently give rise to incompatibility include amino acids, mannitol, and sodium bicarbonate.

Bactericides Bactericides such as chlorocresol 0.1% or phenylmercuric nitrate 0.001% are present in some injection solutions. The total volume of such solutions added to a container for infusion on one occasion should not exceed 15 mL.

Method
Ready-prepared infusions should be used whenever available. Potassium chloride is usually available in concentrations of 20, 27, and 40 mmol/litre in sodium chloride intravenous infusion (0.9%), glucose intravenous infusion (5%) or sodium chloride and glucose intravenous infusion. Lidocaine hydrochloride is usually available in concentrations of 0.1 or 0.2% in glucose intravenous infusion (5%). When addition is required to be made extemporaneously, any product reconstitution instructions such as those relating to concentration, vehicle, mixing, and handling precautions should be strictly followed using an aseptic technique throughout. Once the product has been reconstituted, addition to the infusion fluid should be made immediately in order to minimise microbial contamination and, with certain products, to prevent degradation or other formulation change which may occur; e.g. reconstituted ampicillin injection degrades rapidly on standing, and also may form polymers which could cause sensitivity reactions. It is also important in certain instances that an infusion fluid of specific pH be used (e.g. furosemide injection requires dilution in infusions of pH greater than 5.5).

When drug additions are made it is important to mix thoroughly; additions should not be made to an infusion container that has been connected to a giving set, as mixing is hampered. If the solutions are not thoroughly mixed or coalescence of fat globules and separation of phases, the solutions may become opalescent or precipitate.
differences in density. **Potassium chloride** is particularly prone to this ‘layering’ effect when added without adequate mixing to infusions packed in non-rigid infusion containers; if such a mixture is administered it may have a serious effect on the heart.

A time limit between addition and completion of administration must be imposed for certain admixtures to guarantee satisfactory drug potency and compatibility. For admixtures in which degradation occurs without the formation of toxic substances, an acceptable limit is the time taken for 10% decomposition of the drug. When toxic substances are produced stricter limits may be imposed. Because of the risk of microbial contamination a maximum time limit of 24 hours may be appropriate for additions made elsewhere than in hospital pharmacies offering central additive service.

Certain injections must be protected from light during continuous infusion to minimise oxidation, e.g. dacarbazine and sodium nitroprusside. Dilution with a small volume of an appropriate vehicle and administration using a motorised infusion pump is advocated for preparations such as unfractionated heparin where strict control over administration is required. In this case the appropriate dose may be dissolved in a convenient volume (e.g. 24–48 mL) of sodium chloride intravenous infusion (0.9%).

**Information provided in the BNF**

The BNF gives information about preparations given by three methods:

- continuous infusion;
- intermittent infusion;
- addition via the drip tubing.

Drugs for **continuous infusion** must be diluted in a large volume infusion. Penicillins and cephalosporins are not usually given by continuous infusion because of stability problems and because adequate plasma and tissue concentrations are best obtained by intermittent infusion. Where it is necessary to administer them by continuous infusion, detailed literature should be consulted.

Drugs that are both compatible and clinically suitable may be given by **intermittent infusion** in a relatively small volume of infusion over a short period of time, e.g. 100 mL in 30 minutes. The method is used if the product is incompatible or unstable over the period necessary for continuous infusion; the limited stability of ampicillin or amoxicillin in large volume glucose or lactate infusions may be overcome in this way.

Intermittent infusion is also used if adequate plasma and tissue concentrations are not produced by continuous infusion as in the case of drugs such as dacarbazine, gentamicin, and ticarcillin.

An in-line burette may be used for intermittent infusion techniques in order to achieve strict control over the time and rate of administration, especially for infants and children and in intensive care units. Intermittent infusion may also make use of the ‘piggy-back’ technique provided that no additions are made to the primary infusion. In this method the drug is added to a small secondary container connected to a Y-type injection site on the primary infusion giving set; the secondary solution is usually infused within 30 minutes.

**Addition via the drip tubing** is indicated for a number of cytotoxic drugs in order to minimise extravasation. The preparation is added aseptically via the rubber septum of the injection site of a fast-running infusion. In general, drug preparations intended for a bolus effect should be given directly into a separate vein where possible. Failing this, administration may be made via the drip tubing provided that the preparation is compatible with the infusion fluid when given in this manner.

**Drugs given by intravenous infusion**

The BNF includes information on addition to **Glucose intravenous infusion 5 and 10%**, and **Sodium chloride intravenous infusion 0.9%**. Compatibility with glucose 5% and with sodium chloride 0.9% indicates compatibility with **Sodium chloride and glucose intravenous infusion**. Infusion of a large volume of hypotonic solution should be avoided therefore care should be taken if water for injections is used. The information relates to the proprietary preparations indicated; for other preparations suitability should be checked with the manufacturer.
Prescribing in children

Overview
For detailed advice on medicines used for children, consult BNF for Children. Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care. At this age, the risk of toxicity is increased by reduced drug clearance and differing target organ sensitivity. Whenever possible, intramuscular injections should be avoided in children because they are painful. Where possible, medicines for children should be prescribed within the terms of the marketing authorisation (product licence). However, many children may require medicines not specifically licensed for paediatric use. Although medicines cannot be promoted outside the limits of the licence, the Human Medicines Regulations 2012 does not prohibit the use of unlicensed medicines. It is recognised that the informed use of unlicensed medicines or of licensed medicines for unlicensed applications (‘off-label’ use) is often necessary in paediatric practice.

Adverse drug reactions in children
Suspected adverse drug reactions in children and young adults under 18 years should be reported through the Yellow Card Scheme. Yellow cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines. Yellow Cards can also be used to report medical device incidents, defective medicines, and suspected fake medicines.

Report all suspected adverse drug reactions that are:

- serious, medically significant or result in harm.

Serious events are fatal, life-threatening, a congenital abnormality, disabling or incapacitating, or resulting in hospitalisation;
- associated with newer drugs and vaccines; the most up to date list of black triangle medicines is available at: www.mhra.gov.uk/blacktriangle

If in doubt whether to report a suspected adverse drug reaction, please complete a Yellow Card.

The identification and reporting of adverse reactions to drugs in children and neonates is particularly important because:

- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs may not have been extensively tested in children;
- many drugs are not specifically licensed for use in children and are used either ‘off-label’ or as unlicensed products;
- drugs may affect the way a child grows and develops or may cause delayed adverse reactions which do not occur in adults;
- suitable formulations may not be available to allow precise dosing in children or they may contain excipients that should be used with caution in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

Even if reported through the British Paediatric Surveillance Unit’s Orange Card Scheme, any identified suspected adverse drug reactions should also be submitted to the Yellow Card Scheme.

Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRSL). If reported to the NRSL, these will be shared with the MHRA. If the NRSL is not available and harm occurs, report using a Yellow Card.

Prescription writing
Prescriptions should be written according to the guidelines in Prescription Writing. Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for all prescriptions for children.

It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, they may contain sugar which encourages dental decay. Sugar-free medicines are preferred for long-term treatment.

Many children are able to swallow tablets or capsules and may prefer a solid dose form; involving the child and parents in choosing the formulation is helpful.

When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL an oral syringe will be supplied. Parents should be advised not to add any medicines to the infant’s feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents.

Parents must be warned to keep all medicines out of reach of children.

Rare paediatric conditions
Information on substances such as biotin and sodium benzoate used in rare metabolic conditions is included in BNF for Children; further information can be obtained from:

- Alder Hey Children’s Hospital
- Drug Information Centre, Liverpool, L2 2AP
- Great Ormond Street Hospital for Children Pharmacy, Great Ormond St, London, WC1N 3JH

Dosage in children
Children’s doses in the BNF are stated in the individual drug entries.

Doses are generally based on body-weight (in kilograms) or specific age ranges. In the BNF and BNF for Children, the term neonate is used to describe a newborn infant aged 0–28 days. The terms child or children are used generically to describe the entire range from infant to adolescent (1 month–17 years). An age range is specified when the dose information applies to a narrower age range than a child from 1 month–17 years.

Dose calculation
Many children’s doses are standardised by weight (and therefore require multiplying by the body-weight in kilograms to determine the child’s dose); occasionally, the doses have been standardised by body surface area (in m²).

These methods should be used rather than attempting to calculate a child’s dose on the basis of doses used in adults. For most drugs the adult maximum dose should not be exceeded. For example if the dose is stated as 8 mg/kg (max. 300 mg), a child weighing 10 kg should receive 80 mg but a child weighing 40 kg should receive 300 mg (rather than 320 mg).

Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such
cases, dose should be calculated from an ideal weight, related to height and age. **Body surface area (BSA) estimates** are sometimes preferable to body-weight for calculation of paediatric doses since many physiological phenomena correlate better with body surface area. Body surface area can be estimated from weight. For more information, refer to **BNF for Children**. Where the dose for children is not stated, prescribers should consult **BNF for Children** or seek advice from a medicines information centre.

**Prescribing in hepatic impairment**

**Overview**
Liver disease may alter the response to drugs in several ways as indicated below, and drug prescribing should be kept to a minimum in all patients with severe liver disease. The main problems occur in patients with jaundice, ascites, or evidence of encephalopathy.

**Impaired drug metabolism**
Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large and liver disease has to be severe before important changes in drug metabolism occur. Routine liver-function tests are a poor guide to the capacity of the liver to metabolise drugs, and in the individual patient it is not possible to predict the extent to which the metabolism of a particular drug may be impaired. A few drugs, e.g. rifampicin p. 582 and fusidic acid p. 571, are excreted in the bile unchanged and can accumulate in patients with intrahepatic or extrahepatic obstructive jaundice.

**Hypoproteinaemia**
The hypoalbuminaemia in severe liver disease is associated with reduced protein binding and increased toxicity of some highly protein-bound drugs such as phenytoin p. 323 and prednisolone p. 678.

**Reduced clotting**
Reduced hepatic synthesis of blood-clotting factors, indicated by a prolonged prothrombin time, increases the sensitivity to oral anticoagulants such as warfarin sodium p. 140 and phenindione p. 140.

**Hepatic encephalopathy**
In severe liver disease many drugs can further impair cerebral function and may precipitate hepatic encephalopathy. These include all sedative drugs, opioid analgesics, those diuretics that produce hypokalaemia, and drugs that cause constipation.

** Fluid overload**
Oedema and ascites in chronic liver disease can be exacerbated by drugs that give rise to fluid retention e.g. NSAIDs and corticosteroids.

**Hepatotoxic drugs**
Hepatotoxicity is either dose-related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function, and some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. These drugs should be avoided or used very carefully in patients with liver disease. Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

**Prescribing in renal impairment**

**Issues encountered in renal impairment**
The use of drugs in patients with reduced renal function can give rise to problems for several reasons:
- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs.

If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug which requires dose modification.

**General guidance**
Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug monograph in the BNF. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma-drug concentration. Dose recommendations are based on the severity of renal impairment. The total daily maintenance dose of a drug can
be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration.

**Important: dosage adjustment advice in the BNF**

Clinical laboratories routinely report renal function in adults based on estimated glomerular filtration rate (eGFR) or Cockcroft and Gault formula or the Modification of Diet in Renal disease (MDRD) formula. However, in product literature, the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance as a surrogate for GFR. The information on dosage adjustment in the BNF is usually expressed in terms of eGFR. Exceptions to the use of eGFR include toxic drugs, in elderly patients and in patients at extremes of muscle mass (see Estimating renal function in elderly patients, below) where calculation of CrCl is recommended. Although these two measures of renal function are not interchangeable, for most drugs and for most adult patients of average build and height, eGFR (rather than CrCl) can be used to determine dosage adjustments.

**Nephrotic drugs**

Nephrotic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephroticity are likely to be more serious when renal reserve is already reduced. During intercurrent illness the risk of acute kidney injury is increased in patients with an eGFR of less than 60 mL/min/1.73 m²; potentially nephrotic or renally excreted drugs may require dose reduction or temporary discontinuation.

**Renal replacement therapy and transplantation**

For prescribing in patients who have received a renal transplant or who are on renal replacement therapy (peritoneal dialysis or haemodialysis), consult specialist literature.

**Estimating renal function**

Direct measure of Glomerular filtration rate (GFR) using plasma or urinary clearance is considered the best overall index of renal function. However, this is difficult to do in practice. As an alternative, the estimated Glomerular filtration rate (eGFR) based on serum creatinine is used to assess renal function. Creatinine clearance (CrCl) is also used as an estimate of GFR. Various equations for estimating glomerular filtration rate exist, however there is no compelling evidence to support the superiority of any given method for drug dosing in all patient populations or clinical situations. There is also insufficient evidence to provide definitive guidance about dosage adjustment of all drugs in patients with reduced renal function. Therefore, an understanding of drug pharmacokinetics is necessary in order to make appropriate dosing decisions. Using serum creatinine to derive eGFR has a number of limitations; serum creatinine levels are dependent on muscle mass and diet, therefore estimates should be interpreted with caution in certain individuals (such as the elderly, body builders, amputees, in muscle-wasting disorders and vegans)—estimates will be higher or lower than the true value. Creatinine-derived measurements are also not useful in periods of rapidly changing renal function or in patients with AKI.

**Estimated glomerular filtration rate**

**Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula**

The CKD-EPI formula is the recommended method for estimating GFR and calculating drug doses in most patients with renal impairment. CKD-EPI is adjusted for body surface area (BSA) and utilises serum creatinine, age, sex and race as variables. Clinical laboratories should use the CKD-EPI formula to routinely report eGFR.

**CKD-EPI equation**

\[
eGFR \text{ (ml/min/1.73} \text{ m}^2) = 141 \times \min(\text{SCr/K}, 1)^{\ast} \times \max(\text{SCr/K}, 1)^{0.209} \times 0.993^{\ast} \times 1.018 \text{ if female} \times 1.159 \text{ if black}
\]

Where:

- \( \text{SCr} = \) serum creatinine in mg/dl;
- \( K = 0.7 \) for females and 0.9 for males;
- \( a = -0.329 \) for females and -0.411 for males;
- \( \min(\text{SCr/K}, 1) \) indicates the minimum of SCr/K or 1;
- \( \max(\text{SCr/K}, 1) \) indicates the maximum of SCr/K or 1.

**Modification of Diet in Renal disease (MDRD)**

The MDRD formula, like CKD–EPI, is expressed in terms of body surface area. It is less accurate than the CKD–EPI formula when eGFR is greater than 60 mL/min/1.73 m². It also overestimates GFR in elderly patients.

**Estimated creatinine clearance**

**Cockcroft and Gault**

The Cockcroft and Gault formula is the preferred method for estimating renal function or calculating drug doses in patients with renal impairment who are elderly or at extremes of muscle mass (see below); it provides an estimate of CrCl (which is not equivalent to eGFR).

**Estimated Creatinine Clearance**

\[
\text{Creatinine Clearance} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}} \text{in ml/minute}
\]

- Age in years
- Weight in kilograms (use ideal body weight where fat is likely to be the major contributor to body mass)
- Serum creatinine in micromol/litre
- Constant = 1.23 for men; 1.04 for women

**Estimating renal function in patients at extremes of muscle mass**

In patients at both extremes of muscle mass, eGFR should be interpreted with caution. Reduced muscle mass will lead to overestimation of GFR and increased muscle mass will lead to underestimation of the GFR. Creatinine clearance or absolute glomerular filtration rate should be used to adjust drug doses in patients with a BMI less than 18 kg/m² or greater than 40 kg/m². Ideal body weight should be used to calculate the CrCl.

Where the patient’s actual body weight is less than their ideal body weight, actual body weight should be used instead.

The absolute glomerular filtration rate is determined by removing the normalisation for BSA from the eGFR using the following formula:

\[
\text{GFR (Absolute)} = \text{eGFR} \times (\text{individual’s body surface area} / 1.73)
\]

The ideal body weight is calculated as follows:

**Ideal body weight (kilograms) = Constant \times 0.91**

**Height - 152.4**

Where:

- Constant = 50 for men; 45.5 for women
- Height in centimetres

**Estimating renal function in elderly patients**

The Cockcroft and Gault formula is the preferred method for estimating renal function in elderly patients aged 75 years and over.
Chronic kidney disease

Classification of chronic kidney disease using GFR and ACR categories

Chronic kidney disease is classified using a combination of GFR and albumin:creatinine ratio (ACR). A decreased GFR and an increased ACR is associated with an increased risk of adverse outcomes. For example, a person with an eGFR of 25 ml/min/1.73 m² and an ACR of 15 mg/mmol has a CKD classification of G4A2.

**Classification of chronic kidney disease using GFR and ACR categories**

![Diagram showing the classification of chronic kidney disease using GFR and ACR categories.](image)

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73m²), description and range</th>
<th>ACR categories (mg/mmol), description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 Normal to mild increase</td>
<td>A1</td>
</tr>
<tr>
<td>3–30 Moderate increase</td>
<td>A2</td>
</tr>
<tr>
<td>&gt;30 Severe increase</td>
<td>A3</td>
</tr>
</tbody>
</table>

- **Normal or high** (≥90 ml/min/1.73m²)
- **Mild reduction relative to normal range for a young adult** (60–89 ml/min/1.73m²)
- **Mild-moderate reduction** (45–59 ml/min/1.73m²)
- **Moderate-severe reduction** (30–44 ml/min/1.73m²)
- **Severe reduction** (15–29 ml/min/1.73m²)
- **Kidney failure** (<15 ml/min/1.73m²)

**Abbreviations:** ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

*Adapted with the kind permission of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013.*
Advanced Pharmacy Services

Patients with renal impairment may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.
Prescribing in pregnancy

Overview
Drugs can have harmful effects on the embryo or fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of childbearing age or for men trying to father a child.

During the first trimester drugs can produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy. During the second and third trimesters drugs can affect the growth or functional development of the fetus, or they can have toxic effects on fetal tissues.

Drugs given shortly before term or during labour can have adverse effects on labour or on the neonate after delivery.

Not all the damaging effects of intra-uterine exposure to drugs are obvious at birth, some may only manifest later in life. Such late-onset effects include malignancy, e.g. adenocarcinoma of the vagina after puberty in females exposed to diethylstilbestrol in the womb, and adverse effects on intellectual, social, and functional development.

The BNF and BNF for Children identify drugs which:
- may have harmful effects in pregnancy and indicates the trimester of risk
- are not known to be harmful in pregnancy

The information is based on human data, but information from animal studies has been included for some drugs when its omission might be misleading. Maternal drug doses may require adjustment during pregnancy due to changes in maternal physiology but this is beyond the scope of the BNF and BNF for Children.

Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF and BNF for Children.

Important
Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used. Few drugs have been shown conclusively to be teratogenic in humans, but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available when there is a known risk of certain defects.

Absence of information does not imply safety. It should be noted that the BNF and BNF for Children provide independent advice and may not always agree with the product literature.

Information on drugs and pregnancy is also available from the UK Teratology Information Service. www.uktis.org.

Tel: 0344 892 0909 (09.00–17.00 Monday to Friday; urgent enquiries only outside these hours).

MHRA/CHM advice: Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed? (March 2019)
Guidance is available on contraceptive methods and frequency of pregnancy testing to reduce inadvertent exposures during pregnancy in a woman taking a medicine of teratogenic potential. When using these medicines, a woman should be advised of the risks and encouraged to use the most effective contraceptive method taking into account her personal circumstances. The likelihood of pregnancy should be assessed before each prescription of a medicine with known teratogenic potential, by performing a pregnancy test. If pregnancy cannot be excluded, the decision to start or continue treatment will depend on individual circumstances, such as the urgency for treatment and alternative treatment options. If feasible, treatment with a medicine with teratogenic potential should be delayed until pregnancy has been excluded by a repeat test.


Prescribing in breast-feeding

Overview
Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds.

Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:
- the amount of drug or active metabolite of the drug delivered to the infant (dependent on the pharmacokinetic characteristics of the drug in the mother);
- the efficiency of absorption, distribution, and elimination of the drug by the infant (infant pharmacokinetics);
- the nature of the effect of the drug on the infant (pharmacodynamic properties of the drug in the infant).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernible effect on the infant. This applies particularly to drugs that are poorly absorbed and need to be given parenterally. However, there is a theoretical possibility that a small amount of drug present in breast milk can induce a hypersensitivity reaction.

A clinical effect can occur in the infant if a pharmacologically significant quantity of the drug is present in milk. For some drugs (e.g. fluvastatin p. 203), the ratio between the concentration in milk and that in maternal plasma may be high enough to expose the infant to adverse effects. Some infants, such as those born prematurely or who have jaundice, are at a slightly higher risk of toxicity.

Some drugs inhibit the infant’s sucking reflex (e.g. phenobarbital p. 335) while others can affect lactation (e.g. bromocriptine p. 419).

The BNF identifies drugs:
- that should be used with caution or are contra-indicated in breast-feeding;
- that can be given to the mother during breast-feeding because they are present in milk in amounts which are too small to be harmful to the infant;
that might be present in milk in significant amount but are not known to be harmful.

Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.

**Important**

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast-feeding, absence of information does not imply safety.
Prescribing in palliative care

Overview
Palliative care is an approach that improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team.

Specialist palliative care is available in most areas as day hospice care, home-care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams.

Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish.

Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, support can be provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

Drug treatment
The number of drugs should be as few as possible, for even the taking of medicine may be an effort.

Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain
Pain management in palliative care is focused on achieving control of pain by administering the right drug in the right dose at the right time. Analgesics can be divided into three broad classes: non-opioid (paracetamol p. 444, NSAID), opioid (e.g. codeine phosphate p. 454 ‘weak’, morphine p. 463 ‘strong’) and adjuvant (e.g. antidepressants, antiepileptics). Drugs from the different classes are used alone or in combination according to the type of pain and response to treatment. Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

Paracetamol p. 444 or a NSAID given regularly will often be sufficient to manage mild pain. If non-opioid analgesics alone are not sufficient, then an opioid analgesic alone or in combination with a non-opioid analgesic at an adequate dosage, may be helpful in the control of moderate pain. Codeine phosphate p. 454 or tramadol hydrochloride p. 471 can be considered for moderate pain. If these preparations do not control the pain then morphine p. 463 is the most useful opioid analgesic. Alternatives to morphine p. 463, including transdermal buprenorphine p. 447, transdermal fentanyl p. 458, hydromorphone hydrochloride p. 462, methadone hydrochloride p. 502, or oxycodone hydrochloride p. 466, should be initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Bone metastases
In addition to the above approach, radiotherapy, bisphosphonates, and radioactive isotopes of strontium chloride (Megace® available from GE Healthcare) may be useful for pain due to bone metastases.

Neuropathic pain
Patients with neuropathic pain may benefit from a trial of a tricyclic antidepressant. An antiepileptic may be added or substituted if pain persists; gabapentin p. 315 and pregabalin p. 324 are licensed for neuropathic pain. Ketamine p. 1345 is sometimes used under specialist supervision for neuropathic pain that responds poorly to opioid analgesics. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone p. 675, which reduces oedema around the tumour, thus reducing compression. Nerve blocks or regional anaesthesia techniques (including the use of epidural and intrathecal catheters) can be considered when pain is localised to a specific area.

Pain management with opioids

Oral route
Treatment with morphine p. 463 is given by mouth as immediate-release or modified-release preparations. During the titration phase the initial dose is based on the previous medication used, the severity of the pain, and other factors such as presence of renal impairment, increasing age, or frailty. The dose is given either as an immediate-release preparation 4-hourly or as a modified-release preparation 12-hourly, in addition to rescue doses. If pain occurs between regular doses of morphine p. 463 ('breakthrough pain'), an additional dose ('rescue dose') of immediate-release morphine p. 463 should be given. An additional dose should also be given 30 minutes before an activity that causes pain, such as wound dressing. The standard dose of a strong opioid for breakthrough pain is usually one-tenth to one-sixth of the regular 24-hour dose, repeated every 2–4 hours as required (up to hourly may be needed if pain is severe or in the last days of life). Review pain management if rescue analgesic is required frequently (twice daily or more). Each patient should be assessed on an individual basis. Formulations of fentanyl p. 458 that are administered nasally, buccally or sublingually are also licensed for breakthrough pain.

When adjusting the dose of morphine p. 463, the number of rescue doses required and the response to them should be taken into account; increments of morphine p. 463 should not exceed one-third to one-half of the total daily dose every 24 hours. Thereafter, the dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics should also be considered. Upward titration of the dose of morphine p. 463 stops when either the pain is relieved or unacceptable adverse effects occur, after which it is necessary to consider alternative measures.

Morphine immediate-release 30mg 4-hourly (or modified-release 100 mg 12-hourly) is usually adequate for most patients; some patients require morphine immediate-release up to 200mg 4-hourly (or modified-release 600 mg 12-hourly), occasionally more is needed. Once their pain is controlled, patients started on 4-hourly immediate-release morphine p. 463 can be transferred to the same total 24-hour dose of morphine p. 463 given as the modified-release preparation for 12-hourly or 24-hourly administration. The first dose of the modified-release preparation is given with, or within 4 hours of, the last dose of the immediate-release preparation. For preparations suitable for 12-hourly or 24-hourly administration see modified-release preparations under morphine p. 463. Increments should be made to the dose, not to the frequency of administration. The patient must be monitored closely for efficacy and side-effects, particularly constipation, and nausea and vomiting. A suitable laxative should be prescribed routinely.

Oxycodone hydrochloride p. 466 can be used in patients who require an opioid but cannot tolerate morphine p. 463. If the patient is already receiving an opioid, oxycodone hydrochloride p. 466 should be started at a dose equivalent to the current analgesic (see below). Oxycodone hydrochloride p. 466 immediate-release preparations can be given for breakthrough pain.
### Equivalent doses of opioid analgesics.

<table>
<thead>
<tr>
<th>Analgesic/Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine: PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Diamorphine: IM, IV, SC</td>
<td>3 mg</td>
</tr>
<tr>
<td>Dihydrocodeine: PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hydromorphone: PO</td>
<td>2 mg</td>
</tr>
<tr>
<td>Morphine: PO</td>
<td>10 mg</td>
</tr>
<tr>
<td>Morphine: IM, IV, SC</td>
<td>5 mg</td>
</tr>
<tr>
<td>Oxycodone: PO</td>
<td>6.6 mg</td>
</tr>
<tr>
<td>Tramadol: PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>PO = by mouth; IM = intramuscular; IV = intravenous; SC = subcutaneous</td>
<td></td>
</tr>
</tbody>
</table>

**Parenteral route** The equivalent parenteral dose of morphine p. 463 (subcutaneous, intramuscular, or intravenous) is about half of the oral dose. If the patient is unable to swallow, generally morphine p. 463 is administered as a continuous subcutaneous infusion (for details, see Continuous Subcutaneous Infusions below). Diamorphine hydrochloride p. 456 is sometimes preferred, because being more soluble, it can be given in a smaller volume. The equivalent subcutaneous dose of diamorphine hydrochloride p. 456 is about one-third of the oral dose of morphine p. 463.

If the patient can resume taking medicines by mouth, then oral morphine p. 463 may be substituted for subcutaneous infusion of morphine p. 463 or diamorphine hydrochloride p. 456, see table above of approximate equivalent doses of morphine p. 463 and diamorphine hydrochloride p. 456. The infusion is discontinued when the first oral dose of morphine p. 463 is given.

**Rectal route** Morphine p. 463 is also available for rectal administration as suppositories; alternatively oxycodone hydrochloride suppositories p. 466 can be obtained on special order.

**Transdermal route** Transdermal preparations of fentanyl p. 458 and buprenorphine p. 447 are available, they are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations, see under buprenorphine p. 447 and fentanyl p. 458 (inappropriate use has caused fatalities). Immediate-release morphine p. 463 can be given for breakthrough pain.

The following 24-hour oral doses of morphine p. 463 are considered to be approximately equivalent to the buprenorphine p. 447 and fentanyl p. 458 patches shown, however when switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

### Buprenorphine patches are approximately equivalent to the following 24-hour doses of oral morphine

<table>
<thead>
<tr>
<th>Morphine Dose</th>
<th>Buprenorphine Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mg daily</td>
<td>‘5’ patch</td>
</tr>
<tr>
<td>24 mg daily</td>
<td>‘10’ patch</td>
</tr>
<tr>
<td>36 mg daily</td>
<td>‘15’ patch</td>
</tr>
<tr>
<td>48 mg daily</td>
<td>‘20’ patch</td>
</tr>
<tr>
<td>84 mg daily</td>
<td>‘35’ patch</td>
</tr>
<tr>
<td>126 mg daily</td>
<td>‘52.5’ patch</td>
</tr>
<tr>
<td>168 mg daily</td>
<td>‘70’ patch</td>
</tr>
</tbody>
</table>

Formulations of transdermal patches are available as 72-hourly, 96-hourly and 7-day patches, for further information see buprenorphine p. 447. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

### 72-hour Fentanyl patches are approximately equivalent to the following 24-hour doses of oral morphine

<table>
<thead>
<tr>
<th>Morphine Dose</th>
<th>Fentanyl Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg daily</td>
<td>‘12’ patch</td>
</tr>
<tr>
<td>60 mg daily</td>
<td>‘25’ patch</td>
</tr>
<tr>
<td>120 mg daily</td>
<td>‘50’ patch</td>
</tr>
<tr>
<td>180 mg daily</td>
<td>‘75’ patch</td>
</tr>
<tr>
<td>240 mg daily</td>
<td>‘100’ patch</td>
</tr>
</tbody>
</table>

Fentanyl equivalences in this table are for patients on well-tolerated opioid therapy for long periods; for patients who are opioid naive or who have been stable on oral morphine or other immediate-release opioid for only several weeks, see Transdermal Route. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

### Symptom control

Several recommendations in this section involve unlicensed indications or routes.

**Anorexia** Anorexia may be helped by prednisolone p. 678 or dexamethasone p. 675.

**Bowel colic and excessive respiratory secretions** Bowel colic and excessive respiratory secretions may be reduced by a subcutaneous injection of hyoscine hydrobromide p. 439, hyoscine butylbromide p. 85, or glycopyrronium bromide p. 1335. These antimuscarinics are generally given every 4 hours when required, but hourly use is occasionally necessary, particularly in excessive respiratory secretions. If symptoms persist, they can be given regularly via a continuous infusion device. Care is required to avoid the discomfort of dry mouth.

**Capillary bleeding** Capillary bleeding can be treated with tranexamic acid p. 110 by mouth; treatment is usually discontinued one week after the bleeding has stopped, or, if necessary, it can be continued at a reduced dose. Alternatively, gauze soaked in tranexamic acid 100 mg/mL p. 110 or adrenaline/epinephrine solution 1 mg/mL (1 in 1000) p. 222 can be applied to the affected area. Vitamin K may be useful for the treatment and prevention of bleeding associated with prolonged clotting in liver disease. In severe chronic cholestasis, absorption of vitamin K may be impaired; either parenteral or water-soluble oral vitamin K (see phytomenadione p. 1089 and menadiol sodium phosphate p. 1089) should be considered.

**Constipation** Constipation is a common cause of distress and is almost invariable after administration of an opioid.
analgesic. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramine p. 62) or lactulose solution p. 56 with a senna preparation p. 63 should be used. Methylnaltrexone bromide p. 64 is licensed for the treatment of opioid-induced constipation.

**Convolusions** Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin p. 323 or carbamazepine p. 311 should be considered. When oral medication is no longer possible, diazepam p. 343 given rectally, or phenobarbital p. 335 by injection is continued as prophylaxis. For the use of midazolam p. 340 by subcutaneous infusion using a continuous infusion device see below.

**Dry mouth** Dry mouth may be relieved by good mouth care and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva, dry mouth associated with candidiasis can be treated by oral preparations of nystatin p. 1219 or miconazole p. 1219, alternatively, fluconazole p. 595 can be given by mouth. Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiemetics; if possible, an alternative preparation should be considered.

**Dysphagia** A corticosteroid such as dexamethasone p. 675 may help, temporarily, if there is an obstruction due to tumour. See also *Dry mouth*, above.

**Dyspnoea** Breathlessness at rest may be relieved by regular oral morphine p. 463 in carefully titrated doses. Diazepam p. 343 may be helpful for dyspnoea associated with anxiety. A corticosteroid, such as dexamethasone p. 675, may also be helpful if there is bronchospasm or partial obstruction.

**Fungating tumours** Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole p. 542 is often required to reduce malodour but topical metronidazole p. 1230 is also used.

**Gastro-intestinal pain** The pain of bowel colic may be reduced by loperamide hydrochloride p. 66. Hyoscine hydrobromide p. 439 may also be helpful, given sublingually as *Kwells*™ tablets. Subcutaneous injections of hyoscine butylbromide p. 85, hyoscine hydrobromide p. 439, and glycopyrronium bromide p. 1335 can also be used to treat bowel colic. Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiemetic such as domperidone p. 85, and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva, dry mouth associated with candidiasis can be treated by oral preparations of nystatin p. 1219 or miconazole p. 1219, alternatively, fluconazole p. 595 can be given by mouth. Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiemetics; if possible, an alternative preparation should be considered.

**Hiccup** Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiemetic such as domperidone p. 85, and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva, dry mouth associated with candidiasis can be treated by oral preparations of nystatin p. 1219 or miconazole p. 1219, alternatively, fluconazole p. 595 can be given by mouth. Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiemetics; if possible, an alternative preparation should be considered.

**Insomnia** Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam p. 488, may be useful.

**Intractable cough** Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine p. 463. Methadone hydrochloride linctus p. 502 should be avoided because it has a long duration of action and tends to accumulate.

**Muscle spasm** The pain of muscle spasm can be helped by a muscle relaxant such as diazepam p. 343 or baclofen p. 1128.

**Nausea and vomiting** Nausea and vomiting are common in patients with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic is started. A prokinetic antiemetic may be a preferred choice for first-line therapy. Nausea and vomiting may occur with opioid therapy particularly in the initial stages but can be prevented by giving an antiemetic such as haloperidol p. 386 or metoclopramide hydrochloride p. 432. An antiemetic is usually necessary only for the first 4 or 5 days and therefore combined preparations containing an opioid with an antiemetic are not recommended because they lead to unnecessary antiemetic therapy (and associated side-effects when used long-term).

Metoclopramide hydrochloride p. 432 has a prokinetic action and is used by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not be used concurrently.

Haloperidol p. 386 is used by mouth for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure). Cyclizine p. 430 is given rectally. It is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness. Levomepromazine p. 441 is used as an antiemetic, it is given by mouth or by subcutaneous injection at bedtime. For the dose by subcutaneous infusion see below. Dexamethasone p. 675 by mouth can be used as an adjunct. Antiemetic therapy should be reviewed every 24 hours; it may be necessary to substitute the antiemetic or to add another one.

For the administration of antiemetics by subcutaneous infusion using a continuous infusion device, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy see *Cytoxic drugs* p. 888.

**Pruritus** Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients. In the case of obstructive jaundice, further measures include administration of ciclosporin p. 197.

**Raised intracranial pressure** Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone p. 675 and should be given before 6 p.m. to reduce the risk of insomnia.

**Restlessness and confusion** Restlessness and confusion may require treatment with an antipsychotic, e.g. haloperidol p. 386 or levomepromazine p. 441, by mouth or by subcutaneous injection, both repeated every 2 hours if required. The dose and frequency is adjusted according to the level of patient distress and the response. A regular maintenance dose should also be considered, given twice daily either by mouth or by subcutaneous injection; alternatively use a continuous infusion device. Levomepromazine p. 441 is licensed to treat pain in palliative care—this use is reserved for distressed patients with severe pain unresponsive to other measures (seek specialist advice).

**Continuous subcutaneous infusions** Although drugs can usually be administered by mouth to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. Repeated administration of intramuscular injections can be difficult in a cachectic patient. This has led to the use of portable continuous infusion devices, such as syringe drivers, to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the parenteral route are:

- the patient is unable to take medicines by mouth owing to nausea and vomiting, dysphagia, severe weakness, or coma

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there is malignant bowel obstruction in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube)
occasionally when the patient does not wish to take regular medication by mouth.

**Syringe driver rate settings** Staff using syringe drivers should be adequately trained and different rate settings should be clearly identified and differentiated; incorrect use of syringe drivers is a common cause of medication errors.

**Bowel colic and excessive respiratory secretions** Hyoscine hydrobromide p. 439 effectively reduces respiratory secretions and bowel colic and is sedative (but occasionally causes paradoxical agitation). Hyoscine butyrylbromide p. 85 is used for bowel colic and for excessive respiratory secretions, and is less sedative than hyoscine hydrobromide p. 439. Glycopyrronium bromide p. 1335 may also be used to treat bowel colic or excessive respiratory secretions.

**Confusion and restlessness** Haloperidol p. 386 has little sedative effect. Levomepromazine p. 441 has a sedative effect. Midazolam p. 340 is a sedative and an antiepileptic that may be used in addition to an antipsychotic drug in a very restless patient. Midazolam p. 340 is also used for myoclonus.

**Convulsions** If a patient has previously been receiving an antiepileptic drug or has a primary or secondary cerebral tumour or is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam p. 340 is the benzodiazepine antiepileptic of choice for continuous subcutaneous infusion.

**Nausea and vomiting** Haloperidol p. 386 and levomepromazine p. 441 can both be given as a subcutaneous infusion but sedation can limit the dose of levomepromazine p. 441.

Cyclizine is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below). Metoclopramide hydrochloride p. 432 can cause skin reactions. Octreotide p. 950, which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion to reduce intestinal secretions and to reduce vomiting due to bowel obstruction.

**Pain control** Diamorphine hydrochloride p. 456 is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table shows approximate equivalent doses of morphine p. 463 and diamorphine hydrochloride p. 456.

**Mixing and compatibility** The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine hydrochloride p. 384, prochlorperazine p. 389, and diazepam p. 343 are contra-indicated as they cause skin reactions at the injection site; to a lesser extent cyclizine p. 430 and levomepromazine p. 441 also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9% p. 1040) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

**Compatibility with diamorphine** Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either water for injections or physiological saline (sodium chloride 0.9%) is a suitable diluent—above that strength only water for injections is used (to avoid precipitation).

The following can be mixed with diamorphine:

- **Cyclizine**, may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
- **Dexamethasone**, special care is needed to avoid precipitation of dexamethasone when preparing it.
- **Haloperidol**, mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
- **Hyoscine butyrylbromide**
- **Hyoscine hydrobromide**
- **Levomepromazine**
- **Metoclopramide**, under some conditions infusions containing metoclopramide become discoloured; such solutions should be discarded.
- **Midazolam**

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discolouration) and to ensure that the infusion is running at the correct rate.

**Problems encountered with syringe drivers** The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs too quickly check the rate setting and the calculation;
- if the subcutaneous infusion runs too slowly check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an injection site reaction make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.
Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours

These equivalences are *approximate only* and should be adjusted according to response

<table>
<thead>
<tr>
<th>ORAL MORPHINE</th>
<th>PARENTERAL MORPHINE</th>
<th>PARENTERAL DIAMORPHINE</th>
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<tbody>
<tr>
<td>Oral morphine sulfate over 24 hours</td>
<td>Subcutaneous infusion of morphine sulfate over 24 hours</td>
<td>Subcutaneous infusion of diamorphine hydrochloride over 24 hours</td>
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<td>30 mg</td>
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If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection subcutaneously—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle). To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
Prescribing in the elderly

Overview
Old people, especially the very old, require special care and consideration from prescribers. *Medicines for Older People*, a component document of the National Service Framework for Older People (Department of Health, National Service Framework for Older People. London: Department of Health, March 2001), describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

Appropriate prescribing
Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance. The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients’ medicines should be reviewed regularly and medicines which are not of benefit should be stopped. Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and light-headedness when associated with social stress as in widowhood, loneliness, and family dispersal. In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help poor prognosis or with poor overall health. Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance. The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients’ medicines should be reviewed regularly and medicines which are not of benefit should be stopped. Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and light-headedness when associated with social stress as in widowhood, loneliness, and family dispersal. In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help poor prognosis or with poor overall health.

Form of medicine
Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and whilst in an upright position to avoid the possibility of oesophageal ulceration. It can be helpful to discuss with the patient the possibility of taking the drug as a liquid if available.

Manifestations of ageing
In the very old, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. In addition, age-related muscle weakness and difficulty in maintaining balance should not be confused with neurological disease. Disorders such as light-headedness not associated with postural or postprandial hypotension are unlikely to be helped by drugs.

Sensitivity
The nervous system of elderly patients is more sensitive to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as anti-hypertensives and NSAIDs.

Pharmacokinetics
Pharmacokinetic changes can markedly increase the tissue concentration of a drug in the elderly, especially in debilitated patients. The most important effect of age is reduced renal clearance. Many aged patients thus excrete drugs slowly, and are highly susceptible to nephrotoxic drugs. Acute illness can lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin p. 109) can rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory-infection. The hepatic metabolism of lipid soluble drugs is reduced in elderly patients because there is a reduction in liver volume. This is important for drugs with a narrow therapeutic window.

Adverse reactions
Adverse reactions often present in the elderly in a vague and non-specific fashion. Confusion is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are constipation (with antimuscarinics and many tranquillisers) and postural hypotension and falls (with diuretics and many psychotropics).

Hypnotics
Many hypnotics with long half-lives have serious hangover effects, including drowsiness, unsteady gait, slurred speech, and confusion. Hypnotics with short half-lives should be used but they too can present problems. Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence. Benzodiazepines impair balance, which can result in falls.

Diuretics
Diuretics are overprescribed in old age and should not be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs
Bleeding associated with aspirin and other NSAIDs is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk. Owing to the increased susceptibility of the elderly to the side-effects of NSAIDs the following recommendations are made:

- for osteoarthritis, soft-tissue lesions, and back pain, first try measures such as weight reduction (if obese), warmth, exercise, and use of a walking stick;
- for osteoarthritis, soft-tissue lesions, back pain, and pain in rheumatoid arthritis, paracetamol p. 444 should be used first and can often provide adequate pain relief;
- alternatively, a low-dose NSAID (e.g. ibuprofen p. 1141 up to 1.2g daily) may be given;
- for pain relief when either drug is inadequate, paracetamol in a full dose plus a low-dose NSAID may be given;
- if necessary, the NSAID dose can be increased or an opioid analgesic given with paracetamol p. 444;
- do not give two NSAIDs at the same time.

Prophylaxis of NSAID-induced peptic ulcers may be required if continued NSAID treatment is necessary see, NSAID-associated ulcers under Peptic ulceration p. 72.

Other drugs
Other drugs which commonly cause adverse reactions are antiparkinsonian drugs, antihypertensives, psychotropics, and digoxin p. 109. The usual maintenance dose of digoxin p. 109 in very old patients is 125 micrograms daily (62.5 micrograms in those with renal disease); lower doses are often inadequate but toxicity is common in those given 250 micrograms daily. Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. co-trimoxazole p. 562, mianserin
hydrochloride p. 371) should be avoided unless there is no acceptable alternative. The elderly generally require a lower maintenance dose of warfarin sodium p. 140 than younger adults; once again, the outcome of bleeding tends to be more serious.

**Guidelines**
Always consider whether a drug is indicated at all.

**Limit range**
It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

**Reduce dose**
Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. long-acting antidiabetic drugs such as glibenclamide p. 709) should be avoided altogether.

**Review regularly**
Review repeat prescriptions regularly. In many patients it may be possible to stop some drugs, provided that clinical progress is monitored. It may be necessary to reduce the dose of some drugs as renal function declines.

**Simplify regimens**
Elderly patients benefit from simple treatment regimens. Only drugs with a clear indication should be prescribed and whenever possible given once or twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

**Explain clearly**
Write full instructions on every prescription (including repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like ‘as directed’. Child-resistant containers may be unsuitable.

**Repeats and disposal**
Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities. If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.

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**Anti-doping**
UK Anti-Doping, the national body responsible for the UK’s anti-doping policy, advises that athletes are personally responsible should a prohibited substance be detected in their body. Information regarding the use of medicines in sport is available from:

- UK Anti-doping
- Fleetbank House
- 2-6 Salisbury Square
- London
- EC4Y 8AE
- (020) 7842 3450
- ukad@ukad.org.uk
- [www.ukad.org.uk](http://www.ukad.org.uk)

Information about the prohibited status of specific medications based on the current World Anti-Doping Agency Prohibited List is available from Global Drug Reference Online: [www.globaldro.com/UK/search](http://www.globaldro.com/UK/search)

**General Medical Council’s advice**
Doctors who prescribe or collude in the provision of drugs or treatment with the intention of improperly enhancing an individual’s performance in sport contravene the GMC’s guidance, and such actions would usually raise a question of a doctor’s continued registration. This does not preclude the provision of any care or treatment where the doctor’s intention is to protect or improve the patient’s health.
Prescribing in dental practice

General guidance
Advice on the drug management of dental and oral conditions has been integrated into the main text. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections of the BNF.

The following is a list of topics of particular relevance to dentists.
- Prescribing by dentists, see Prescription writing p. 5
- Oral side-effects of drugs, see Adverse reactions to drugs p. 12
- Medical emergencies in dental practice, see below
- Medical problems in dental practice, see below

Drug management of dental and oral conditions

Dental and orofacial pain
- Neuropathic pain p. 483
- Non-opioid analgesics and compound analgesic preparations, see Analgesics p. 442
- Opioid analgesics, see Analgesics p. 442
- Non-steroidal anti-inflammatory drugs p. 1130

Oral infections
- Bacterial infections, see Antibacterials, principles of therapy p. 505
- Phenoxybenzylpenicillin p. 548
- Broad-spectrum penicillins (amoxicillin p. 548 and ampicillin p. 550)
- Cephalosporins (cefalexin p. 524 and cefradine p. 525)
- Tetracyclines p. 564
- Macrolides (clarithromycin p. 538, erythromycin p. 539 and azithromycin p. 536)
- Clindamycin p. 535
- Metronidazole p. 542
- Fusidic acid p. 571

Fungal infections, see Antifungals, systemic use p. 591
- Local treatment, see Oropharyngeal fungal infections p. 1218
- Systemic treatment, see Antifungals, systemic use p. 591

Viral infections
- Herpetic gingivostomatitis, local treatment, see Oropharyngeal viral infections p. 1219
- Herpetic gingivostomatitis, systemic treatment, see Oropharyngeal viral infections p. 1219
- Herpesvirus infections p. 632
- Herpes labialis, see Skin infections p. 1228

Anaesthetics, anxiolytics and hypnotics
- Sedation, anaesthesia, and resuscitation in dental practice p. 1329
- Hypnotics, see Hypnotics and anxiolytics p. 484
- Sedation for dental procedures, see Hypnotics and anxiolytics p. 484
- Anaesthesia (local) p. 1347

Minerals
- Fluoride imbalance p. 1212

Orofacial pain
- Oral ulceration and inflammation p. 1214
- Mouthwashes, gargles and dentifrices, see Mouthwashes and other preparations for oropharyngeal use p. 1210
- Dry mouth, see Treatment of dry mouth p. 1208
- Aromatic inhalations, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 296
- Nasal decongestants, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 296

Dental Practitioners’ Formulary p. 1615

Medical emergencies in dental practice

This section provides guidelines on the management of the more common medical emergencies which may arise in dental practice. Dentists and their staff should be familiar with standard resuscitation procedures, but in all circumstances it is advisable to summon medical assistance as soon as possible. See also algorithm of the procedure for Cardiopulmonary resuscitation p. 222.

The drugs referred to in this section include:
- Adrenaline/epinephrine Injection, adrenaline 1 in 1000, (adrenaline 1 mg/mL as acid tartrate), 1 mL amps p. 222
- Aspirin Dispersible Tablets 300 mg p. 121
- Glucagon Injection p. 724, glucagon (as hydrochloride), 1-unit vial (with solvent) p. 724
- Glucose p. 1041 (for administration by mouth)
- Glyceryl trinitrate Spray p. 218
- Midazolam Oromucosal Solution p. 340
- Oxygen
- Salbutamol Aerosol Inhalation, salbutamol 100 micrograms-metered inhalation p. 252

Adrenal insufficiency
Adrenal insufficiency may follow prolonged therapy with corticosteroids and can persist for years after stopping. A patient with adrenal insufficiency may become hypotensive under the stress of a dental visit (important: see individual monographs for details of corticosteroid cover before dental surgical procedures under general anaesthesia).

Management
- Lay the patient flat
- Give oxygen
- Transfer patient urgently to hospital

Anaphylaxis
A severe allergic reaction may follow oral or parenteral administration of a drug. Anaphylactic reactions in dentistry may follow the administration of a drug or contact with substances such as latex in surgical gloves. In general, the more rapid the onset of the reaction the more profound it tends to be. Symptoms may develop within minutes and rapid treatment is essential.

Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens (including those for topical application, particularly if they are intended for use in the mouth or for application to the nasal mucosa).

Symptoms and signs
- Paraesthesia, flushing, and swelling of face
- Generalised itching, especially of hands and feet
- Bronchospasm and laryngospasm (with wheezing and difficulty in breathing)
- Rapid weak pulse together with fall in blood pressure and pallor; finally cardiac arrest

Management
First-line treatment includes securing the airway, restoration of blood pressure (laying the patient flat and raising the feet, or in the recovery position if unconscious or nauseous and at risk of vomiting), and administration of adrenaline/epinephrine injection p. 222. This is given intramuscularly in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) may be appropriate for immediate self-administration. The dose is repeated if necessary at 5-minute intervals according to blood pressure,
pulse, and respiratory function. **Oxygen** administration is also of primary importance. Arrangements should be made to transfer the patient to hospital urgently.

### Asthma

Patients with asthma may have an attack while at the dental surgery. Most attacks will respond to 2 puffs of the patient’s short-acting beta, agonist inhaler such as salbutamol 100 micrograms/puff p. 252; further puffs are required if the patient does not respond rapidly. If the patient is unable to use the inhaler effectively, further puffs should be given through a large-volume spacer device (or, if not available, through a plastic or paper cup with a hole in the bottom for the inhaler mouthpiece). If the response remains unsatisfactory, or if further deterioration occurs, then the patient should be transferred urgently to hospital. Whilst awaiting transfer, **oxygen** should be given with salbutamol 5 mg p. 252 or terbutaline sulfate 10 mg p. 255 by nebuliser; if a nebuliser is unavailable, then 2–10 puffs of salbutamol 100 micrograms/ metered inhalation should be given (preferably by a large-volume spacer), and repeated every 10–20 minutes if necessary. If asthma is part of a more generalised anaphylactic reaction, an intramuscular injection of adrenaline/epinephrine p. 222 (as detailed under **Anaphylaxis**) should be given.

Patients with severe chronic asthma or whose asthma has deteriorated previously during a dental procedure may require an increase in their prophylactic medication before a dental procedure. This should be discussed with the patient’s medical practitioner and may include increasing the dose of inhaled or oral corticosteroid.

### Cardiac emergencies

If there is a history of **angina** the patient will probably carry glyceryl trinitrate spray or tablets p. 218 (or isosorbide dinitrate tablets p. 220) and should be allowed to use them. Hospital admission is not necessary if symptoms are mild and resolve rapidly with the patient’s own medication. See also **Coronary Artery Disease** below.

**Arrhythmias** may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also **Pacemakers** below.

The pain of **myocardial infarction** is similar to that of angina but generally more severe and more prolonged. For general advice see also **Coronary Artery Disease** below.

### Symptoms and signs of myocardial infarction:

- Progressive onset of severe, crushing pain across front of chest; pain may radiate towards the shoulder and down arm, or into neck and jaw
- Skin becomes pale and clammy
- Nausea and vomiting are common
- Pulse may be weak and blood pressure may fall
- Breathlessness

### Initial management of myocardial infarction:

Call immediately for medical assistance and an ambulance, as appropriate.

Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. **Oxygen** may be administered.

Sublingual glyceryl trinitrate p. 218 may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug.

Reassure the patient as much as possible to relieve further anxiety. If available, **aspirin** p. 121 in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see **Management of ST-Segment Elevation Myocardial Infarction**.

If the patient collapses and loses consciousness attempt standard resuscitation measures. See also **algorithm** of the procedure for Cardiopulmonary resuscitation p. 222.

### Epileptic seizures

Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

### Symptoms and signs

- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

### Management

During a convulsion try to ensure that the patient is not at risk from injury but make no attempt to put anything in the mouth or between the teeth (in mistaken belief that this will protect the tongue). Give **oxygen** to support respiration if necessary.

Do not attempt to restrain convulsive movements. After convulsive movements have subsided place the patient in the coma (recovery) position and check the airway. After the convulsion the patient may be confused (‘post-ictal confusion’) and may need reassurance and sympathy. The patient should not be sent home until fully recovered. Seek medical attention or transfer the patient to hospital if it was the first episode of epilepsy, or if the convulsion was atypical, prolonged (or repeated), or if injury occurred. Medication should only be given if convulsive seizures are prolonged (convulsive movements lasting 5 minutes or longer) or repeated rapidly.

**Midazolam** oromucosal solution p. 340 can be given by the buccal route in adults as a single dose of 10 mg [unlicensed]. For further details on the management of status epilepticus, including details of paediatric doses of midazolam p. 340, see Drugs used in status epilepticus (Epilepsy p. 305).

Focal seizures similarly need very little active management (in an automatism only a minimum amount of restraint should be applied to prevent injury). Again, the patient should be observed until post-ictal confusion has completely resolved.

### Hypoglycaemia

Insulin-treated diabetic patients attending for dental treatment under local anaesthesia should inject insulin and eat meals as normal. If food is omitted the blood glucose will fall to an abnormally low level (hypoglycaemia). Patients can often recognise the symptoms themselves and this state responds to sugar in water or a few lumps of sugar. Children may not have such prominent changes but may appear unduly lethargic.

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Symptoms and signs
- Shaking and trembling
- Sweating
- Pins and needles’ in lips and tongue
- Hunger
- Palpitation
- Headache (occasionally)
- Double vision
- Difficulty in concentration
- Slurring of speech
- Confusion
- Change of behaviour; truculence
- Convulsions
- Unconsciousness

Management
Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of Lucozade® Energy Original 110 mL, Coca-Cola® 100 mL, Ribena® Blackcurrant 19 mL (to be diluted), 2 teaspoons sugar, and also from 3 sugar lumps. (Proprietary products of quick-acting carbohydrate e.g. GlucoGel®, Dextrogel®, GSF-Syrup®, Rapilose® gel) are available on prescription for the patient to keep to hand in case of hypoglycaemia). If necessary this may be repeated in 10–15 minutes.

Note: the carbohydrate content of some commercially available glucose-containing drinks is currently subject to change—individual product labels should be checked. Patients should be aware that for a time, both old and new bottles and cans may be available—individual product labels should be checked.

If glucose cannot be given by mouth, if it is ineffective, or if the hypoglycaemia causes unconsciousness, glucagon 1 mg (1 unit) should be given by intramuscular (or subcutaneous) injection; a child under 8 years or of body-weight under 25 kg should be given 500 micrograms. Once the patient regains consciousness oral glucose should be administered as above. If glucagon is ineffective or contra-indicated, the patient should be transferred urgently to hospital. The patient must also be admitted to hospital if hypoglycaemia is caused by an oral antidiabetic drug.

Syncope
Insufficient blood supply to the brain results in loss of consciousness. The commonest cause is a vasovagal attack or simple faint (syncope) due to emotional stress.

Symptoms and signs
- Patient feels faint
- Low blood pressure
- Pallor and sweating
- Yawning and slow pulse
- Nausea and vomiting
- Dilated pupils
- Muscular twitching

Management
- Lay the patient as flat as is reasonably comfortable and, in the absence of associated breathlessness, raise the legs to improve cerebral circulation
- Loosen any tight clothing around the neck
- Once consciousness is regained, give sugar in water or a cup of sweet tea

Other possible causes
- Postural hypotension can be a consequence of rising abruptly or of standing upright for too long; antihypertensive drugs predispose to this. When rising, susceptible patients should take their time. Management is as for a vasovagal attack.
- Under stressful circumstances, some patients hyperventilate. This gives rise to feelings of faintness but does not usually result in syncope. In most cases reassurance is all that is necessary; rebreathing from cupped hands or a bag may be helpful but calls for careful supervision.
- Adrenal insufficiency or arrhythmias are other possible causes of syncope.

Medical problems in dental practice
Individuals presenting at the dental surgery may also suffer from an unrelated medical condition; this may require modification to the management of their dental condition. If the patient has systemic disease or is taking other medication, the matter may need to be discussed with the patient’s general practitioner or hospital consultant.

Allergy
Patients should be asked about any history of allergy; those with a history of atopic allergy (asthma, eczema, hay fever, etc.) are at special risk. Those with a history of a severe allergy or of anaphylactic reactions are at high risk—it is essential to confirm that they are not allergic to any medication, or to any dental materials or equipment (including latex gloves). See also Anaphylaxis above.

Arrhythmias
Patients, especially those who suffer from heart failure or who have sustained a myocardial infarction, may have irregular cardiac rhythm. Atrial fibrillation is a common arrhythmia even in patients with normal hearts and is of little concern except that dentists should be aware that such patients may be receiving anticoagulant therapy. The patient’s medical practitioner should be asked whether any special precautions are necessary. Premedication (e.g. with temazepam p. 488) may be useful in some instances for very anxious patients.

See also Cardiac emergencies above, and Dental Anaesthesia (Anaesthesia (local) p. 1347).

Cardiac protheses
For an account of the risk of infective endocarditis in patients with prosthetic heart valves, see Infective Endocarditis below. For advice on patients receiving anticoagulants, see Thromboembolic disease below.

Coronary artery disease
Patients are vulnerable for at least 4 weeks following a myocardial infarction or following any sudden increase in the symptoms of angina. It would be advisable to check with the patient’s medical practitioner before commencing treatment. See also Cardiac Emergencies above.

Treatment with low-dose aspirin (75 mg daily), clopidogrel p. 123, or dipyridamole p. 124 should not be stopped routinely nor should the dose be altered before dental procedures.

A Working Party of the British Society for Antimicrobial Chemotherapy has not recommended antibiotic prophylaxis for patients following coronary artery bypass surgery.

Cyanotic heart disease
Patients with cyanotic heart disease are at risk in the dental chair, particularly if they have pulmonary hypertension. In such patients a syncopal reaction increases the shunt away from the lungs, causing more hypoxia which worsens the syncopal reaction—a vicious circle that may prove fatal. The advice of the cardiologist should be sought on any patient with congenital cyanotic heart disease. Treatment in hospital is more appropriate for some patients with this condition.

Hypertension
Patients with hypertension are likely to be receiving antihypertensive drugs. Their blood pressure may fall dangerously low under general anaesthesia, see also under Dental Anaesthesia (Anaesthesia (local) p. 1347).
Immunosuppression and indwelling intraperitoneal catheters
Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis. The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

Infective endocarditis
While almost any dental procedure can cause bacteraemia, there is no clear association with the development of infective endocarditis. Routine daily activities such as tooth brushing also produce a bacteraemia and may present a greater risk of infective endocarditis than a single dental procedure. Antibacterial prophylaxis and chlorhexidine mouthwash p. 1211 are not recommended for the prevention of endocarditis in patients undergoing dental procedures. Such prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Reduction of oral bacteraemia Patients at risk of endocarditis including those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be advised to maintain the highest possible standards of oral hygiene in order to reduce the:

- need for dental extractions or other surgery;
- chances of severe bacteraemia if dental surgery is needed;
- possibility of ‘spontaneous’ bacteraemia.

Postoperative care Patients at risk of endocarditis including those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be warned to report to the doctor or dentist any unexplained illness that develops after dental treatment.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

Patients on anticoagulant therapy
For general advice on dental surgery in patients receiving oral anticoagulant therapy see Thromboembolic Disease below.

Joint prostheses
Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive. The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

Pacemakers
Pacemakers prevent asystole or severe bradycardia. Some ultrasonic scalers, electronic apex locators, electro-analgesic devices, and electrocautery devices interfere with the normal function of pacemakers (including shielded pacemakers) and should not be used. The manufacturer’s literature should be consulted whenever possible. If severe bradycardia occurs in a patient fitted with a pacemaker, electrical equipment should be switched off and the patient placed supine with the legs elevated. If the patient loses consciousness and the pulse remains slow or is absent, cardiopulmonary resuscitation may be needed. Call immediately for medical assistance and an ambulance, as appropriate.


Thromboembolic disease
Patients receiving a heparin or an oral anticoagulant such as warfarin sodium p. 140, acenocoumarol p. 139 (nicoumalone), phenindione p. 140, apixaban p. 125, dabigatran etexilate p. 136 or rivaroxaban p. 128 may be liable to excessive bleeding after extraction of teeth or other dental surgery. Often dental surgery can be delayed until the anticoagulant therapy has been completed. For a patient requiring long-term therapy with warfarin sodium p. 140, the patient’s medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure. This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin sodium p. 140 without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If it is necessary to remove several teeth, a single extraction may be done at one visit; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding. For a patient on long-term warfarin sodium p. 140, the advice of the clinician responsible for the patient’s anticoagulation should be sought if:

- the INR is unstable, or if the INR is greater than 4.0;
- the patient has thrombocytopenia, haemophilia, or other disorders of haemostasis, or suffers from liver impairment, alcoholism, or renal failure;
- the patient is receiving antiplatelet drugs, cytotoxic drugs or radiotherapy.

Intramuscular injections are contra–indicated in patients taking anticoagulants with an INR above the therapeutic range, and in those with any disorder of haemostasis. In patients taking anticoagulants who have a stable INR within the therapeutic range, intramuscular injections should be avoided if possible; if an intramuscular injection is necessary, the patient should be informed of the increased risk of localised bleeding and monitored carefully.
A local anaesthetic containing a vasoconstrictor should be given by infiltration, or by intraligamentary or mental nerve injection if possible. If regional nerve blocks cannot be avoided the local anaesthetic should be given cautiously using an aspirating syringe.

Drugs which have potentially serious interactions with anticoagulants include aspirin and other NSAIDs, carbamazepine p. 311, imidazole and triazole antifungals (including miconazole p. 830), erythromycin p. 539, clarithromycin p. 538, and metronidazole p. 542; for details of these and other interactions with anticoagulants, see Appendix 1 (dabigatran etexilate, heparins, phenindione, rivaroxaban, and coumarins). Although studies have failed to demonstrate an interaction, common experience in anticoagulant clinics is that the INR can be altered following a course of an oral broad-spectrum antibiotic, such as ampicillin p. 550 or amoxicillin p. 548. Information on the treatment of patients who take anticoagulants is available at www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant.

Liver disease
Liver disease may alter the response to drugs and drug prescribing should be kept to a minimum in patients with severe liver disease. Problems are likely mainly in patients with jaundice, ascites, or evidence of encephalopathy. For guidance on prescribing for patients with hepatic impairment, see Prescribing in hepatic impairment p. 19. Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

Renal impairment
The use of drugs in patients with reduced renal function can give rise to many problems. Many of these problems can be avoided by reducing the dose or by using alternative drugs. Special care is required in renal transplantation and immunosuppressed patients; if necessary such patients should be referred to specialists. For guidance on prescribing in patients with renal impairment, see Prescribing in renal impairment p. 19. Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Pregnancy
Drugs taken during pregnancy can be harmful to the fetus and should be prescribed only if the expected benefit to the mother is thought to be greater than the risk to the fetus; all drugs should be avoided if possible during the first trimester. For guidance on prescribing in pregnancy, see Prescribing in pregnancy p. 23. Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF.

Breast-feeding
Some drugs taken by the mother whilst breast-feeding can be transferred to the breast milk, and may affect the infant. For guidance on prescribing in breast-feeding, see Prescribing in breast-feeding p. 23. Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.
Chapter 1
Gastro-intestinal system

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1 Chronic bowel disorders

1.1 Coeliac disease

Coeliac disease

Description of condition
Coeliac disease is an autoimmune condition which is associated with chronic inflammation of the small intestine. Dietary proteins known as gluten, which are present in wheat, barley and rye, activate an abnormal immune response in the intestinal mucosa, which can lead to malabsorption of nutrients.

Aims of treatment
The management of coeliac disease is aimed at eliminating symptoms (such as diarrhoea, bloating and abdominal pain) and reducing the risk of complications, including those resulting from malabsorption of nutrients.

Non-drug treatment

The only effective treatment for coeliac disease is a strict, life-long, gluten-free diet. A range of gluten-free products is available for prescription (see Borderline substances).

Drug treatment

Patients who have coeliac disease are at an increased risk of malabsorption of key nutrients (such as calcium and vitamin D). Their risk of osteoporosis and the need for active treatment of bone disease should form part of the ongoing management of coeliac disease. Supplementation of key nutrients may be required if dietary intake is insufficient.

Patients who have coeliac disease should be advised not to self-medicate with over-the-counter vitamins or mineral supplements. Initiation of supplementation should involve a discussion with a member of the patient’s healthcare team in order to identify the individual needs of the patient and to allow for appropriate ongoing monitoring.

Confirmed cases of refractory coeliac disease should be referred to a specialist centre. Treatment with prednisolone p. 678 can be considered for initial management while awaiting specialist advice.

Useful Resources

1.2 Diverticular disease and diverticulitis

Diverticular disease and diverticulitis

Description of condition
Diverticular disease is a condition where diverticula (sac-like protrusions of mucosa through the muscular colonic wall) cause intermittent lower abdominal pain in the absence of inflammation or infection. The prevalence of diverticula increases with age, with the majority of patients older than 50 years.

Diverticulitis occurs when the diverticula become inflamed and infected, causing marked lower abdominal pain usually accompanied by fever and general malaise, and occasionally, with large rectal bleeds. Complicated diverticulitis includes episodes associated with an abscess, free perforation, fistula, obstruction, or stricture.

To ensure that an accurate diagnosis of diverticular disease and diverticulitis is made, consider and exclude all other causes of lower abdominal pain prior to treatment.

Aims of treatment
The aim of treatment is to relieve symptoms of diverticular disease, cure episodes of diverticulitis, and reduce the risk of recurrences and complications.
Drug treatment

A high-fibre diet is recommended for the treatment of symptomatic diverticular disease, although evidence supporting this is inconsistent and of low quality. Bulk-forming drugs have also been used, but evidence of their effectiveness is lacking.

Treatment of uncomplicated diverticulitis includes a low residue diet and bowel rest. Antibacterials are recommended only when the patient presents with signs of infection or is immunocompromised, as there is no evidence to support routine administration.

Patients with complicated diverticulitis or with severe presentation, require hospital admission, treatment with intravenous antibacterials (covering Gram-negative organisms and anaerobes), and bowel rest.

There is insufficient evidence to justify the role of fibre, rifaximin p. 575, antisepsmodics, mesalazine p. 41, and probiotics in the prevention or treatment of diverticulitis.

Elective surgery to provide symptomatic relief or prevent recurrence, should be considered for patients following recovery from an episode of complicated diverticulitis. This includes episodes associated with free perforation, abscess, fistula, obstruction, or stricture. Urgent sigmoid colectomy is required for patients with diffuse peritonitis or for those in whom non-operative management of acute diverticulitis fails.

1.3 Inflammatory bowel disease

Inflammatory bowel disease

Chronic inflammatory bowel diseases include Crohn’s disease below and Ulcerative colitis p. 39.

Drugs used in chronic bowel disorders

Aminosalicylates

Sulfasalazine p. 44 is a combination of 5-aminosalicylic acid (‘5-ASA’) and sulfapyridine; sulfapyridine acts only as a carrier to the colonic site of action but still causes side-effects. In the newer aminosalicylates, mesalazine p. 41 (5-aminosalicylic acid), balsalazide sodium p. 41 (a pro-drug of 5-aminosalicylic acid) and olsalazine sodium p. 44 (a dimer of 5-aminosalicylic acid which cleaves in the lower bowel), the sulfonamide-related side-effects of sulfasalazine are avoided, but 5-aminosalicylic acid alone can still cause side-effects including blood disorders and lupus-like syndrome also seen with sulfasalazine.

Drugs affecting the immune response

Folic acid p. 1025 should be given to reduce the possibility of methotrexate p. 913 toxicity [unlicensed indication]. Folic acid is usually given once weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

Cytokine modulators

Infliximab p. 1116, adalimumab p. 1108, and golimumab p. 1115 are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They should be used under specialist supervision.

Crohn’s disease

Description of condition

Crohn’s disease is a chronic, inflammatory bowel disease that mainly affects the gastro-intestinal tract. It is characterised by thickened areas of the gastro-intestinal wall with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas; affected areas may occur in any part of the gastro-intestinal tract, interspersed with areas of relatively normal tissue. Crohn’s disease may present as recurrent attacks, with acute exacerbations combined with periods of remission or less active disease. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

Complications of Crohn’s disease include intestinal strictures, abscesses in the wall of the intestine or adjacent structures, fistulae, anaemia, malnutrition, colorectal and small bowel cancers, and growth failure and delayed puberty in children. Crohn’s disease may also be associated with extra-intestinal manifestation: the most common are arthritis and abnormalities of the joints, eyes, liver and skin. Crohn’s disease is also a cause of secondary osteoporosis and those at greatest risk should be monitored for osteopenia and assessed for the risk of fractures.

Fistulizing Crohn’s disease

Fistulizing Crohn’s disease is a complication that involves the formation of a fistula between the intestine and adjacent structures, such as perianal skin, bladder, and vagina. It occurs in about one quarter of patients, mostly when the disease involves the ileocolonic area.

Aims of treatment

Treatment is largely directed at the induction and maintenance of remission and the relief of symptoms. Active treatment of acute Crohn’s disease should be distinguished from preventing relapse. The aims of drug treatment are to reduce symptoms and maintain or improve quality of life, while minimising toxicity related to drugs over both the short and long term.

In fistulating Crohn’s disease, surgery and medical treatment aim to close and maintain closure of the fistula.

Non-drug treatment

In addition to drug treatment, management options for Crohn’s disease include Smoking cessation p. 497 and attention to nutrition, which plays an important role in supportive care. Surgery may be considered in certain patients with early disease limited to the distal ileum and in severe or chronic active disease.

Drug treatment

Treatment of acute disease

Monotherapy

A corticosteroid (either prednisolone p. 678 or methylprednisolone p. 678 or intravenous hydrocortisone p. 676), is used to induce remission in patients with a first presentation or a single inflammatory exacerbation of Crohn’s disease in a 12-month period.

In patients with distal ileal, ileocaecal or right-sided colonic disease, in whom a conventional corticosteroid is unsuitable or contra-indicated, budesonide p. 45 may be considered. Budesonide is less effective but may cause fewer side-effects than other corticosteroids, as systemic exposure is limited. Aminosalicylates (such as sulfasalazine p. 44 and mesalazine p. 41) are an alternative option in these patients. They are less effective than a corticosteroid or budesonide, but may be preferred because they have fewer side-effects. Aminosalicylates and budesonide are not appropriate for severe presentations or exacerbations.

Add-on treatment

Add on treatment is prescribed if there are two or more inflammatory exacerbations in a 12-month period, or the corticosteroid dose cannot be reduced.

Azathioprine p. 836 or mercaptopurine p. 912 [unlicensed indications] can be added to a corticosteroid or budesonide to induce remission. In patients who cannot tolerate azathioprine or mercaptopurine or in whom thiopurine methyltransferase (TPMT) activity is deficient, methotrexate p. 913 can be added to a corticosteroid.
Under specialist supervision, monoclonal antibody therapies, adalimumab p. 1108 and infliximab p. 1116, are options for the treatment of severe, active Crohn’s disease, following inadequate response to conventional therapies or in those who are intolerant of or have contra-indications to conventional therapy. Vedolizumab p. 46 is recommended as a treatment option for moderate to severely active Crohn’s disease when therapy with adalimumab or infliximab is unsuccessful, is contra-indicated or not tolerated. See also National funding/access decisions for adalimumab, infliximab and vedolizumab.

Adalimumab and infliximab can be used as monotherapy or combined with an immunosuppressant although there is uncertainty about the comparative effectiveness and long-term side-effects of therapy.

Maintenance of remission

Patients who choose not to receive maintenance treatment during remission should be made aware of the symptoms that may suggest a relapse (most frequently unintended weight loss, abdominal pain, diarrhoea and general ill-health). For those who choose not to receive maintenance treatment during remission, a suitable follow up plan should be agreed upon and information provided on how to access healthcare if a relapse should occur.

Azathioprine or mercaptopurine [unlicensed indications] as monotherapy can be used to maintain remission when previously used with a corticosteroid to induce remission. They may also be used in patients who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, corticosteroid use at presentation, and severe presentations). Methotrexate can be used to maintain remission only in patients who required methotrexate to induce remission, or who are intolerant of or are not suitable for azathioprine or mercaptopurine for maintenance. Corticosteroids or budesonide should not used.

Maintaining remission following surgery

Azathioprine or mercaptopurine [unlicensed indications] can be considered to maintain remission after surgery in patients with adverse prognostic factors such as more than one resection, or previously complicated or debilitating disease (for example abscess, involvement of adjacent structures, fistulating or penetrating disease). Aminosalicylates can also be considered as an option, however budesonide or enteral nutrition should not be used.

Other treatments

Loperamide hydrochloride p. 66 or codeine phosphate p. 454 can be used to manage diarrhoea associated with Crohn’s disease in those who do not have colitis. Colestyramine p. 197 is licensed for the relief of diarrhoea associated with Crohn’s disease. See also Diarrhoea (acute) p. 65.

Fistulating Crohn’s disease

Perianal fistulae are the most common occurrence in patients with fistulating Crohn’s disease. Treatment may not be necessary for simple, asymptomatic perianal fistulae. When fistulae are symptomatic, local drainage and surgery may be required in conjunction with the medical therapy.

Metronidazole p. 542 or ciprofloxacin p. 558 [unlicensed indications], alone or in combination, can improve symptoms of fistulating Crohn’s disease but complete healing occurs rarely. Metronidazole is usually given for 1 month, but no longer than 3 months because of concerns about peripheral neuropathy. Other antibiotics should be given if specifically indicated (e.g. in sepsis associated with fistulae and perianal disease) and for managing bacterial overgrowth in the small bowel.

Either azathioprine or mercaptopurine [unlicensed indications] is used to control the inflammation in fistulating Crohn’s disease and they are continued for maintenance. Infliximab is recommended for patients with active fistulating Crohn’s disease who have not responded to conventional therapy (including antibacterials, drainage and immunsuppressive treatments), or who are intolerant of or have contra-indications to conventional therapy. Infliximab p. 1116 should be used after ensuring that all sepsis is actively draining.

Abscess drainage, fistulotomy, and seton insertion may be appropriate, particularly before infliximab treatment.

Azathioprine p. 836, mercaptopurine p. 912, or infliximab should be continued as maintenance treatment for at least one year.

For the management of non-perianal fistulating Crohn’s disease (including entero-gynaecological and enterovesical fistulae) surgery is the only recommended approach.

Useful Resources


www.nice.org.uk/guidance/cg152

Ulcerative colitis

Description of condition

Ulcerative colitis is a chronic inflammatory condition, characterised by diffuse mucosal inflammation—it has a relapsing-remitting pattern. It is a life-long disease that is associated with significant morbidity. It most commonly presents between the ages of 15 and 25 years, although diagnosis can be made at any age.

The pattern of inflammation is continuous, extending from the rectum upwards to a varying degree. Inflammation of the rectum is referred to as proctitis, and inflammation of the rectum and sigmoid colon as proctosigmoiditis. Left-sided colitis refers to disease involving the colon distal to the splenic flexure. Extensive colitis affects the colon proximal to the splenic flexure, and includes pan-colitis, where the whole colon is involved. Common symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defaecate, and abdominal pain.

Ulcerative colitis is classified as subacute if it is moderate-to-severely active disease which can be managed in an outpatient setting, and does not require hospitalisation or consideration of urgent surgical intervention.

Complications associated with ulcerative colitis include an increased risk of colorectal cancer, secondary osteoporosis, venous thromboembolism and toxic megacolon.

Aims of treatment

Treatment is focused on treating active disease to manage symptoms and to induce and maintain remission.

Drug treatment

Overview

Management of ulcerative colitis is dependent on factors such as clinical severity, extent of disease, and patient preference. Clinical and laboratory investigations are used to determine the extent and severity of disease and to guide treatment. Severity is classified as mild, moderate or severe by using the Truelove and Witts’ Severity Index to assess bowel movements, heart rate, erythrocyte sedimentation rate and the presence of pyrexia, melaena or anaemia—see the NICE guideline for Ulcerative Colitis for further information (Useful resources below).

The extent of disease should be considered when choosing the route of administration for aminosalicylates and corticosteroids; whether oral treatment, topical treatment or
both are to be used. If the inflammation is distal, a rectal preparation is adequate but if the inflammation is extended, systemic medication is required. Either suppositories or enemas can be offered, taking into account the patient’s preferences.

Rectal foam preparations and suppositories can be used when patients have difficulty retaining liquid enemas. Diarrhoea associated with ulcerative colitis is sometimes treated with anti-diarrhoeal drugs (such as loperamide hydrochloride p. 66 or codeine phosphate p. 454) on the advice of a specialist; however their use is contra-indicated in acute ulcerative colitis as they can increase the risk of toxic megacolon.

A macrogol-containing osmotic laxative (such as macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride p. 57) may be useful for proximal faecal loading in proctitis.

Oral aminosalicylates for the treatment of ulcerative colitis are available in different preparations and release forms. The preparation and dosing schedule should be chosen taking into account the delivery characteristics and suitability for the patient. When used to maintain remission, single daily doses of oral aminosalicylates can be more effective than multiple daily dosing, but may result in more side-effects.

Treatment of acute mild-to-moderate ulcerative colitis

Acute treatment to induce remission generally consists of an aminosalicylate with or without a corticosteroid.

Oral and rectal aminosalicylate in combination can be used as first line treatment in patients with acute, mild-to-moderate extensive ulcerative colitis; as this is associated with higher rates of improvement in disease activity.

Proctitis and proctosigmoiditis

Aminosalicylates are recommended as first-line treatment for patients with a mild-to-moderate initial presentation or inflammatory exacerbation. Using a rectal aminosalicylate (mesalazine p. 41 or sulfasalazine p. 44) alone is likely to be more effective for patients with proctitis and proctosigmoiditis. Monotherapy with an oral aminosalicylate (balsalazide sodium p. 41, mesalazine, olsalazine sodium p. 44, sulfasalazine) can be considered for patients who prefer not to use enemas or suppositories, although this may not be as effective.

A rectal corticosteroid (budesonide p. 45, hydrocortisone p. 676 or prednisolone p. 676) or oral prednisolone can be considered in patients who are intolerant to, or decline, or have a contra-indication to aminosalicylates.

Oral prednisolone should be considered for the treatment of patients with subacute proctitis or proctosigmoiditis.

Left-sided or extensive ulcerative colitis

First-line treatment in patients with left-sided or extensive ulcerative colitis is a high induction dose of an oral aminosalicylate, with addition of a rectal aminosalicylate or oral beclometasone dipropionate if necessary. Oral prednisolone alone is recommended for patients who cannot tolerate or who decline aminosalicylates, in whom aminosalicylates are contra-indicated or in patients with subacute left-sided or extensive ulcerative colitis.

Initial treatment failure in all extents of mild-to-moderate disease

In all patients who are treated with an aminosalicylate, if there are no improvements within four weeks of initial treatment or if symptoms worsen, addition of oral prednisolone to aminosalicylate therapy can be considered (disclosure beclometasone dipropionate p. 45 if adding oral prednisolone). If there is still no response after 2–4 weeks of prednisolone, consider adding oral tacrolimus p. 841 [unlicensed indication] to induce remission. Budesonide multimatrix (a corticosteroid that is taken orally but exerts its action topically in the colon) is licensed for inducing remission in mild-to-moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient and can be considered as an additional therapeutic option.

Moderate disease may require treatment with a monoclonal antibody due to inadequate response to conventional treatment or if conventional treatment is not tolerated or contra-indicated (see Monoclonal antibodies for ulcerative colitis below).

Treatment of acute severe ulcerative colitis

Acute severe ulcerative colitis of any extent can be life-threatening and is regarded as a medical emergency.

Intravenous corticosteroids (such as hydrocortisone or methylprednisolone p. 678) should be given to induce remission in patients with acute severe ulcerative colitis (at first presentation or an exacerbation) while assessing the need for surgery. If intravenous corticosteroids are contra-indicated, declined or cannot be tolerated, then intravenous ciclosporin p. 838 [unlicensed indication] or surgery should be considered. A combination of intravenous ciclosporin with intravenous corticosteroids, or surgery is second line therapy for patients who have little or no improvement within 72 hours of starting intravenous corticosteroids or whose symptoms worsen despite treatment.

Research has shown that infliximab p. 1116 is as effective as ciclosporin and, in practice, it is commonly used in these patients instead of ciclosporin—see also Monoclonal antibodies for acute ulcerative colitis, below.

In patients who experience an initial response to steroids followed by deterioration, stool cultures should be taken to exclude the presence of pathogens; cytomegalovirus activation should be considered.

Monoclonal antibodies for acute ulcerative colitis

Adalimumab p. 1108, golimumab p. 1115, infliximab p. 1116 and vedolizumab p. 46 can be used to treat moderate-to-severe active ulcerative colitis following an inadequate response to conventional treatment options, or if conventional treatment options are not tolerated or contra-indicated. Treatment with these agents is continued into the maintenance phase, if effective and tolerated. See also National funding/access decisions for adalimumab, golimumab, infliximab and vedolizumab.

Infliximab can be used to treat acute exacerbations of severely active ulcerative colitis if ciclosporin p. 838 is contra-indicated or clinically inappropriate.

Maintaining remission in mild, moderate or severe ulcerative colitis

To reduce the chances of relapse occurring, maintenance therapy with an aminosalicylate is recommended in most patients. Corticosteroids are not suitable for maintenance treatment because of their side-effects.

After a mild-to-moderate inflammatory exacerbation of proctitis or proctosigmoiditis, a rectal aminosalicylate can be started alone or in combination with an oral aminosalicylate, administered daily or as part of an intermittent regimen (such as twice to three times weekly or the first seven days of each month). An oral aminosalicylate can be used alone in patients who prefer not to use enemas or suppositories, although this may not be as effective.

A low-dose of oral aminosalicylate is given to maintain remission in patients after a mild-to-moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis.

When used to maintain remission, single daily doses of oral aminosalicylates can be more effective than multiple daily dosing, but may result in more side-effects.

Oral azathioprine p. 836 or mercaptopurine p. 912 [unlicensed indications] can be considered to maintain remission, if there has been two or more inflammatory exacerbations in a 12-month period that required treatment with systemic corticosteroids, or if remission is not
maintained by aminosalicylates, or following a single acute severe episode. There is no evidence to support the use of methotrexate
p. 913 to induce or maintain remission in ulcerative colitis, though its use is common in clinical practice.

Monoclonal antibodies for maintaining remission of ulcerative colitis
Treatment with these agents is continued into the maintenance phase, if effective and tolerated in acute disease. See also National funding/access decisions for adalimumab, golimumab, infliximab and vedolizumab.

Non-drug treatment
Surgery may be necessary as emergency treatment for severe ulcerative colitis that does not respond to drug treatment. Patients can also choose to have elective surgery for unresponsive or frequently relapsing disease that is affecting their quality of life.

Useful Resources

Other drugs used for Inflammatory bowel disease
Tofacitinib, p. 1105. Ustekinumab, p. 1103

AMINOSALICYLATES

Aminosalicylates

- SIDE-EFFECTS
  - Common or very common Arthralgia · cough · diarrhoea · dizziness · fever · gastrointestinal discomfort · headache · leucopenia · nausea · skin reactions · vomiting
  - Uncommon Alopecia · depression · dyspnoea · myalgia · photosensitivity reaction · thrombocytopenia
  - Rare or very rare Agranulocytosis · bone marrow disorders · cardiac inflammation · hepatitis · neutropenia · pancreatitis · peripheral neuropathy · renal impairment · respiratory disorders
  - Frequency not known Angioedema · eosinophilia · haemolytic anaemia · nephritis tubulointerstitial · oligozaospermia (reversible) · ulcerative colitis aggravated
  - SIDE-EFFECTS, FURTHER INFORMATION A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.
  - ALLERGY AND CROSS-SENSITIVITY Contra-indicated in salicylate hypersensitivity.
  - RENAL IMPAIRMENT Monitoring Renal function should be monitored more frequently in renal impairment.
  - MONITORING REQUIREMENTS Renal function should be monitored before starting an oral aminosalicylate, at 3 months of treatment, and then annually during treatment.
  - PATIENT AND CARER ADVICE Blood disorders Patients receiving aminosalicylates, and their carers, should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

Balsalazide sodium

- INDICATIONS AND DOSE
  - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
    - Adult: 2.25 g 3 times a day until remission occurs or for up to maximum of 12 weeks
  - Maintenance of remission of ulcerative colitis
    - BY MOUTH
    - Adult: 1.5 g twice daily (max. per dose 3 g), adjusted according to response; maximum 6 g per day

- CAUTIONS History of asthma
- INTERACTIONS Appendix 1: balsalazide
- SIDE-EFFECTS Blood disorder · cholelithiasis · lupus-like syndrome
- PREGNANCY Manufacturer advises avoid.
- BREAST FEEDING Diarrhoea may develop in the infant. Monitoring Monitor breast-fed infants for diarrhoea.
- HEPATIC IMPAIRMENT Manufacturer advises caution; avoid in severe impairment (no information available).
- RENAL IMPAIRMENT Manufacturer advises avoid in moderate to severe impairment.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
  - Capsule CAUTIONARY AND ADVISORY LABELS 21, 25
    - Colazide (Almirall Ltd) Balsalazide disodium 750 mg Colazide 750mg capsules [ ] 130 capsule £30.42 DT = £30.42

Mesalazine

- INDICATIONS AND DOSE
  - DOSE EQUIVALENCE AND CONVERSION
  - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
    - Adult: 2.4–4.8 g daily in divided doses
  - Maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis
    - BY MOUTH
    - Adult: 1.2–2.4 g daily in divided doses

- ASACOL® MR 800MG TABLETS
  - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
    - Adult: 2.4–4.8 g daily in divided doses

- ASACOL® MR 400MG TABLETS
  - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
    - Adult: 2.4 g daily in divided doses

- Maintenance of remission of ulcerative colitis
  - BY MOUTH
  - Adult: Up to 2.4 g once daily, alternatively up to 2.4 g daily in divided doses

- Maintenance of remission of Crohn’s ileo-colitis
  - BY MOUTH
  - Adult: Up to 2.4 g daily in divided doses
ASACOL® FOAM ENEMA
Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
- BY RECTUM
- Adult: 1 g daily for 4–6 weeks, to be administered into the rectum

Treatment of acute attack of mild to moderate ulcerative colitis, affecting the descending colon
- BY RECTUM
- Adult: 2 g once daily for 4–6 weeks, to be administered into the rectum

ASACOL® SUPPOSITORIES
Treatment of acute attack of mild to moderate ulcerative colitis and maintenance of remission
- BY RECTUM
- Adult: 0.75–1.5 g daily in divided doses, last dose to be administered at bedtime

MEZAVANT® XL
Treatment of mild to moderate ulcerative colitis, acute attack
- BY MOUTH
- Adult: 2.4–4.8 g once daily, increased if necessary to 4.8 g once daily, review treatment at 8 weeks

Maintenance of remission of ulcerative colitis
- BY MOUTH
- Adult: 2.4 g once daily

OCTASA®
Treatment of mild to moderate ulcerative colitis, acute attack
- BY MOUTH
- Adult: 2.4–4.8 g once daily, alternatively 2.4–4.8 g daily in divided doses, dose over 2.4 g daily in divided doses only

Maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis
- BY MOUTH
- Adult: 1.2–2.4 g once daily, alternatively daily in divided doses

PENTASA® GRANULES
Treatment of mild to moderate ulcerative colitis, acute attack
- BY MOUTH
- Child 5–17 years (body-weight up to 40 kg): 10–20 mg/kg 3 times a day
- Child 5–17 years (body-weight 40 kg and above): 1–2 g twice daily, total daily dose may alternatively be given in 3–4 divided doses
- Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–4 divided doses

Maintenance of remission of ulcerative colitis
- BY MOUTH
- Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
- Child 5–17 years (body-weight 40 kg and above): 2 g once daily
- Adult: 2 g once daily

PENTASA® RETENTION ENEMA
Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission
- BY RECTUM
- Adult: 1 g once daily, dose to be administered at bedtime

Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region
- BY RECTUM
- Child 12–17 years: 1 g once daily, dose to be administered at bedtime

PENTASA® SUPPOSITORIES
Treatment of acute attack, ulcerative proctitis
- BY RECTUM
- Adult: 1 g daily for 2–4 weeks

Maintenance, ulcerative proctitis
- BY RECTUM
- Adult: 1 g daily

PENTASA® TABLETS
Treatment of mild to moderate ulcerative colitis, acute attack
- BY MOUTH
- Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–3 divided doses

Maintenance of remission of ulcerative colitis
- BY MOUTH
- Adult: 2 g once daily

SALOFALK® ENEMA
Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission
- BY RECTUM
- Adult: 2 g once daily, dose to be administered at bedtime

SALOFALK® GRANULES
Treatment of mild to moderate ulcerative colitis, acute attack
- BY MOUTH
- Child 5–17 years (body-weight up to 40 kg): 30–50 mg/kg once daily, dose preferably given in the morning, alternatively 10–20 mg/kg 3 times a day
- Child 5–17 years (body-weight 40 kg and above): 1.5–3 g once daily, dose preferably given in the morning, alternatively 0.5–1 g 3 times a day
- Adult: 1.5–3 g once daily, dose preferably taken in the morning, alternatively 0.5–1 g 3 times a day

Maintenance of remission of ulcerative colitis
- BY MOUTH
- Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
- Child 5–17 years (body-weight 40 kg and above): 500 mg 3 times a day
- Adult: 500 mg 3 times a day

SALOFALK® RECTAL FOAM
Treatment of mild ulcerative colitis affecting sigmoid colon and rectum
- BY RECTUM
- Child 12–17 years: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses
- Adult: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses

SALOFALK® SUPPOSITORIES
Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum, sigmoid colon and descending colon
- BY RECTUM
- Adult: 0.5–1 g 2–3 times a day, adjusted according to response, dose to be given using 500 mg suppositories

Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum
- BY RECTUM
- Adult: 1 g daily, preferably at bedtime, dose to be given using 1 g suppositories
Inflammatory bowel disease

**SALOFALK® TABLETS**

**Treatment of mild to moderate ulcerative colitis, acute attack**
- **BY MOUTH**
  - Child 5-17 years (body-weight up to 40 kg): 10–20 mg/kg 3 times a day
  - Child 5-17 years (body-weight 40 kg and above): 0.5–1 g 3 times a day
  - Adult: 0.5–1 g 3 times a day

**Maintenance of remission of ulcerative colitis**
- **BY MOUTH**
  - Child 5-17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
  - Child 5-17 years (body-weight 40 kg and above): 500 mg 3 times a day
  - Adult: 500 mg 3 times a day

- **UNLICENSED USE**

- **CONTRA-INDICATIONS**
  - Blood clotting abnormalities (in children)

- **CAUTIONS**
  - Elderly: pulmonary disease

- **INTERACTIONS** → Appendix 1: mesalazine

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Rare or very rare: Cholestasis exacerbated - drug fever - flatulence - nephritis
  - **SPECIFIC SIDE-EFFECTS**
    - Rare or very rare: Constipation
  - **PREGNANCY**
    - Negligible quantities cross placenta.
  - **BREAST FEEDING**
    - Diarrhoea reported in breast-fed infants, but negligible amounts of mesalazine detected in breast milk.
    - Monitor: Monitor breast-fed infant for diarrhoea.
  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
  - **RENAL IMPAIRMENT**
    - In adults: Use with caution. Avoid if eGFR less than 20 mL/minute/1.73 m².
    - In children: Use with caution. Avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**
  - **PENTASA® TABLETS** Tablets may be halved, quartered, or dispersed in water, but should not be chewed.
  - **PENTASA® GRANULES** Granules should be placed on tongue and washed down with water or orange juice without chewing.
    - In children: Contents of one sachet should be weighed and divided immediately before use; discard any remaining granules.
  - **SALOFALK® GRANULES** Granules should be placed on tongue and washed down with water without chewing.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - There is no evidence to show that any oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary.
  - Flavours of granule formulations of Salofalk® may include vanilla.
  - **PATIENT AND CARER ADVICE**
    - If it is necessary to switch a patient to a different brand of mesalazine, the patient should be advised to report any changes in symptoms. Some products may require special administration advice; patients and carers should be informed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Modified-release tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 21 (does not apply to Pentasa® tablets), 25 (does not apply to Pentasa® tablets)
  - **Mezavant XL** (Shire Pharmaceuticals Ltd)
    - Mesalazine 1.2 gram Mezavant XL 1200mg tablets | 60 tablet (PDR) £42.95 DT + £42.95
  - **Pentasa** (Ferring Pharmaceuticals Ltd)
    - Mesalazine 500 mg Pentasa 500mg modified-release tablets | 100 tablet (PDR) £30.74 DT + £30.74
    - Mesalazine 1 gram Pentasa 1g modified-release tablets | 60 tablet (PDR) £36.89 DT + £36.89

- **Foam**
  - **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polyglycols, propylene glycol, sodium metabisulphite.
  - **Salofalk** (Dr. Falk Pharma UK Ltd)
    - Mesalazine 1 gram per 1 application Salofalk 1g/application foam enema | 14 dose (PDR) £30.17 DT + £30.17

- **Gastro-resistant tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 5 (does not apply to Octasa®)
  - **Asacol MR** (Allergan Ltd)
    - Mesalazine 400 mg Asacol 400mg MR gastro-resistant tablets | 84 tablet (PDR) £27.45 DT + £27.45 | 168 tablet (PDR) £54.90
    - Asacol 800mg MR gastro-resistant tablets | 84 tablet (PDR) £54.90 DT + £54.90
  - **Octasa MR** (Tillotson Pharmaceuticals Ltd)
    - Mesalazine 400 mg Octasa 400mg MR gastro-resistant tablets | 90 tablet (PDR) £16.58 DT + £16.58 | 120 tablet (PDR) £22.10
    - Mesalazine 800 mg Octasa 800mg MR gastro-resistant tablets | 90 tablet (PDR) £40.38 | 180 tablet (PDR) £80.75 DT + £80.75
  - **Salofalk** (Dr. Falk Pharma UK Ltd)
    - Mesalazine 250 mg Salofalk 250mg gastro-resistant tablets | 100 tablet (PDR) £16.19 DT + £16.19
    - Mesalazine 500 mg Salofalk 500mg gastro-resistant tablets | 100 tablet (PDR) £32.38 DT + £32.38

- **Suppository**
  - **Pentasa** (Ferring Pharmaceuticals Ltd)
    - Mesalazine 1 gram Pentasa 1g suppositories | 28 suppository (PDR) £40.01 DT + £40.01
  - **Salofalk** (Dr. Falk Pharma UK Ltd)
    - Mesalazine 500 mg Salofalk 500mg suppositories | 30 suppository (PDR) £14.81 DT + £14.81
  - **Mesalazine 1 gram Salofalk 1g suppositories | 30 suppository (PDR) £29.62

- **Modified-release granules**
  - **CAUTIONARY AND ADVISORY LABELS** 25 (does not apply to Pentasa® granules)
  - **EXCIPIENTS**: May contain Asparatame
  - **Pentasa** (Ferring Pharmaceuticals Ltd)
    - Mesalazine 1 gram Pentasa 1g modified-release granules sachets sugar-free | 50 sachet (PDR) £30.74 DT + £30.74
    - Mesalazine 2 gram Pentasa 2g modified-release granules sachets sugar-free | 60 sachet (PDR) £73.78 DT + £73.78
  - **Salofalk** (Dr. Falk Pharma UK Ltd)
    - Mesalazine 1 gram Salofalk 1g gastro-resistant modified-release granules sachets sugar-free | 50 sachet (PDR) £28.74 DT + £28.74
    - Mesalazine 1.5 gram Salofalk 1.5g gastro-resistant modified-release granules sachets sugar-free | 60 sachet (PDR) £48.85 DT + £48.85
    - Mesalazine 3 gram Salofalk 3g gastro-resistant modified-release granules sachets sugar-free | 60 sachet (PDR) £97.70 DT + £97.70
44 Chronic bowel disorders

**Olsalazine sodium**

**INDICATIONS AND DOSE**

_Treatment of acute attack of mild ulcerative colitis_

- **BY MOUTH**
  - Adult: 1 g daily in divided doses, doses to be taken after meals, then increased if necessary up to 3 g daily in divided doses (max. per dose 1 g), dose to be increased over 1 week

_Maintenance of remission of mild ulcerative colitis_

- **BY MOUTH**
  - Adult: Maintenance 500 mg twice daily, dose to be taken after food

**INTERACTIONS** → Appendix 1: olsalazine

**SIDE-EFFECTS**

- Uncommon Paraesthesia - tachycardia
- Frequency not known Palpitations - vision blurred
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING**

Monitoring Monitor breast-fed infants for diarrhoea.

**RENAL IMPAIRMENT** Use with caution; manufacturer advises avoid in significant impairment.

**DIRECTIONS FOR ADMINISTRATION** Capsules can be opened and contents sprinkled on food.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

_Cautory and Advisory Labels 21_

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 500 mg Olsalazine 500mg tablets 60 tablet
    - **Price** £161.00 DT = £161.00

_Capsule_ Cautory and Advisory Labels 21

- **Olsalazine sodium (Non-proprietary)**
  - Olsalazine sodium 250 mg Olsalazine 250mg capsules 112 capsule
    - **Price** £144.00 DT = £144.00

**Sulfasalazine**

(Sulphasalazine)

**INDICATIONS AND DOSE**

_Treatment of acute attack of mild to moderate and severe ulcerative colitis_** Active Crohn’s disease_

- **BY MOUTH**
  - Adult: 1–2 g 4 times a day until remission occurs, corticosteroids may also be given, if necessary

- **BY RECTUM**
  - Adult: 0.5–1 g twice daily, administered alone or in conjunction with oral therapy, morning and night after a bowel movement

_Maintenance of remission of mild to moderate and severe ulcerative colitis_

- **BY MOUTH**
  - Adult: 500 mg 4 times a day

**INTERACTIONS** → Appendix 1: sulfasalazine

**SIDE-EFFECTS**

- Common or very common Insomnia - stomatitis - taste altered - tinnitus - urine abnormalities
- Uncommon Face oedema - seizure - vasculitis - vertigo
- Frequency not known Anaemia - appetite decreased - ataxia - cyanosis - encephalopathy - haematuria - hallucination - hepatic failure - hypoprothrombinemia - lymphadenopathy - macrocytosis - meningitis aseptic - methaemoglobinemia - nephrotic syndrome - parotitis - periorbital oedema - pseudomembranous enterocolitis - serum sickness - severe cutaneous adverse reactions (SCARs) - smell disorders - systemic lupus erythematosus (SLE) - yellow discolouration of body fluids

**SIDE-EFFECTS, FURTHER INFORMATION** Incidence of side-effects increases with higher doses.

**Blood disorders** Haematological abnormalities occur usually in the first 3 to 6 months of treatment—discontinue if these occur.

**PREGNANCY** Theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother.

**BREAST FEEDING** Small amounts in milk (1 report of bloody diarrhoea); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT** Risk of toxicity, including crystalluria, in moderate impairment—ensure high fluid intake. Avoid in severe impairment.

**MONITORING REQUIREMENTS**

- Blood disorders Close monitoring of full blood counts (including differential white cell count and platelet count) is necessary initially, and at monthly intervals during the first 3 months.
- Renal function Although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory.
- Liver function Liver function tests should be performed at monthly intervals for first 3 months.

**PATIENT AND CARER ADVICE**

Contact lenses Some soft contact lenses may be stained.

**IMPORTANT SAFETY INFORMATION**

SAFE PRACTICE

Sulfasalazine has been confused with sulfadiazine; care must be taken to ensure the correct drug is prescribed and dispensed.

- **CAUTIONS**
  - Acute porphyrias p. 1058 · G6PD deficiency · history of allergy · history of asthma · maintain adequate fluid intake · risk of haemato logical toxicity · risk of hepatic toxicity · slow acetylator status

- **INTERACTIONS** → Appendix 1: sulfasalazine

- **SIDE-EFFECTS**
  - Common or very common Insomnia - stomatitis - taste altered - tinnitus - urine abnormalities
  - Uncommon Face oedema - seizure - vasculitis - vertigo
  - Frequency not known Anaemia - appetite decreased - ataxia - cyanosis - encephalopathy - haematuria - hallucination - hepatic failure - hypoprothrombinemia - lymphadenopathy - macrocytosis - meningitis aseptic - methaemoglobinemia - nephrotic syndrome - parotitis - periorbital oedema - pseudomembranous enterocolitis - serum sickness - severe cutaneous adverse reactions (SCARs) - smell disorders - systemic lupus erythematosus (SLE) - yellow discolouration of body fluids

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- Renal function Although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory.
- Liver function Liver function tests should be performed at monthly intervals for first 3 months.

**PATIENT AND CARER ADVICE**

Contact lenses Some soft contact lenses may be stained.
**INDICATIONS AND DOSE**

**BUDENOFALK® CAPSULES**

Mild to moderate Crohn’s disease affecting the ileum or ascending colon
- **BY MOUTH**
  - Adult: 9 mg once daily for 8 weeks, to be taken in the morning, alternatively 3 mg 3 times a day for 8 weeks, reduce dose gradually over two weeks following treatment

Collagenous colitis
- **BY MOUTH**
  - Adult: 9 mg once daily for 8 weeks, to be taken in the morning, reduce dose gradually over two weeks following treatment

Autoimmune hepatitis, induction of remission
- **BY MOUTH**
  - Adult: 3 mg 3 times a day

Autoimmune hepatitis, maintenance
- **BY MOUTH**
  - Adult: 3 mg twice daily

**BUDENOFALK® GRANULES**

Mild to moderate Crohn’s disease affecting the ileum or ascending colon | Collagenous colitis
- **BY MOUTH**
  - Adult: 9 mg once daily for 8 weeks, to be taken in the morning about 30 minutes before breakfast, reduce dose gradually over two weeks following treatment

**BUDENOFALK® RECTAL FOAM**

Ulcerative colitis affecting sigmoid colon and rectum
- **BY RECTUM**
  - Adult: 1 metered application once daily for up to 8 weeks

**DOSE EQUIVALENCE AND CONVERSION**

For **Budenofalk®** rectal foam: 1 metered application is equivalent to budesonide 2 mg.

**CORTIMENT®**

Induction of remission of mild-to-moderate active ulcerative colitis
- **BY MOUTH**
  - Adult: 9 mg once daily, to be taken in the morning

Mild to moderate Crohn’s disease affecting the ileum or ascending colon
- **BY MOUTH**
  - Adult: 9 mg once daily for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment, to be taken in the morning

**ENTOCORT® CAPSULES**

Active microscopic colitis
- **BY MOUTH**
  - Adult: 9 mg once daily, to be taken in the morning

**ENTOCORT® ENEMA**

Ulcerative colitis involving rectal and recto-sigmoid disease
- **BY RECTUM**
  - Adult: 1 enema daily for 4 weeks, to be administered at bedtime

**CAUTIONS**

Autoimmune hepatitis

**INTERACTIONS**

Appendix 1: corticosteroids
**IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES, ANTI-LYMPHOCYTE**

**Vedolizumab**

**DRUG ACTION**
Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is expressed on gut homing T helper lymphocytes and causes a reduction in gastrointestinal inflammation.

**INDICATIONS AND DOSE**
Moderate to severe active ulcerative colitis in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 10 weeks of initial dose

Moderate to severe active Crohn's disease in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if no response is observed, an additional dose of 300 mg may be given 10 weeks after initial dose; if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 14 weeks of initial dose

**CONTRA-INDICATIONS**
Severe active infection

**CAUTIONS**
Controlled chronic severe infection - history of recurring severe infection - previous treatment with natalizumab (wait at least 12 weeks between natalizumab use and initiation of vedolizumab unless potential benefit outweighs risk) - previous treatment with rituximab

**CAUTIONS, FURTHER INFORMATION**
Risk of infection. Patients must be screened for tuberculosis before starting treatment; if latent tuberculosis is diagnosed, appropriate treatment must be initiated prior to vedolizumab treatment; if tuberculosis is diagnosed during treatment, discontinue vedolizumab until infection is resolved.

Patients should be brought up to date with current immunisation schedule before initiating treatment.

**INTERACTIONS**
- Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**
Common or very common Arthralgia - constipation - cough - fatigue - fever - gastrointestinal discomfort - gastrointestinal disorders - headache - hypertension - increased risk of infection - muscle spasms - muscle
Irritable bowel syndrome

Description of condition
Irritable bowel syndrome (IBS) is a common, chronic, relapsing, and often life-long condition, mainly affecting people aged between 20 and 30 years. It is more common in women. Symptoms include abdominal pain or discomfort, disordered defaecation (either diarrhoea, or constipation with straining, urgency, and incomplete evacuation), passage of mucus, and bloating. Symptoms are usually relieved by defaecation. Obtaining an accurate clinical diagnosis of IBS prior to treatment is crucial.

Aims of treatment
The treatment of IBS is focused on symptom control, in order to improve quality of life.

Non-drug treatment

Diet and lifestyle changes are important for effective self-management of IBS. Patients should be encouraged to increase physical activity, and advised to eat regularly, without missing meals or leaving long gaps between meals. Dietary advice should also include, limiting fresh fruit consumption to no more than 3 portions per day. The fibre intake of patients with IBS should be reviewed. If an increase in dietary fibre is required, soluble fibre such as ispaghula husk p. 55, or foods high in soluble fibre such as oats, are recommended. Intake of insoluble fibre (e.g. bran) and ‘resistant starch’ should be reduced or discouraged as they may exacerbate symptoms. Fluid intake (mostly water) should be increased to at least 8 cups each day and the intake of caffeine, alcohol and fizzy drinks reduced. The artificial sweetener sorbitol should be avoided in patients with diarrhoea. Where probiotics are being used, continue for at least 4 weeks while monitoring the effect.

If a patient’s symptoms persist following lifestyle and dietary advice, single food avoidance and exclusion diets may be an option under the supervision of a dietitian or medical specialist.

BNF 78

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NICE decisions

Vedolizumab for treating moderately to severely active Crohn’s disease after prior therapy (August 2015) NICE TA352

Vedolizumab is recommended as an option for the treatment of moderate to severe active Crohn’s disease in adults if:

- a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or
- a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contra-indicated,
- and the manufacturer provides vedolizumab with the discount agreed in the patient access scheme.

Vedolizumab should be given as a planned course of treatment until treatment fails, or surgery is needed, or until 12 months after starting treatment, whichever is the shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

Patients currently receiving vedolizumab whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (July 2015) that vedolizumab (Entyvio®) is accepted for restricted use within NHS Scotland for the treatment of adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to a TNF-α antagonist; it is also accepted for use in NHS Scotland for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist.

- MEDICINAL FORMS
  - Powder for solution for infusion
  - Entyvio (Takeda UK Ltd)
  - Vedolizumab 300 mg

1.4 Irritable bowel syndrome

24-Feb-2016
Drug treatment

The choice of drug treatment depends on the nature and severity of the symptoms. Many drug treatment options for IBS are available over-the-counter.

Antispasmodics (such as alverine citrate p. 86, mebeverine hydrochloride p. 86 and peppermint oil below) can be taken in addition to dietary and lifestyle changes. A laxative (excluding lactulose p. 56 as it may cause bloating) can be used to treat constipation. Patients who have not responded to laxatives from the different classes and who have had constipation for at least 12 months, can be treated with linaclotide below. Loperamide hydrochloride p. 66 is the first-line choice of anti-motility drug for relief of diarrhoea. Patients with IBS should be advised how on to adjust their dose of laxative or anti-motility drug according to stool consistency, with the aim of achieving a soft, well-formed stool.

A low-dose tricyclic antidepressant, such as amitriptyline hydrochloride p. 372 [unlicensed indication], can be used for abdominal pain or discomfort as a second-line option in patients who have not responded to antispasmodics, anti-motility drugs, or laxatives. A selective serotonin reuptake inhibitor may be considered in those who do not respond to a tricyclic antidepressant [unlicensed indication].

Psychological intervention can be offered to patients who have no relief of IBS symptoms after 12 months of drug treatment.

Useful Resources


ANTISPASMODICS

Mebeverine with ispaghula husk

04-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, mebeverine hydrochloride p. 86, ispaghula husk p. 55.

- **INDICATIONS AND DOSE**
  - Irritable bowel syndrome
    - **BY MOUTH**
      - Child 12-17 years: 1 sachet twice daily, in water, morning and evening, 30 minutes before food and 1 sachet daily if required, taken 30 minutes before midday meal
      - Adult: 1 sachet twice daily, in water, morning and evening, 30 minutes before food and 1 sachet daily if required, taken 30 minutes before midday meal

- **DIRECTIONS FOR ADMINISTRATION**
  Contents of one sachet should be stirred into a glass (approx. 150 mL) of cold water and drunk immediately.

- **PATIENT AND CARER ADVICE**
  Patients or carers should be given advice on how to administer ispaghula husk with mebeverine granules.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Effervescent granules**
  - **CAUTIONARY AND ADVISORY LABELS** 13, 22
  - **EXCipients:** May contain Aspartame
  - **ELECTROLYTES:** May contain Potassium
  - **Fybogel Mebeverine** (Reckitt Benckiser Healthcare (UK) Ltd)
    - Mebeverine hydrochloride 135 mg, Ispaghula husk
    - 3.5 gram Fybogel Mebeverine effervescent granules sachets orange sugar-free | 10 sachet (£4.81 DT = £4.81)

Peppermint oil

- **INDICATIONS AND DOSE**
  - **COLPERMIN ®**
    - Relief of abdominal colic and distension, particularly in irritable bowel syndrome
      - **BY MOUTH**
        - Child 15-17 years: 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water
        - Adult: 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water

  - **MINTEC ®**
    - Relief of abdominal colic and distension, particularly in irritable bowel syndrome
      - **BY MOUTH**
        - Adult: 1–2 capsules 3 times a day for up to 2–3 months if necessary, dose to be taken before meals, swallowed whole with water

- **CAUTIONS**
  - Sensitivity to menthol

- **INTERACTIONS**
  - Appendix 1: peppermint oil

- **SIDE-EFFECTS**
  - Ataxia · bradycardia · gastrointestinal discomfort · gastrooesophageal reflux disease · headache · nausea · paraesthesia · rash erythematous · tremor · vomiting

- **PREGNANCY**
  - Not known to be harmful.

- **BREAST FEEDING**
  - Significant levels of menthol in breast milk unlikely.

- **DIRECTIONS FOR ADMINISTRATION**
  Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Gastro-resistant capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 5, 22, 25
  - **Mintec** (Almirall Ltd)
    - Peppermint oil 200 microtitre Mintec 0.2ml gastro-resistant capsules | 84 capsule (£0.40 DT = £0.70)

  - **Modified-release capsule**
    - **CAUTIONARY AND ADVISORY LABELS** 5, 22, 25
    - **EXCipients:** May contain Arachis (peanut) oil
    - **Colpermin** (Johnson & Johnson Ltd)
      - Peppermint oil 200 microtitre Colpermin gastro-resistant modified-release capsules | 20 capsule (£3.77 | 100 capsule (£14.33 DT = £14.33)

LAXATIVES > GUANYLATE CYCLASE-C RECEPTOR AGONISTS

Linaclotide

- **INDICATIONS AND DOSE**
  - Moderate to severe irritable bowel syndrome with constipation
    - **BY MOUTH**
      - Adult: 290 micrograms once daily, dose to be taken at least 30 minutes before meals, review treatment if no response after 4 weeks

- **CONTRA-INDICATIONS**
  - Gastro-intestinal obstruction · inflammatory bowel disease

- **CAUTIONS**
  - Predisposition to fluid and electrolyte disturbances

- **SIDE-EFFECTS**
  - Common or very common: Diarrhoea · dizziness · gastrointestinal discomfort · gastrointestinal disorders
  - Uncommon: Appetite decreased · dehydration · haemorrhage · hypokalaemia · nausea · postural hypotension · vomiting

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1.5 Short bowel syndrome

### Short bowel syndrome

**Description of condition**

Patients with a shortened bowel due to large surgical resection (with or without stoma formation) may require medical management to ensure adequate absorption of nutrients and fluid. Absorption of oral medication is also often impaired.

**Aims of treatment**

The management of short bowel syndrome focuses on ensuring adequate nutrition and drug absorption, thereby reducing the risk of complications resulting from these effects.

**Drug treatment**

#### Nutritional deficiencies

- **Antimotility drugs**
  - Loperamide hydrochloride p. 66 and codeine phosphate p. 454 reduce intestinal motility and thus exert antidiarrhoeal actions. Loperamide hydrochloride is preferred as it is not sedative and does not cause dependence or fat malabsorption. High doses of loperamide hydrochloride [unlicensed] may be required in patients with a short bowel due to disrupted enterohepatic circulation and rapid gastrointestinal transit time. If the desired response is not obtained with loperamide hydrochloride, codeine phosphate may be added to therapy.
  - Co-phenotrope p. 66 has traditionally been used alone or in combination with other medications to help decrease faecal output. Co-phenotrope crosses the blood–brain barrier and can produce central nervous system side-effects, which may limit its use; the potential for dependence and anticholinergic effects may also restrict its use.

- **Colestyramine**
  - In patients with an intact colon and less than 100 cm of ileum resected, colestyramine p. 197 can be used to bind the unabsorbed bile salts and reduce diarrhoea. When colestyramine is given to these patients, it is important to monitor for evidence of fat malabsorption (steatorrhoea) or fat-soluble vitamin deficiencies.

- **Antisecretory drugs**
  - Drugs that reduce gastric acid secretion reduce jejunoostomy output. Omeprazole p. 88 is readily absorbed in the duodenum and upper small bowel, but if less than 50 cm of jejunum remains, it may need to be given intravenously.
  - Octreotide [unlicensed indication] reduces ileostomy diarrhoea and large volume jejunostomy output by inhibiting multiple pro-secretory substances. There is insufficient evidence to establish its role in the management of short bowel syndrome.

- **Growth factors**
  - Growth factors can be used to facilitate intestinal adaptation after surgery in patients with short bowel syndrome, thus enhancing fluid, electrolyte, and micronutrient absorption.
  - Opioid antagonists should have been optimised.
  - Antidiarrhoeal agents, intravenous fluids, or oral rehydration salts.
  - Use of a proton pump inhibitor alone does not eliminate the need for further intervention for fluid control (such as antimitotic agents, intravenous fluids, or oral rehydration salts).

- **Enteric-coated and modified-release preparations**
  - Enteric-coated and modified-release preparations are unsuitable for use in patients with short bowel syndrome.
50 Constipation and bowel cleansing

AMINO ACIDS AND DERIVATIVES

Teduglutide

- **DRUG ACTION** Teduglutide is an analogue of human glucagon-like peptide-2 (GLP-2), which preserves mucosal integrity by promoting growth and repair of the intestine.

- **INDICATIONS AND DOSE**
  - **Short bowel syndrome (initiated under specialist supervision)**
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: 0.05 mg/kg once daily, dose to be administered to alternating quadrants of the abdomen; alternatively the thigh can be used, for optimal injection volume per body weight, consult product literature. Review treatment after 6 months

- **CONTRA-INDICATIONS** Active or suspected malignancy - history of gastro-intestinal malignancy (in previous 5 years)

- **CAUTIONS** Abrupt withdrawal of parenteral support (reduce gradually with concomitant monitoring of fluid status) - cardiac insufficiency - cardiovascular disease - colo-rectal polyps - hypertension

- **SIDE-EFFECTS**
  - **Common or very common** Anxiety · appetite decreased · congestive heart failure · cough · dysphoria · fluid imbalance · gallbladder disorders · gastrointestinal discomfort · gastrointestinal disorders · gastrointestinal stoma complication · headache · influenza like illness · insomnia · nausea · pancreatitis · peripheral oedema · respiratory tract infection · vomiting
  - **Uncommon** Syncope

- **ALLERGY AND CROSS-SENSITIVITY** Manufacturer advises caution in patients with tetracycline hypersensitivity.

- **PREGNANCY** Specialist sources indicate use if necessary—no human data available.

- **BREAST FEEDING** Manufacturer advises avoid—toxicity in animal studies.

- **RENAIL IMPAIRMENT**
  - **Dose adjustments** Manufacturer advises use half the daily dose in moderate or severe impairment and end-stage renal disease.

- **MONITORING REQUIREMENTS** Manufacturer advises monitoring of small bowel function, gall bladder, bile ducts and pancreas during treatment.

- **TREATMENT CESSATION** Caution when discontinuing treatment—risk of dehydration.

- **PATIENT AND CARER ADVICE** Patients with cardiovascular disease should seek medical attention if they notice sudden weight gain, swollen ankles or dyspnoea—may indicate increased fluid absorption.

Other drugs used for Short bowel syndrome Cimetidine, p. 74

LAXATIVES

Citric acid with magnesium carbonate

- **INDICATIONS AND DOSE**
  - **Bowel evacuation for surgery, colonoscopy or radiological examination**
    - **BY MOUTH**
      - Child 5–9 years: One-third of a sachet to be given at 8 a.m. the day before the procedure and, one-third of a sachet to be given between 2 and 4 p.m. the day before the procedure
      - Child 10–17 years: 0.5–1 sachet, given at 8 a.m. the day before the procedure and 0.5–1 sachet, given between 2 and 4 p.m. the day before the procedure
      - Adult: 1 sachet, given at 8 a.m. the day before the procedure and 1 sachet, given between 2 and 4 p.m. the day before the procedure, use half the dose in frail elderly patients

- **CONTRA-INDICATIONS** Acute severe colitis · gastric retention · gastro-intestinal obstruction · gastro-intestinal perforation · toxic megacolon

- **CAUTIONS** Children · colitis (avoid if acute severe colitis) · dehydrated · elderly · hypovolaemia (should be corrected before administration of bowel cleansing preparations) · impaired gag reflex or possibility of regurgitation or aspiration · patients with fluid and electrolyte disturbances

- **INTERACTIONS** Adequate hydration should be maintained during treatment.

- **SIDE-EFFECTS**
  - **Common or very common** Gastrointestinal discomfort · nausea · vomiting
  - **Uncommon** Dehydration · dizziness · electrolyte imbalance · headache

- **PREGNANCY** Use with caution.

- **BREAST FEEDING** Use with caution.

- **RENAIL IMPAIRMENT**
  - In adults Avoid if eGFR less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.
  - In children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia.

Other drugs used for Bowel cleansing Bisacodyl, p. 61 · Docusate sodium, p. 61 · Magnesium sulfate, p. 1051

www.getintopharma.com
Macrogol 3350 with anhydrous sodium sulfate, ascorbic acid, potassium chloride, sodium ascorbate and sodium chloride

(Polyethylene glycols)

01-Mar-2018

- **Indications and dose**

  MOVIPREP®

  Bowel cleansing [before any procedure requiring a clean bowel]
  
  - **By mouth**
  
  Adult: 1 litre daily for 2 doses; first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure; alternatively 2 litres daily for 1 dose; reconstituted solution to be taken on the evening before the procedure, or on the morning of the procedure, treatment should be completed at least 1 hour before clinical procedures conducted without general anaesthesia, and at least 2 hours before clinical procedures conducted under general anaesthesia

  PLENVU®

  Bowel cleansing [before any procedure requiring a clean bowel]
  
  - **By mouth**
  
  Adult: 500 mL daily for 2 doses; first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively 1 litre daily in 2 divided doses, reconstituted solution to be taken either on the evening before the procedure, or in the morning of the procedure—separate doses by at least 1 hour, treatment should be completed at least 1 hour before clinical procedures conducted without general anaesthesia, and at least 2 hours before clinical procedures conducted under general anaesthesia

- **Contra-indications**

  Disorders of gastric emptying - G6PD deficiency - gastrointestinal obstruction - gastrointestinal perforation - ileus - toxic megacolon

- **Caution**

  Debilitated patients - dehydration (correct before administration) - impaired consciousness - impaired gag reflex or possibility of regurgitation or aspiration - moderate to severe cardiac impairment - patients at risk of arrhythmia (including those with thyroid disease or electrolyte imbalance) - severe acute inflammatory bowel disease

- **Interactions**

  → Appendix 1: bowel cleansing preparations

- **Side-effects**

  - Common or very common: Chills - dehydration - dizziness - fever - gastrointestinal discomfort - headaches - hunger - malaise - nausea - sleep disorder - thirst - vomiting
  
  
  - Frequency not known: Flatulence - hyponatraemic seizure

- **Further information**

  Abdominal pain is usually transient and can be reduced by taking preparation more slowly.

- **Pregnancy**

  Manufacturer advises use only if essential—no or limited information available.

- **Breast feeding**

  Manufacturer advises use only if essential—no information available.

- **Renal impairment**

  Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

- **Monitoring requirements**

  Manufacturer advises consider monitoring baseline and post-treatment electrolytes, renal function and ECG as appropriate, in debilitated patients, those with significant renal impairment, arrhythmia, or at risk of electrolyte imbalance.

- **Directions for administration**

  PLENVU®

  Manufacturer advises the contents of the single sachet for Dose 1 should be made up to 500 mL with water and taken over 30 minutes; the contents of the 2 sachets (A and B) should be made up to 500 mL with water and taken over 30 minutes. Each dose should be followed by 500 mL of clear fluid taken over 30 minutes.

  MOVIPREP®

  Manufacturer advises one pair of sachets (A and B) should be made up to 1 litre with water and taken over 1–2 hours; 1 litre of other clear fluid should also be taken during treatment.

- **Prescribing and dispensing information**

  PLENVU®

  Dose 1 (single sachet) when reconstituted up to 500 mL with water provides Na+: 160.9 mmol, K+: 13.3 mmol, Cl−: 47.6 mmol; Dose 2 (sachets A and B) when reconstituted up to 500 mL with water provides Na+: 297.6 mmol, K+: 16.1 mmol, Cl−: 70.9 mmol.

  MOVIPREP®

  1 pair of sachets (A+B) when reconstituted up to 1 litre with water provides Na+: 181.6 mmol (Na+: 56.2 mmol absorbable), K+: 14.2 mmol, Cl−: 59.8 mmol.

- **Patient and carer advice**

  Manufacturer advises solid food should not be taken during treatment until procedure completed.

- **Medicinal forms**

  There can be variation in the licensing of different medicines containing the same drug.

  **Oral powder**

  **Cautionary and advisory labels** 10, 13

  **Excipients:** May contain Aspartame

  **Electrolytes:** May contain Chloride, potassium, sodium

  MOVIPREP (Forum Health Products Ltd)

  MOVIPREP oral powder sachets sugar-free | 1 sachet £0.36

  PLENVO (Forum Health Products Ltd)

  PLENVO oral powder sachets sugar-free | 3 sachet £12.43
Macrogol 3350 with anhydrous sodium sulfate, potassium chloride, sodium bicarbonate and sodium chloride
*(Formulated as a bowel cleansing preparation)*

- **INDICATIONS AND DOSE**
  - Bowel cleansing before radiological examination, colonoscopy, or surgery
    - **INITIALLY BY MOUTH**
    - Adult: Initially 2 litres daily for 2 doses: first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively (by mouth) initially 250 mL every 10–15 minutes, reconstituted solution to be administered, alternatively (by nasogastric tube) initially 20–30 mL/minute, starting on the day before procedure until 4 litres have been consumed

- **CONTRA-INDICATIONS**
  - Acute severe colitis - gastric retention - gastro-intestinal obstruction - gastro-intestinal perforation - toxic megacolon

- **CAUTIONS**
  - Colitis (avoid if acute severe colitis) - debilitated patients - elderly - fluid and electrolyte disturbances - heart failure - hypovolaemia (should be corrected before administration of bowel cleansing preparations) - impaired gag reflex or possibility of regurgitation or aspiration

- **INTERACTIONS**
  - Appendix 1: bowel cleansing preparations

- **SIDE-EFFECTS**

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Abdominal pain is usually transient and can be reduced by taking preparation more slowly.

- **PREGNANCY**
  - Manufacturers advise use only if essential — no information available.

- **BREAST FEEDING**
  - Manufacturers advise use only if essential — no information available.

- **MONITORING REQUIREMENTS**
  - Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

- **DIRECTIONS FOR ADMINISTRATION**
  - 1 sachet should be reconstituted with 1 litre of water. Flavouring such as clear fruit cordials may be added if required. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Each Klean-Prep® sachet provides Na+: 125 mmol, K+: 10 mmol, Cl: 35 mmol and HCO₃⁻ 20mmol when reconstituted with 1 litre of water.

- **PATIENT AND CARER ADVICE**
  - Solid food should not be taken for 2 hours before starting treatment. Adequate hydration should be maintained during treatment. Treatment can be stopped if bowel motions become watery and clear.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Powder**
  - **CAUTIONARY AND ADVISORY LABELS** 10, 13
  - **EXCIPIENTS:** May contain Aspartame
  - **ELECTROLYTES:** May contain Bicarbonate, chloride, potassium, sodium
  - **Klean-Prep** (Forum Health Products Ltd)
  - Potassium chloride 742.5 mg, Sodium chloride 1.465 gram, Sodium bicarbonate 1.685 gram, Sodium sulfate anhydrous

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LAXATIVES

Magnesium citrate with sodium picosulfate
*(Formulated as a bowel cleansing preparation)*

- **INDICATIONS AND DOSE**
  - **CITRAFLEET® SACHETS**
    - Bowel evacuation on day before radiological examination, endoscopy, or surgery
      - **BY MOUTH**
      - Adult: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours
      - Child 2–3 years: 0.5 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
      - Child 4–8 years: 1 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
      - Child 9–17 years: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours
      - Adult: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours

  - **PICOLAX® SACHETS**
    - Bowel evacuation on day before radiological procedure, endoscopy, or surgery
      - **BY MOUTH**
      - Child 1 year: 0.25 sachet taken before 8 a.m., then 0.25 sachet after 6–8 hours
      - Child 2–3 years: 0.5 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
      - Child 4–8 years: 1 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
      - Child 9–17 years: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours
      - Adult: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours

- **CONTRA-INDICATIONS**
  - Acute severe colitis - ascites - congestive cardiac failure - gastric retention - gastro-intestinal obstruction - gastro-intestinal perforation - gastro-intestinal ulceration - toxic megacolon

- **CAUTIONS**
  - Cardiac disease (avoid in congestive cardiac failure) - children - colitis (avoid if acute severe colitis) - debilitated patients - elderly - fluid and electrolyte disturbances - hypovolaemia (should be corrected before administration) - impaired gag reflex or possibility of regurgitation or aspiration - recent gastro-intestinal surgery

- **SIDE-EFFECTS**
  - **Common or very common** Gastrointestinal discomfort - headache - nausea
  - **Uncommon** Confusion - electrolyte imbalance - gastrointestinal disorders - seizures - skin reactions - vomiting

- **PREGNANCY**
  - Caution.

- **BREAST FEEDING**
  - Caution.

- **HEPATIC IMPAIRMENT**
  - Avoid in hepatic coma if risk of renal failure.

- **RENAL IMPAIRMENT**
  - In adults: Avoid if eGFR less than 30 mL/minute/1.73 m² — risk of hypermagnesaemia.
  - In children: Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m² — risk of hypermagnesaemia.

- **DIRECTIONS FOR ADMINISTRATION**
  - One sachet of sodium picosulfate with magnesium citrate powders should be reconstituted with 150 mL (approx. half a glass) of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking.
**Descripción de la condición**

La constipación es defecación que es insatisfactoria porque de frecuentes heces, dificultad de deposición, o incompleta evacuación. Puede ocurrir en la edad y es comúnmente visto en mujeres, el ancianos, y durante inmadura evacuación. Se puede presentar en cualquier edad y es un problema en la digestión y motilidad intestinal. Los pacientes y los cuidadores deben ser informados de que el calor se genera durante el reconstrucción y que los líquidos recomendados durante el procedimiento. Se recomienda el uso de co-danthramer y co-danthrusate en la constipación de los pacientes hospitalizados. El líquido parafinas p. 61 también se puede usar como un lubricante para el uso de enemas y promover un movimiento intestinal. El uso de co-danthramer y co-danthrusate se limitan en la constipación de los pacientes que presentan hipertensión y otros síntomas como astenia, dolor abdominal y pérdida de peso. Se ha utilizado la gelatina de aracíis y el aceite de girasol en la constipación de los pacientes que no toleran el bran. Methylcellulose también actúa como un estimulante. 

**Sintomáticos laxativos**

Los laxativos pueden ser de uso oral o rectal. Se pueden clasificar en diferentes categorías: estímulos, osmóticos y de masa. Los laxativos deben ser usados con cuidado y evitar el abuso. Se puede ver en las tablas de dosis y precauciones.

**Otros usos de la constipación**

Linaclotide p. 48 es un guanylate ciclasa-C receptor agonista que es licenciado para el tratamiento de la constipación en adultos y mayores. Incrementa la excreción de líquido intestinal y reduce la depresión, y disminuye el dolor. 

**Prucalopride p. 60 es un agonista de serotonina 5HT4 receptor con propiedades prokinéticas. Se ha licenciado para el tratamiento de la constipación crónica en adultos.**

**Preparaciones de limpieza fecal**

Las preparaciones de limpieza fecal son usadas después de la cirugía, colonoscopia o radiológicamente para asegurarse que el paciente está libre de contenido sólido; ejemplos incluyen macroglis 3350 con anhidrados de sodio sulfato, potasio y otros aditivos. 

**Referencias**


chloride, sodium bicarbonate and sodium chloride p. 52, citric acid with magnesium carbonate p. 50, magnesium citrate with sodium picosulfate p. 52 and sodium acid phosphate with sodium phosphate p. 59. Bowel cleansing treatments are not treatments for constipation.

Management

Short-duration constipation

In the management of short-duration constipation (where dietary measures are ineffective) treatment should be started with a bulk-forming laxative, ensuring adequate fluid intake. If stools remain hard, add or switch to an osmotic laxative. If stools are soft but difficult to pass or the person complains of inadequate emptying, a stimulant laxative should be added.

Opioid-induced constipation

See also Constipation under Prescribing in palliative care p. 25. In patients with opioid-induced constipation, an osmotic laxative (or docusate sodium to soften the stools) and a stimulant laxative is recommended. Bulk-forming laxatives should be avoided. Naloxegol p. 65 is recommended for the treatment of opioid-induced constipation when response to other laxatives is inadequate.

Methylnaltrexone bromide p. 64 is licensed for the treatment of opioid-induced constipation when response to other laxatives is inadequate. Manufacturer advises that in patients receiving palliative care, methylmaltrexone bromide should be used as an adjunct to existing laxative therapy.

Faecal impaction

The treatment of faecal impaction depends on the stool consistency. In patients with hard stools, a high dose of an oral macrogol (such as macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride) may be considered. In those with soft stools, or with hard stools after a few days treatment with a macrogol, an oral stimulant laxative should be started or added to the previous treatment. If the response to oral laxatives is inadequate, for soft stools consider rectal administration of bisacodyl, and for hard stools rectal administration of glycerol, or glycerol plus bisacodyl. Alternatively, a docusate sodium or sodium citrate enema p. 789 may be tried.

If the response is still insufficient, a sodium acid phosphate with sodium phosphate or arachis oil retention enema may be necessary. For hard faeces it can be helpful to give the arachis oil enema p. 60 overnight before giving a sodium acid phosphate with sodium phosphate p. 59 or sodium citrate enema p. 789 the following day. Enemas may need to be repeated several times to clear hard impacted faeces.

Chronic constipation

In the management of chronic constipation, treatment should be started with a bulk-forming laxative, whilst ensuring good hydration. If stools remain hard, add or change to an osmotic laxative such as a macrogol. Lactulose p. 56 is an alternative if macrogols are not effective, or not tolerated. If the response is inadequate, a stimulant laxative can be added. The dose of laxative should be adjusted gradually to produce one or two soft, formed stools per day.

If at least two laxatives (from different classes) have been tried at the highest tolerated recommended doses for at least 6 months, the use of prucalopride p. 60 (in women only) should be considered. If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.

Laxatives can be slowly withdrawn when regular bowel movements occur without difficulty, according to the frequency and consistency of the stools. If a combination of laxatives has been used, reduce and stop one laxative at a time; if possible, the stimulant laxative should be reduced first. However, it may be necessary to also adjust the dose of the osmotic laxative to compensate.

Constipation in pregnancy and breast-feeding

If dietary and lifestyle changes fail to control constipation in pregnancy, fibre supplements in the form of bran or wheat are likely to help women experiencing constipation in pregnancy, and raise no serious concerns about side-effects to the mother or fetus. A bulk-forming laxative is the first choice during pregnancy if fibre supplements fail. An osmotic laxative, such as lactulose, can also be used. Bisacodyl p. 61 or senna p. 63 may be suitable if a stimulant effect is necessary but use of senna should be avoided near term or if there is a history of unstable pregnancy. Stimulant laxatives are more effective than bulk-forming laxatives but are more likely to cause side-effects (diarrhoea and abdominal discomfort), reducing their acceptability to patients. Docusate sodium p. 61 and glycerol suppositories p. 63 can also be used. A bulk-forming laxative is the first choice during breastfeeding, if dietary measures fail. Lactulose or a macrogol may be used if stools remain hard. As an alternative, a short course of a stimulant laxative such as bisacodyl or senna can be considered.

Constipation in children

Early identification of constipation and effective treatment can improve outcomes for children. Without early diagnosis and treatment, an acute episode of constipation can lead to anal fissure and become chronic.

The first-line treatment for children with constipation requires the use of a laxative in combination with dietary modification or with behavioural interventions. Diet modification alone is not recommended as first-line treatment.

In children an increase in dietary fibre, adequate fluid intake, and exercise is advised. Diet should be balanced and contain fruits, and vegetables, high-fibre bread, baked beans, and wholegrain breakfast cereals. Unprocessed bran (which may cause bloating and flatulence and reduces the absorption of micronutrients) is not recommended. If faecal impaction is not present (or has been treated), the child should be treated promptly with a laxative. A macrogol (such as macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride p. 57) is preferred as first-line management. If the response is inadequate, add a stimulant laxative or change to a stimulant laxative if the first-line therapy is not tolerated. If stools remain hard, lactulose or another laxative with softening effects, such as docusate sodium can be added.

In children with chronic constipation, laxatives should be continued for several weeks after a regular pattern of bowel movements or toilet training is established. The dose of laxatives should then be tapered gradually, over a period of months, according to response. Some children may require laxative therapy for several years.

A shorter duration of laxative treatment may be possible in some children with a short history of constipation.

Laxatives should be administered at a time that produces an effect that is likely to fit in with the child’s toilet routine.

Faecal impaction in children

Treatment of faecal impaction may initially increase symptoms of soiling and abdominal pain. In children over 1 year of age with faecal impaction, an oral preparation containing a macrogol (such as macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride) is used to clear faecal mass and to establish and maintain soft well-formed stools, using an escalating dose regimen depending on symptoms and response. If disimpaction does not occur after 2 weeks, a stimulant laxative can be added or if stools are hard, used in
LAXATIVES > BULK-FORMING LAXATIVES

**Ispaghula husk**

**DRUG ACTION** Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

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**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Child 1 month-5 years: 2.5–5 mL twice daily, dose to be taken only when prescribed by a doctor, as half or whole level spoonful in water, preferably after meals, morning and evening.
  - Child 6-11 years: 2.5–5 mL twice daily, dose to be given as a half or whole level spoonful in water, preferably after meals, morning and evening.
  - Child 12–17 years: 1 sachet twice daily, dose to be given in water preferably after meals, morning and evening.
  - Adult: 1 sachet twice daily, dose to be given in water preferably taken after food, morning and evening.

**DOSE EQUIVALENCE AND CONVERSION**

- 1 sachet equivalent to 2 level 5 mL spoonfuls.

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**CONTRA-INDICATIONS**

- Colonic atony, faecal impaction, intestinal obstruction, reduced gut motility.

**CAUTIONS**

- Adequate fluid intake should be maintained to avoid intestinal obstruction.

**SIDE-EFFECTS**

- Abdominal distension, bronchospasm, conjunctivitis, gastrointestinal disorders, hypersensitivity, rhinitis, skin reactions.

**DIRECTIONS FOR ADMINISTRATION**

- Dose to be taken with at least 150 mL liquid.

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of soluble granules formulations may include plain, lemon, or orange.

**HANDLING AND STORAGE**

- Ispaghula husk contains potent allergens. Individuals exposed to the product (including those handling the product) can develop hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm and in some cases, anaphylaxis.

**PATIENT AND CARER ADVICE**

- Manufacturer advises that preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed. Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

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**Methylcellulose**

**DRUG ACTION** Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

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**INDICATIONS AND DOSE**

**Constipation | Diarrhoea**

- **BY MOUTH USING TABLETS**
  - Adult: 3–6 tablets twice daily.

**CONTRA-INDICATIONS**

- Colonic atony, difficulty in swallowing, faecal impaction, infective bowel disease, intestinal obstruction.

**CAUTIONS**

- Adequate fluid intake should be maintained to avoid intestinal obstruction.

**CAUTIONS, FURTHER INFORMATION**

- It may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility to ensure adequate fluid intake.

**SIDE-EFFECTS**

- Abdominal distension, gastrointestinal disorders.

**DIRECTIONS FOR ADMINISTRATION**

- In constipation the dose should be taken with at least 300 mL liquid. In diarrhoea, ileostomy, and colostomy control, avoid liquid intake for 30 minutes before and after dose.

**PATIENT AND CARER ADVICE**

- Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

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**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Celevac (Advanz Pharma)
  - Methylcellulose "450" 500 mg
  - 112 tablet
  - £3.22 DT = £3.22

**Sterculia**

**DRUG ACTION** Sterculia is a bulk-forming laxative. It relieves constipation by increasing faecal mass which stimulates peristalsis.

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**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Child 6-11 years: 0.5–1 sachet 1–2 times a day, alternatively, half to one heaped 5 mL spoonful once or twice a day; washed down without chewing with plenty of liquid after meals.
  - Child 12–17 years: 1–2 sachets 1–2 times a day, alternatively, one to two heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals.
  - Adult: 1–2 sachets 1–2 times a day, alternatively, one to two heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals.
Gastro-intestinal system

MEDICINAL FORMS

LAXATIVES > OSMOTIC LAXATIVES

Lactulose

INDICATIONS AND DOSE

Constipation

BY MOUTH

- Adult: 1–2 sachets 1–2 times a day, alternatively, 1–2 heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals

Constitution

BY MOUTH

- Adult: 1–2 sachets 1–2 times a day, alternatively, 1–2 heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals

PREGNANCY

Manufacturer advises avoid.

PANST AND CARER ADVICE

Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Granules

CAUTIONARY AND ADVISORY LABELS 25, 27

- Normacol (Forum Health Products Ltd)
  - Sterculia 620 mg per 1 gram
  - Normacol granules 7g sachets | 60 sachet $8.45 DT + $8.45
  - Normacol granules | 500 gram $51.72 DT + $7.92

Unlicensed Use

In adults Lactulose doses in the BNF may differ from those in product literature.

CONTRA-INDICATIONS

- Galactosaemia · intestinal obstruction
- Lactose intolerance
- Common or very common: Abdominal pain · diarrhoea · flatulence · nausea · vomiting
- Uncommon: Electrolyte imbalance
- Not known to be harmful.

Pregnancy

Medicines for Children leaflet: Lactulose for constipation www.medicinesforchildren.org.uk/lactulose-constipation

INDICATIONS AND DOSE

After haemorrhoidectomy

BY MOUTH

- Adult: 1–2 sachets 1–2 times a day, alternatively, 1–2 heaped 5 mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals

PREGNANCY

Manufacturer advises avoid.

BREAST FEEDING

Manufacturer advises avoid.

PATIENT AND CARER ADVICE

Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Granules

- Normacol Plus (Forum Health Products Ltd)
  - Frangula 80 mg per 1 gram, Sterculia 620 mg per 1 gram
  - Normacol Plus granules 7g sachets | 60 sachet $17.12 DT + $17.12
  - Normacol Plus granules | 500 gram $8.45 DT + $8.45

LACTULOSE
Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride

18-Apr-2018

**INDICATIONS AND DOSE**

**Chronic constipation (dose for ‘paediatric’ sachets)**
- **BY MOUTH**
  - Child 2-5 years: 1 sachet daily, adjust dose to produce regular soft stools; maximum 4 sachets per day
  - Child 6-11 years: 2 sachets daily, adjust dose to produce regular soft stools; maximum 4 sachets per day

**Prevention of faecal impaction (dose for ‘paediatric’ sachets)**
- **BY MOUTH**
  - Child 5-11 years: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be taken over a 12-hour period, after disimpaction, switch to maintenance laxative therapy; maximum 12 sachets per day

**Chronic constipation (dose for ‘half-strength’ sachets)**
- **BY MOUTH**
  - Child 12-17 years: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily
  - Adult: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily

**Faecal impaction (dose for ‘half-strength’ sachets)**
- **BY MOUTH**
  - Child 12-17 years: 8 sachets on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 16 sachets per day
  - Adult: 8 sachets on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 16 sachets per day

**Chronic constipation (dose for ‘full-strength’ sachets)**
- **BY MOUTH**
  - Child 12-17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
  - Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

**Faecal impaction (dose for ‘full-strength’ sachets)**
- **BY MOUTH**
  - Child 12-17 years: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
  - Adult: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

**DOSE EQUIVALENCE AND CONVERSION**
- Each paediatric sachet contains 6.563 g of macrogol 3350; each ‘half-strength’ sachet contains 6.563 g of macrogol 3350; each ‘full-strength’ sachet contains 13.125 g of macrogol 3350.

**MOVICOL® READY TO TAKE SACHETS**

**Chronic constipation**
- **BY MOUTH**
  - Child 12-17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
  - Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

**Faecal impaction**
- **BY MOUTH**
  - Child 12-17 years: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period; patients should also take an additional 1 litre of fluid daily, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
  - Adult: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

**VISTAPREP® ORAL POWDER**

**Bowel cleansing before colonoscopy**
- **BY MOUTH**
  - Adult: 3–4 litres, reconstituted solution taken over 4 hours, generally on the day of procedure; alternatively, it can be taken on the evening before procedure or started on the evening before procedure and completed on the morning of procedure

**UNLICENSED USE**
- In children Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride may be used as detailed below, although these situations are considered outside the scope of its licence:
  - (VFG) dose for chronic constipation/prevention of faecal impaction in children aged 6 years;
  - dose titration schedule for faecal impaction in children aged 12–17 years.
- In adults Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride may be used as detailed below, although this is considered outside the scope of its licence: (VFG) dose titration schedule for faecal impaction.
CONTRA-INDICATIONS
Intestinal obstruction - intestinal perforation - paralytic ileus - severe inflammatory conditions of the intestinal tract (including Crohn’s disease, ulcerative colitis and toxic megacolon) - use of 'paediatric' sachets for faecal impaction in impaired cardiovascular function (no information available) (in children).

VISTAPREP® ORAL POWDER
Impaired consciousness - impaired swallowing reflex - moderate-to-severe heart failure—limited safety information available - risk of regurgitation or aspiration - severe dehydration—limited safety information available

CAUTIONS
Cardiovascular impairment (should not take more than 2 'full-strength' sachets or 4 'half-strength' sachets in any one hour) - impaired consciousness (with high doses) - impaired gag reflex (with high doses).

VISTAPREP® ORAL POWDER
Chronic inflammatory bowel disease - elderly - heart rhythm abnormalities - reflux oesophagitis (with high doses)

SIDE-EFFECTS
Electrolyte imbalance (discontinue if symptoms occur) - flatulence - gastrointestinal discomfort - nausea - vomiting

PREGNANCY
Manufacturers advise may be used—limited data available.

HEPATIC IMPAIRMENT

VISTAPREP® ORAL POWDER
Manufacturer advises avoid (limited information available).

RENAL IMPAIRMENT
In children Manufacturers advise avoid use of 'paediatric' sachets for faecal impaction—no information available.

VISTAPREP® ORAL POWDER
Manufacturer advises avoid—limited safety information available.

DIRECTIONS FOR ADMINISTRATION
Manufacturers advise dissolve contents of each 'half-strength' sachet of oral powder in 62.5 mL of water, and each 'full-strength' sachet of oral powder in 125 mL of water; after reconstitution the solution should be kept in a refrigerator—for further information consult product literature.

In children Manufacturers advise dissolve contents of each 'paediatric' sachet of oral powder in 62.5 mL of water; after reconstitution the solution should be kept in a refrigerator—for further information consult product literature.

MOVICOL® LIQUID
Manufacturer advises dilute 25 mL of oral concentrate with 100 mL of water; after dilution the solution should be discarded if unused after 24 hours.

VISTAPREP® ORAL POWDER
Manufacturer advises dissolve the contents of each sachet in 1 L water; if not consumed immediately, the reconstituted solution should be kept in a refrigerator and discarded if unused after 48 hours.

PATIENT AND CARER ADVICE
Patients or carers should be counselled on how to take the oral powder and oral solution.

• Medicines for Children leaflet: Movicol for constipation www.medicinesforchildren.org.uk/movicol-constipation

VISTAPREP® ORAL POWDER
Manufacturer advises treatment can be stopped if bowel motions become watery and clear.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral solution

CAUTIONARY AND ADVISORY LABELS 13

ELECTROLYTES: May contain Bicarbonate, chloride, potassium, sodium

Movicol (Forum Health Products Ltd)

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre Movicol Ready to Take oral solution 25ml sachets sugar-free | 30 sachet (£6.72 DT = £7.72)

Powder

CAUTIONARY AND ADVISORY LABELS 11,13

ELECTROLYTES: May contain Bicarbonate, chloride, potassium, sodium

Macrogol '3350' with potassium chloride, sodium bicarbonate and sodium chloride (Non-proprietary)

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Macrogol compound oral powder sachets sugar-free sugar-free | 20 sachet (£2.56 - £4.45 sugar-free | 30 sachet (£6.68 DT = £8.84)

Macrogol compound oral powder sachets sugar-free plain sugar-free | 20 sachet (£2.87 sugar-free | 30 sachet (£4.30 DT = £3.84

Macrogol compound oral powder sachets sugar-free citrus sugar-free | 20 sachet (£2.87 sugar-free | 30 sachet (£4.38 DT = £3.84

CosmoCol (Stirling Anglian Pharmaceuticals Ltd)

Macrogol '3350' 52.5 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Macrogol Paediatric oral powder 6.9g sachets sugar-free | 30 sachet (PHS £2.99 DT = £4.38

CosmoCol Paediatric oral powder 6.9g sachets sugar-free | 30 sachet (PHS £2.99 DT = £4.38

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

CosmoCol Orange Lemon and Lime oral powder sachets sugar-free | 30 sachet (£3.95 DT = £3.84

CosmoCol Orange Flavour oral powder sachets sugar-free | 20 sachet (£2.75 sugar-free | 30 sachet (£3.95 DT = £3.84

Laxido (Galen Ltd)

Macrogol '3350' 52.5 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Laxido Paediatric Plain oral powder 6.9g sachets sugar-free | 30 sachet (PHS £2.99 DT = £4.38

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Laxido Orange powder sachets sugar-free | 20 sachet (£2.75 sugar-free | 30 sachet (£3.95 DT = £3.84

Molative (Mylan)

Macrogol '3350' 52.5 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Molative Paediatric oral powder 6.9g sachets sugar-free | 30 sachet (PHS £4.30 DT = £4.38

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Molative Paediatric oral powder 6.9g sachets sugar-free | 30 sachet (PHS £4.30 DT = £4.38

Molaxole (Meda Pharmaceuticals Ltd)

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Molaxole oral powder sachets sugar-free | 20 sachet (£3.78 sugar-free | 30 sachet (£5.68 DT = £3.84

Movicol (Forum Health Products Ltd, Nongine Pharmaceuticals Ltd)

Macrogol '3350' 52.5 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Movicol Paediatric oral powder 6.9g sachets sugar-free | 30 sachet (PHS £4.38 DT = £4.38

Movicol Paediatric Chocolate oral powder 6.9g sachets sugar-free | 30 sachet (PHS £4.38 DT = £4.38

Macrogol '3350' 105 gram per 1 litre, Potassium 5.4 mmol per 1 litre, Bicarbonate 17 mmol per 1 litre, Chloride 53 mmol per 1 litre, Sodium 65 mmol per 1 litre

Movicol Plain oral powder 13.7g sachets sugar-free | 30 sachet (£8.11 DT = £3.84 sugar-free | 50 sachet (£13.49

Movicol Chocolate oral powder 13.9g sachets sugar-free | 30 sachet (£8.11 DT = £3.84 sugar-free | 50 sachet (£13.49

Movicol oral powder 13.9g sachets lemon & lime sugar-free | 20 sachet (£5.41 sugar-free | 30 sachet (£8.11 DT = £3.84 sugar-free | 50 sachet (£13.49
Constipation

Magnesium hydroxide

- **INDICATIONS AND DOSE**
  - **Constipation**
    - By mouth
      - Adult: 30–45 mL as required, dose to be given mixed with water at bedtime.
  - **CONTRA-INDICATIONS** Acute gastro-intestinal conditions
  - **CAUTIONS** Debilitated patients - elderly
  - **INTERACTIONS** → Appendix 1: magnesium
  - **HEPATIC IMPAIRMENT** Avoid in hepatic coma if risk of renal failure.
  - **RENAL IMPAIRMENT** Increased risk of toxicity in renal impairment.
  - **Dose adjustments** Avoid or reduce dose.

- **PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Magnesium Hydroxide Mixture, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Oral suspension**
    - Magnesium hydroxide (Non-proprietary)
      - Magnesium hydroxide 79 mg per 1 ml Magnesium hydroxide 7.45-8.35% oral suspension BP | 500 ml (£5.31)
      - Magnesium hydroxide 80 mg per 1 ml Magnesium hydroxide 8% oral suspension | 500 ml (£8.05)
  - Brands may include Phillips’ Milk of Magnesia

Sodium acid phosphate with sodium phosphate

- **INDICATIONS AND DOSE**
  - **Constipation (using Phosphates Enema BP Formula B)** | Bowel evacuation before abdominal radiological procedures, endoscopy, and surgery (using Phosphates Enema BP Formula B)
    - **By rectum**
      - Child 5-6 years: 45–65 mL once daily
      - Child 7-11 years: 65–100 mL once daily
      - Child 12-17 years: 100–128 mL once daily
      - Adult: 128 mL daily
  - **Fleet® READY-TO-USE ENEMA**
    - Constipation | Bowel evacuation before abdominal radiological procedures | Bowel evacuation before endoscopy | Bowel evacuation before surgery
      - **By rectum**
        - Adult: 118 mL
  - **Fleet® PHOSPHO-SODA**
    - Bowel evacuation before colonoscopy | Bowel evacuation before radiological examination
      - **By mouth**
        - Adult: 45 mL twice daily, each dose must be diluted with half a glass (120 mL) of cold water, followed by one full glass (240 mL) of cold water, timing of doses is dependent on the time of the procedure, for morning procedure, the first dose should be taken at 7 a.m. and second at 7 p.m. on day before the procedure; for afternoon procedure, first dose should be taken at 7 p.m. on day before and second dose at 7 a.m. of the procedure

<table>
<thead>
<tr>
<th>PHARMACOKINETICS</th>
<th>For Fleet® phospho-soda: onset of action is within half to 6 hours of first dose.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONTRA-INDICATIONS</strong></td>
<td>With oral use Acute severe colitis - ascites - congestive cardiac failure - gastric retention - gastro-intestinal obstruction - gastro-intestinal perforation - toxic megacolon</td>
</tr>
<tr>
<td><strong>CAUTIONS</strong></td>
<td>With oral use cardiac disease (avoid in congestive cardiac failure) - colitis (avoid if acute severe colitis) - elderly and debilitated patients - fluid and electrolyte disturbances - hypovolaemia (should be corrected before administration) - impaired gag reflex or possibility of regurgitation or aspiration</td>
</tr>
<tr>
<td><strong>INTERACTIONS</strong> → Appendix 1: bowel cleansing preparations</td>
<td></td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SPECIFIC SIDE-EFFECTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>COMMON OR VERY COMMON</strong> Chills - gastrointestinal discomfort - nausea - vomiting</td>
<td></td>
</tr>
<tr>
<td><strong>UNCOMMON</strong> Dehydration</td>
<td></td>
</tr>
<tr>
<td><strong>RARE OR VERY RARE</strong> Electrolyte imbalance - metabolic acidosis</td>
<td></td>
</tr>
</tbody>
</table>

**GENERAL SIDE-EFFECTS**

- **Common or very common**
  - Chills - gastrointestinal discomfort - nausea - vomiting
- **Uncommon**
  - Dehydration
- **Rare or very rare**
  - Electrolyte imbalance - metabolic acidosis

- **SPECIFIC SIDE-EFFECTS**
  - **Common or very common**
    - With oral use Asthenia - chest pain - dizziness - headache
  - **Rare or very rare**
    - With oral use Allergic dermatitis - arrhythmia - hypotension - loss of consciousness - muscle cramps - myocardial infarction - nephrocalcinosis - paraesthesia - renal impairment - tetany
  - With rectal use Pain

- **PREGNANCY**
  - With oral use Caution.

- **BREAST FEEDING**
  - With oral use Caution.

- **HEPATIC IMPAIRMENT** Use with caution in cirrhosis.

- **RENAL IMPAIRMENT**
  - With oral use Avoid if eGFR less than 60 mL/minute/1.73 m².
  - With rectal use Use with caution.

- **MONITORING REQUIREMENTS**
  - With oral use Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

- **DIRECTIONS FOR ADMINISTRATION**
  - **Fleet® PHOSPHO-SODA** Copious intake of water or other clear fluids (e.g. clear soup, strained fruit juice without pulp, black tea or coffee) recommended until midnight before morning procedure and until 8 a.m. before afternoon procedure. At least one glass (approx 240 mL) of water or other clear fluid should also be taken immediately before each dose.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Phosphates Enema BP Formula B consists of sodium dihydrogen phosphate dihydrate 12.8 g, disodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL.
PATIENT AND CARER ADVICE

FLEET® PHOSPHO-SODA Intake of solid food should be stopped for at least 6 hours before starting treatment and until procedure completed. Patients or carers should be advised that adequate hydration should be maintained during treatment. Patients or carers should be given advice on administration of FLEET® Phospho-soda oral solution.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral solution

CAUTIONARY AND ADVISORY LABELS 10 ELECTROLYTES: May contain Phosphate, sodium

- Fleet Phospho-soda (Casen Recordati S.L.) Disodium hydrogen phosphate dodecahydrate 240 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 542 mg per 1 ml Phospho-soda 24.4g/10.8g oral solution sugar-free | 90 ml

Enema

- Sodium acid phosphate with sodium phosphate (Non-proprietary) Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 100 mg per 1 ml Phospho-soda enema (Formula B) 128ml long tube | 1 enema £4.79
- Fleet Ready-to-use (Casen Recordati S.L.) Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml, Sodium dihydrogen phosphate dihydrate 181 mg per 1 ml Clean Ready-to-use 133ml enema | 1 enema £1.95 DT + £1.95

LAXATIVES > SELECTIVE 5-HT₄ RECEPTOR AGONISTS

Prucalopride 07-Feb-2009

DRUG ACTION A selective serotonin 5-HT₄-receptor agonist with prokinetic properties.

INDICATIONS AND DOSE Chronic constipation when other laxatives fail to provide an adequate response

- BY MOUTH
  - Adult: 2 mg once daily, review treatment if no response after 4 weeks
  - Elderly: Initially 1 mg once daily, increased if necessary to 2 mg once daily, review treatment if no response after 4 weeks

CONTRA-INDICATIONS Crohn’s disease, intestinal obstruction, intestinal perforation, toxic megacolon, ulcerative colitis

CAUTIONS History of arrhythmias, history of ischaemic heart disease

SIDE-EFFECTS

- Common or very common Appetite decreased, diarrhoea, dizziness, fatigue, gastrointestinal discomfort, gastrointestinal disorders, headache, nausea, vomiting
- Uncommon Anorectal haemorrhage, fever, malaise, palpitations, tremor, urinary frequency increased SIDE-EFFECTS, FURTHER INFORMATION Side-effects generally occur at the start of treatment and are usually transient.

CONCEPTION AND CONTRACEPTION Manufacturer recommends effective contraception during treatment.

PREGNANCY Manufacturer advises avoid—limited data available.

BREAST FEEDING Manufacturer advises avoid—present in milk.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (risk of increased exposure, limited information available).

Dose adjustments Manufacturer advises initial dose of 1 mg once daily in severe impairment; if tolerated this may be increased to 2 mg once daily.

RENAI IMPAIRMENT Dose adjustments Manufacturer recommends a reduced dose of 1 mg daily if eGFR less than 30 ml/minute/1.73 m².

PATIENT AND CARER ADVICE

Driving and skilled tasks Manufacturer advises that dizziness and fatigue may initially affect ability to drive or operate machinery.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Prucalopride for the treatment of chronic constipation in women (December 2010) NICE TA211 Prucalopride (Resolor®) is recommended as an option for the treatment of chronic constipation in women for whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered. Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, after careful review of the patient’s previous courses of laxative treatments.

Scottish Medicines Consortium (SMC) decisions

SMC No. 653/10

The Scottish Medicines Consortium has advised (July 2011) that prucalopride (Resolor®) is not recommended for use within NHS Scotland for the symptomatic treatment of chronic constipation of women in whom laxatives fail to provide adequate relief.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Resolor (Shire Pharmaceuticals Ltd) Prucalopride (as Prucalopride succinate) 1 mg | 28 tablet | £38.69 DT + £38.69
- Prucalopride (as Prucalopride succinate) 2 mg | 28 tablet | £59.52 DT + £59.52

LAXATIVES > SOFTENING LAXATIVES

Arachis oil

INDICATIONS AND DOSE To soften impacted faeces

- BY RECTUM
  - Adult: 130 mL as required

CAUTIONS Hypersensitivity to soya - intestinal obstruction

ALLERGY AND CROSS-SENSITIVITY Contra-indicated ifhistory of hypersensitivity to arachis oil or peanuts.

DIRECTIONS FOR ADMINISTRATION Warm enema in warm water before use.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Enema

- Arachis oil (Non-proprietary) Arachis oil 1 ml per 1 ml Arachis oil 130ml enema | 1 enema £47.50 DT + £47.50

www.getintopharma.com
### Docusate sodium

*Trade names: Norgalax, Docusol, Docusol Paediatric*  
*Type: Laxative*

#### INDICATIONS AND DOSE

**Constipation**
- **ERYTHROMYCIN, CHLORAMPHENICOL**: Chronic constipation in children under 12 years of age
- **COLOSTOMY, INTUSSUSCEPTION, PNEUMOTHORAX**: Bowel clearance before radiological procedures and surgery
- **ACUTE Appendicitis, PERFORATED Ulcers**: Acute surgical abdominal conditions (in adults)
- **AMM可用于长期使用**: Electrolyte imbalance with prolonged use (in children)
- **ATTACKS**: Gastrointestinal discomfort • nausea
- **ANGIOEDEMA**: Angioedema

#### DIRECTIONS FOR ADMINISTRATION

**BY MOUTH**
- **DOSAGE**
  - Child 6 months–1 year: 1.25 mg 3 times a day, adjusted according to response, use paediatric oral solution
  - Child 2–11 years: 2.5–25 mg 3 times a day, adjusted according to response, use paediatric oral solution
  - Adult: Up to 500 mg daily in divided doses, adjusted according to response

**BY RECTUM**
- **Adult**: 120 mg for 1 dose
- **Child**: 400 mg, to be administered with barium meal

**PHARMACOKINETICS**
- Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

#### CONTRA-INDICATIONS

-**CHILDREN UNDER 3 YEARS**: Bowel obstruction
-**DISTURBED LACTATION**: Breastfeeding
-**RARE**: Gastrointestinal discomfort, nausea

#### INTERACTIONS

-**DIFFERENT MEDICINES CONTAINING THE SAME DRUG**: None known

#### SIDE-EFFECTS

-**NAUSEA**: Common
-**RASH**: Rare

#### MEDICINAL FORMS

- **ORAL SOLUTION**: Liquid paraffin
- **ENEMA**: Docusate sodium 2.5 mg/1 ml

#### PATIENT AND CARER ADVICE

- **ażel**: Use paediatric oral solution for children 1–7 years
- **anych**: Use adult oral solution

### Liquid paraffin

*Trade names: Domestos, Clearblue*  
*Type: Laxative*

#### INDICATIONS AND DOSE

**Constipation**
- **BY MOUTH**
  - **CHILDREN**: 5–20 mg once daily, increased if necessary up to 20 mg once daily
  - **ADULTS**: 5–10 mg once daily

**BY RECTUM**
- **CHILDREN**: 10 mg once daily
- **ADULTS**: 10 mg twice daily

**PHARMACOKINETICS**
- Tablets act within 10–12 hours; suppositories act in 20–60 minutes.

### Bisacodyl

*Trade names: Co-danthrusate*  
*Type: Stimulant laxative*

#### INDICATIONS AND DOSE

**Constipation**
- **BY MOUTH**
  - **CHILDREN**: 5–20 mg once daily, increased if necessary up to 20 mg once daily
  - **ADULTS**: 5–10 mg once daily

**BY RECTUM**
- **CHILDREN**: 10 mg once daily
- **ADULTS**: 10 mg twice daily

**SIDE-EFFECTS**
- **NAUSEA**: Common
- **VOMITING**: Rare

**CONTRA-INDICATIONS**

-**CHILDREN UNDER 3 YEARS**: Bowel obstruction
-**DISTURBED LACTATION**: Breastfeeding
-**RARE**: Gastrointestinal discomfort, nausea

**MEDICINAL FORMS**

- **ORAL PREPARATIONS**: Docusate sodium 1 mg/1 ml
- **ENEMA**: Docusate sodium 2.5 mg/1 ml

**PATIENT AND CARER ADVICE**

- **ażel**: Use paediatric oral solution for children 1–7 years
- **anych**: Use adult oral solution

**CONTRA-INDICATIONS**

-**CHILDREN UNDER 3 YEARS**: Bowel obstruction
-**DISTURBED LACTATION**: Breastfeeding
-**RARE**: Gastrointestinal discomfort, nausea

**MEDICINAL FORMS**

- **ORAL PREPARATIONS**: Docusate sodium 1 mg/1 ml
- **ENEMA**: Docusate sodium 2.5 mg/1 ml

**PATIENT AND CARER ADVICE**

- **ążel**: Use paediatric oral solution for children 1–7 years
- **anych**: Use adult oral solution

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**Gastrointestinal system**

**BNF 78**

**Constipation**

**Liquid paraffin**

**Bisacodyl**

**Docusate sodium**

**Unlicensed Use**

- Adult oral solution and capsules not licensed for use in children under 12 years.

**Caution**

- Avoid intestinal obstruction
- Do not give with liquid paraffin; excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalaemia.
- Rectal preparations are not indicated if haemorrhoids or anal fissure.

**Interactions**

- There can be variation in the licensing of different medicines containing the same drug.

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Pharmacokinetics**

- Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

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**Unlicensed Use**

- Adult oral solution and capsules not licensed for use in children under 12 years.

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**Interactions**

- There can be variation in the licensing of different medicines containing the same drug.

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Pharmacokinetics**

- Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.
Co-danthramer

**CONTRA-INDICATIONS** Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

**CAUTIONS** Excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalaemia - may cause local irritation - rodent studies indicate potential carcinogenic risk

**CAUTIONS, FURTHER INFORMATION**
- Local irritation - Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies—risk of irritation and excoriation).
- SIDE-EFFECTS Abdominal cramps - asthenia - gastrointestinal disorders - hypermagnesaemia - skin reactions - urine red
- PREGNANCY Manufacturers advise avoid—limited information available.
- BREAST FEEDING Manufacturers advise avoid—no information available.

**PRESCRIBING AND DISPENSING INFORMATION**

Palliative care For further information on the use of co-danthramer in palliative care, see www.medicinescomplete.com/#/content/palliative/stimulant-laxatives.

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Co-danthrusate

**CONTRA-INDICATIONS** Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

**CAUTIONS** Excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalaemia - may cause local irritation - rodent studies indicate potential carcinogenic risk

**CAUTIONS, FURTHER INFORMATION**
- Local irritation - Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies—risk of irritation and excoriation).
- SIDE-EFFECTS Abdominal cramps - asthenia - gastrointestinal disorders - hypermagnesaemia - skin reactions - urine red
- PREGNANCY Manufacturers advise avoid—limited information available.
- BREAST FEEDING Manufacturers advise avoid—no information available.
Gastro-intestinal system

Senna

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH USING TABLETS**
  - Child 6–17 years: 7.5–30 mg once daily, adjusted according to response
  - Adult: 7.5–15 mg daily (max. per dose 30 mg daily), dose usually taken at bedtime; initial dose should be low then gradually increased, higher doses may be prescribed under medical supervision
- **BY MOUTH USING SYRUP**
  - Child 1 month-3 years: 3.75–15 mg once daily, adjusted according to response
  - Child 4–17 years: 3.75–30 mg once daily, adjusted according to response
  - Adult: 7.5–15 mg once daily (max. per dose 30 mg daily), dose usually taken at bedtime, higher doses may be prescribed under medical supervision

**PHARMACOKINETICS**

- Onset of action 8–12 hours.

**UNLICENSED USE**

- Syrup not licensed for use in children under 2 years.

**SIDE-EFFECTS**

- Excessive use can cause hypokalaemia.
- Specialist sources indicate suitable use in pregnancy.

**PREGNANCY**

- Specialist sources indicate suitable use in breast-feeding in infants over 1 month.

**PATIENT AND CARER ADVICE**

- Medicines for Children leaflet: Senna for constipation

**NATIONAL FUNDING/ACCESS DECISIONS**

- NHS restrictions: Senokot® tablets are not prescribable in NHS primary care.

**EXCEPTIONS TO LEGAL CATEGORY**

- Senna is on sale to the public for use in children over 12 years; doses on packs may vary from those in BNF Publications.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- **Senokot** (Forum Health Products Ltd, Reckitt Benckiser Healthcare (UK) Ltd)
  - Sennoside B (as Sennosides) 1.5 mg per 1 ml
  - Syrup Pharmacy sugar free sugar-free 500 ml $4.76 DT + $4.76

**Tablet**

- **Senna** (Non-proprietary)
  - Sennoside B (as Sennosides) 7.5 mg
  - Senokot 7.5mg/5ml Oral solution Pharmacy sugar free sugar-free 20 tablet $1.00 | 60 tablet $1.81 DT + $1.81 | 100 tablet $2.15
  - **Senokot** (Reckitt Benckiser Healthcare (UK) Ltd, Forum Health Products Ltd)
  - Sennoside B (as Sennosides) 15 mg
  - Senokot Max Strength 15mg tablets 24 tablet $3.23 | 48 tablet $5.69

**SIDE-EFFECTS, FURTHER INFORMATION**

- In rare cases, haematuria.
- Pseudomelanosis coli.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Constipation

**Senna with ispaghula husk**

The properties listed below are those particular to the combination only. For the properties of the components please consider, senna above, ispaghula husk p. 55.

**INDICATIONS AND DOSE**

**Constipation**

- **BY MOUTH**
  - Child 12-17 years: 5–10 g once daily, to be taken at night, 5 g equivalent to one level spoonful of granules
  - Adult: 5–10 g once daily, to be taken at night, 5 g equivalent to one level spoonful of granules

**PREGNANCY**

- Manufacturer advises avoid during first trimester. To be used only intermittently and only if dietary and lifestyle changes fail.

**DIRECTIONS FOR ADMINISTRATION**

- Take at night with at least 150 mL liquid.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Granules**

- **CAUTIONARY AND ADVISORY LABELS**
  - 25 EXCipients: May contain Sucrose
  - Manevac (Meda Pharmaceuticals Ltd)

- Senna fruit 124 mg per 1 gram, Ispaghula 542 mg per 1 gram Manevac granules 400 gram $9.50 DT + $9.50
Sodium picosulfate (Sodium picosulphate)

**DRUG ACTION** Sodium picosulfate is a stimulant laxative. After metabolism in the colon it stimulates the mucosa thereby increasing the motility of the large intestine.

**INDICATIONS AND DOSE**
- **Constipation**
  - **BY MOUTH**
    - Child 1 month–3 years: 2.5–10 mg once daily, adjusted according to response
    - Child 4–17 years: 2.5–20 mg once daily, adjusted according to response
    - Adult: 5–10 mg once daily, dose to be taken at bedtime

**SIDE-EFFECTS**
- Common or very common: Diarrhoea, gastrointestinal discomfort
- Uncommon: Dizziness, nausea, vomiting
- Frequency not known: Angioedema, skin reactions, syncope

**CONTRA-INDICATIONS**
- Intestinal obstruction
- Undiagnosed abdominal pain

**UNLICENSED USE**
- Sodium picosulfate doses in BNF
- Publications adhere to national guidelines and may differ from those in product literature.

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.

Methylnaltrexone bromide (Methylnaltrexone bromide)

**DRUG ACTION**
- Methylnaltrexone bromide is a peripherally acting opioid-receptor antagonist. It therefore blocks the gastrointestinal (constipating) effects of opioids without altering their central analgesic effects.

**INDICATIONS AND DOSE**
- **Opioid-induced constipation in patients with chronic pain (except palliative care patients with advanced illness)**
  - **BY SUBCUTANEOUS INJECTION**
    - Adult: 12 mg once daily if required, to be given as 4–7 doses weekly

**SIDE-EFFECTS**
- Frequency not known
- Uncommon
- Common or very common

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**UNLICENSED USE**
- Sodium picosulfate doses in BNF
- Publications adhere to national guidelines and may differ from those in product literature.

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**UNLICENSED USE**
- Sodium picosulfate doses in BNF
- Publications adhere to national guidelines and may differ from those in product literature.

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**UNLICENSED USE**
- Sodium picosulfate doses in BNF
- Publications adhere to national guidelines and may differ from those in product literature.

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**UNLICENSED USE**
- Sodium picosulfate doses in BNF
- Publications adhere to national guidelines and may differ from those in product literature.

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**CONTRA-INDICATIONS**
- Acute surgical abdominal conditions
- Gastro-intestinal obstruction
- Undiagnosed abdominal pain

**INTERACTIONS**
- Appendix 1: sodium picosulfate

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**PHARMACOKINETICS**
- Onset of action 6–12 hours.

**PHARMACOKINETICS**
- May act within 30–60 minutes.
Naloxegol

**DRUG ACTION** Naloxegol is a peripherally acting opioid receptor antagonist. It therefore decreases the constipating effects of opioids without altering their central analgesic effects.

**INDICATIONS AND DOSE**

Opioid-induced constipation when response to laxatives inadequate

- **BY MOUTH**
  - Adult: 25 mg once daily, to be taken in the morning

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises reduce initial dose to 12.5 mg daily with concurrent use of moderate inhibitors of CYP3A4, increasing to 25 mg daily if well tolerated.

**CONTRA-INDICATIONS**

Gastro-intestinal or peritoneum malignancy (risk of gastro-intestinal perforation) - known or suspected gastro-intestinal obstruction - patients at risk of recurrent gastro-intestinal obstruction - recurrent or advanced ovarian cancer (risk of gastro-intestinal perforation) - vascular endothelial growth factor (VEGF) inhibitor treatment (risk of gastro-intestinal perforation)

**CAUTIONS**

- Alzheimer’s disease (advanced) - cardiovascular disease - CNS metastases - congestive heart failure (symptomatic) - Crohn’s disease - diverticulitis (active or recurrent) - multiple sclerosis (active) - peptic ulcer disease (severe) - primary brain malignancies - QT interval over 500 milliseconds - recent history of myocardial infarction (within 6 months)

**CAUTIONS, FURTHER INFORMATION**

- Disruptions to blood-brain barrier
- Manufacturer advises caution in patients with clinically important disruptions to the blood-brain barrier (e.g. advanced Alzheimer’s disease, active multiple sclerosis, primary brain malignancies) — risk of uptake into the CNS.
- Cardiovascular disorders
- Safety and efficacy has not been established in patients with these conditions.

**INTERACTIONS**

- Appendix 1: naloxegol

**SIDE-EFFECTS**

- Common or very common: Abdominal pain - diarrhoea - flatulence - headache - hyperhidrosis - nasopharyngitis - nausea - vomiting
- Uncommon: Withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**

- Manufacturer advises that gastrointestinal side-effects typically occur shortly after initiation of treatment — consider reducing the dose.
- PREGNANCY
- Manufacturer advises avoid — limited data available but toxicity at high doses in animal studies; theoretical risk of opioid withdrawal in fetus.
- BREAST FEEDING
- Manufacturer advises avoid — present in milk in animal studies and theoretical risk of opioid withdrawal in breast-fed infants.
- HEPATIC IMPAIRMENT
- Manufacturer advises avoid in severe impairment (no information available).
- RENAL IMPAIRMENT
- Dose adjustments
- Manufacturer advises lower initial dose in moderate to severe impairment — initially 12.5 mg daily, increase to 25 mg if well tolerated.
- **DIRECTIONS FOR ADMINISTRATION**
- Manufacturer advises tablets can be crushed, mixed with 120 mL of water and taken immediately if patients are unable to swallow tablets whole. The mixture may be administered via a nasogastric tube, if required.
- **PATIENT AND CARER ADVICE**
- Manufacturer advises patients report severe, persistent or worsening gastro-intestinal effects (such as abdominal pain) to their prescriber.

### NATIONAL FUNDING/ACCESS DECISIONS

**NICE decisions**

- Naloxegol for treating opioid-induced constipation (July 2015)

Naloxegol (Moventig®) is recommended as a possible treatment for opioid induced constipation in patients whose response to laxatives is inadequate.

**www.nice.org.uk/guidance/ta345**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 23 |
| Naloxegol (as Naloxegol oxalate) 12.5 mg | Moventig 12.5mg tablets |
| 30 tablet (PO) £55.20 DT + £55.20 |
| Naloxegol (as Naloxegol oxalate) 25 mg | Moventig 25mg tablets |
| 30 tablet (PO) £55.20 DT + £55.20 |

### Diarrhoea (acute)

**Description of condition**

Diarrhoea is the abnormal passing of loose or liquid stools, with increased frequency, increased volume, or both. Acute diarrhoea is that which lasts less than 14 days, but symptoms usually improve within 2–4 days. It can result from infection, as a side-effect of a drug, or as an acute symptom of a chronic gastro-intestinal disorder (such as Inflammatory bowel disease p. 38 or Irritable bowel syndrome p. 47). It may also result from the accumulation of non-absorbed osmotically active solutes in the gastro-intestinal lumen (e.g. in lactase deficiency) or from the gastro-intestinal effects of secretory stimuli (other than the enterotoxins from an infection). It may also occur when intestinal motility or morphology is altered.

Prompt investigation is required to identify or exclude any serious underlying cause if the patient has any red flag symptoms such as unexplained weight loss, rectal bleeding, persistent diarrhoea, a systemic illness, has received recent hospital treatment or antibiotic treatment, or following foreign travel (other than to Western Europe, North America, Australia or New Zealand).

### Aims of treatment

The priority of acute diarrhoea treatment, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion and the management of dehydration when it is present. This is particularly important in infants, frail and elderly patients, when excessive water and electrolyte loss and dehydration can be life-threatening.

### Treatment

Most episodes of acute diarrhoea will settle spontaneously without the need for any medical treatment. Oral rehydration therapy (ORT, such as disodium hydrogen citrate with glucose, potassium chloride and sodium chloride p. 1042; potassium chloride with sodium chloride p. 1040; potassium chloride with rice powder, sodium chloride and sodium citrate p. 1042) is the mainstay of treatment for acute diarrhoea to prevent or correct diarrhoea dehydration and to maintain the appropriate fluid intake once rehydration is achieved—see Fluids and electrolytes p. 1035.

However, in patients with severe dehydration and in those unable to drink, immediate admission to hospital and urgent replacement treatment with an intravenous rehydration fluid is recommended—see Fluids and electrolytes p. 1035.

The antimotility drug loperamide hydrochloride p. 66 is usually considered to be the standard treatment when rapid
control of symptoms is required. It can also be used for mild-to-moderate travellers’ diarrhoea (e.g. where toilet amenities are limited or unavailable) but should be avoided in bloody or suspected inflammatory diarrhoea (febrile patients) and in cases of significant abdominal pain (which also suggests inflammatory diarrhoea).

Loperamide hydrochloride is also the first-line treatment for patients with faecal incontinence [unlicensed indication] after the underlying cause of incontinence has been addressed. 

Racecadotril p. 68 is licensed as an adjunct to rehydration for the symptomatic treatment of uncomplicated acute diarrhoea in adults and children over 3 months.

There is insufficient evidence to recommend adsorbent preparations (such as kaolin p. 68) in acute diarrhoea.

**Antibacterial drugs for acute diarrhoea**

| LSG | Ciprofloxacin p. 558 is occasionally used for prophyaxis against travellers’ diarrhoea, but routine use is not recommended. | See also Gastro-intestinal system infections, antibacterial therapy p. 512. |

**Related drugs**

Other drugs used for diarrhoea: codeine phosphate p. 454, co-phenotrope below, methylcellulose p. 55, rifaximin p. 757.

### Gastro-intestinal obstruction

**Co-phenotrope**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>02-Jul-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunct to rehydration in acute diarrhoea</td>
<td></td>
</tr>
<tr>
<td>BY MOUTH</td>
<td></td>
</tr>
<tr>
<td>Child 4-8 years: 1 tablet 3 times a day</td>
<td></td>
</tr>
<tr>
<td>Child 9-11 years: 1 tablet 4 times a day</td>
<td></td>
</tr>
<tr>
<td>Child 12-15 years: 2 tablets 3 times a day</td>
<td></td>
</tr>
<tr>
<td>Child 16-17 years: Initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled</td>
<td></td>
</tr>
<tr>
<td>Adult: Initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled</td>
<td></td>
</tr>
</tbody>
</table>

**Control of faecal consistency after colostomy or ileostomy**

| BY MOUTH | |
| Child 4-8 years: 1 tablet 3 times a day | |
| Child 9-11 years: 1 tablet 4 times a day | |
| Child 12-15 years: 2 tablets 3 times a day | |
| Child 16-17 years: Initially 4 tablets, then 2 tablets 4 times a day | |
| Adult: Initially 4 tablets, then 2 tablets 4 times a day | |

**INDICATIONS AND DOSE**

**Acute diarrhoea**

- Adult: 10 ml. every 6 hours, dose to be given in water

**CONTRA-INDICATIONS**

Acute abdominal - delayed gastric emptying - heart failure secondary to chronic lung disease - phaeochromocytoma

**CAUTIONS**

Cardiac arrhythmias - pancreatitis - severe cor pulmonale

**INTERACTIONS**

- Appendix 1: atropine - opioids

**BREAST FEEDING**

Therapeutic doses unlikely to affect infant.

**RENAL IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged, and increased cerebral sensitivity occurs.

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Kaolin and Morphine Mixture, BP consists of light kaolin or light kaolin (natural) 20%, sodium bicarbonate 5%, and chloroform and morphine tincture 4% in a suitable vehicle. Contains anhydrous morphine 550–800 micrograms/10 ml.

**LESS SUITABLE FOR PRESCRIBING**

Kaolin and Morphine Mixture, BP (Kaolin and Morphine Oral Suspension) is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

- Co-phenotrope (Non-proprietary)

**Atropine**

- Sulfate 25 microgram, Diphenoxylate hydrochloride 2.5 mg Lomotil 2.5mg/25microgram tablets

100 tablet

**Kaolin with morphine**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>06-Aug-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute diarrhoea</td>
<td></td>
</tr>
<tr>
<td>BY MOUTH</td>
<td></td>
</tr>
<tr>
<td>Adult: 10 ml. every 6 hours, dose to be given in water</td>
<td></td>
</tr>
</tbody>
</table>

**CONTRA-INDICATIONS**

Acute abdominal - delayed gastric emptying - heart failure secondary to chronic lung disease - phaeochromocytoma

**CAUTIONS**

Cardiac arrhythmias - pancreatitis - severe cor pulmonale

**INTERACTIONS**

- Appendix 1: atropine - opioids

**BREAST FEEDING**

Therapeutic doses unlikely to affect infant.

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**LESS SUITABLE FOR PRESCRIBING**

Kaolin and Morphine Mixture, BP (Kaolin and Morphine Oral Suspension) is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

- Kaolin with morphine (Non-proprietary)

**Morphine hydrochloride 91.6 mg per 1 litre, Sodium bicarbonate 50 gram per 1 litre, Kaolin light 200 gram per 1 litre, Chloroform 5 ml per 1 litre**

Kaolin and Morphine mixture | 200 ml

**Loperamide hydrochloride**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th>06-Aug-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic treatment of acute diarrhoea</td>
<td></td>
</tr>
<tr>
<td>BY MOUTH</td>
<td></td>
</tr>
<tr>
<td>Child 4-7 years: 1 mg 3–4 times a day for up to 3 days only</td>
<td></td>
</tr>
<tr>
<td>Child 8-11 years: 2 mg 4 times a day for up to 5 days</td>
<td></td>
</tr>
</tbody>
</table>
Diarrhoea  67

### PATIENT AND CARER ADVICE
Medicines for Children leaflet: Loperamide for diarrhoea
[www.medicinesforchildren.org.uk/loperamide-diarrhoea](http://www.medicinesforchildren.org.uk/loperamide-diarrhoea)

### EXCEPTIONS TO LEGAL CATEGORY
Loperamide can be sold to the public, for use in adults and children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea.

Loperamide can be sold to the public, provided it is licensed and labelled for the treatment of acute diarrhoea associated with irritable bowel syndrome (after initial diagnosis by a doctor) in adults over 18 years of age.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, tablet, capsule, oral solution sugar-free, chewable tablets, orodispersible tablets, and solution.

### Important Safety Information
**MHRA/CHM Advice:** Reports of Serious Cardiac Adverse Reactions with High Doses of Loperamide Associated with Abuse or Misuse (September 2017)

Serious cardiovascular events (such as QT prolongation, torsades de pointes, and cardiac arrest), including fatalities, have been reported in association with large overdoses of loperamide.

Healthcare professionals are reminded that if symptoms of overdose occur, naloxone can be given as an antidote. The duration of action of loperamide is longer than that of naloxone (1–3 hours), so repeated treatment with naloxone might be indicated; patients should be monitored closely for at least 48 hours to detect possible CNS depression.

Pharmacists should remind patients not to take more than the recommended dose on the label.

### Contraindications
Active ulcerative colitis - antibiotic-associated colitis - conditions where abdominal distension develops - conditions where inhibition of peristalsis should be avoided

### Caution
Not recommended for children under 12 years

### Interactions
[Appendix 1: loperamide](#)

### Side-effects
Common or very common - Gastrointestinal disorders - headache - nausea

Uncommon - Dizziness - drowsiness - dry mouth - gastrointestinal discomfort - skin reactions - vomiting

Rare or very rare - Angioedema - consciousness impaired - coordination abnormal - fatigue - miosis - muscle tone increased - severe cutaneous adverse reactions (SCARs) - urinary retention

### Pregnancy
Manufacturers advise avoid — no information available.

### Breast Feeding
Amount probably too small to be harmful.

### Hepatic Impairment
Manufacturer advises caution — risk of reduced first pass metabolism leading to central nervous system toxicity.

### Prescribing and Dispensing Information
Palliative care - For further information on the use of loperamide in palliative care, see [www.medicinescomplete.com/#content/palliative/loperamide](http://www.medicinescomplete.com/#content/palliative/loperamide).

[www.getintopharma.com](http://www.getintopharma.com)
Antidiarrhoeals > Enkephalinase inhibitors

Racecadotril

**INDICATIONS AND DOSE**
Adjuvant to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea

- **BY MOUTH USING CAPSULES**
  - Adult: Initially 100 mg, then 100 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days, dose to be taken preferably before food
  - **BY MOUTH USING GRANULES**
    - Child 3 months–17 years (body-weight up to 9 kg): 10 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
    - Child 3 months–17 years (body-weight 9–12 kg): 20 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
    - Child 3 months–17 years (body-weight 13–27 kg): 30 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
    - Child 3 months–17 years (body-weight 28 kg and above): 60 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days

**CONTRA-INDICATIONS**
Antibiotic-associated diarrhoea

**SIDE-EFFECTS**
- **Uncommon** Skin reactions • Tonsillitis
- **Frequency not known** Angioedema • Erythema nodosum • Eyelid oedema • Face oedema • Oral disorders

**SIDE-EFFECTS, FURTHER INFORMATION**
Severe skin reactions have been reported—discontinue treatment immediately.

**PREGNANCY**
Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- In adults: Manufacturer advises caution.
- In children: Manufacturer advises avoid (no information available).

**RENAL IMPAIRMENT**
- In adults: Manufacturer advises caution.
- In children: Manufacturer advises avoid.

**DIRECTIONS FOR ADMINISTRATION**
Granules may be added to food or mixed with water or bottle feeds and then taken immediately.

**PATIENT AND CARER ADVICE**
Patients and carers should be given advice on how to administer racecadotril granules.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium, has advised (July 2014) that racecadotril (Hidrasec®) is not recommended for use within NHS Scotland for the treatment of acute diarrhoea in children because there is insufficient evidence that it improves the recovery rate.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

Granules

- **EXCIPIENTS:** May contain Sucrose
  - **Hidrasec:** (Lincoln Medical Ltd)
    - Racecadotril 10 mg: Hidrasec infants 10 mg granules sachets: 20 sachets £8.42
    - Racecadotril 30 mg: Hidrasec Children 30 mg granules sachets: 20 sachets £8.42

4 Disorders of gastric acid and ulceration

4.1 Dyspepsia

**Dyspepsia**

**Overview**
Dyspepsia covers upper abdominal pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration and, gastric cancer, but most commonly it is of uncertain origin.

Urgent endoscopic investigation is required if dyspepsia is accompanied by ‘alarm features’ (e.g. bleeding, dysphagia, recurrent vomiting, or weight loss). Urgent investigation should also be considered for patients over 55 years with unexplained, recent-onset dyspepsia that has not responded to treatment.

Patients with dyspepsia should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation p. 497, and raising the head of the bed. Some medications may cause dyspepsia—these should be stopped, if possible.

Antacids may provide some symptomatic relief, however if symptoms persist in uninvestigated dyspepsia, treatment involves a proton pump inhibitor for up to 4 weeks. A proton pump inhibitor can be used intermittently to control symptoms long term. Patients with uninvestigated dyspepsia, who do not respond to an initial trial with a proton pump inhibitor, should be tested for Helicobacter pylori and given eradication therapy if H. pylori is present. Alternatively, particularly in populations where H. pylori infection is more likely, the “test and treat” strategy for H. pylori can be used before a trial with a proton pump inhibitor.

If H. pylori is present in patients with functional (investigated, non-ulcer) dyspepsia, eradication therapy should be provided. If symptoms persist, treatment with either a proton pump inhibitor or a histamine H~2~ receptor antagonist can be given for 4 weeks. These antisecretory drugs can be used intermittently to control symptoms long term. However, most patients with...
functional dyspepsia do not benefit symptomatically from *H. pylori* eradication therapy or antisecretory drugs.

**ANTACIDS**

**Antacids**

**Overview**

Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in *ulcer dyspepsia* and in *non-erosive gastro-oesophageal reflux*; they are also sometimes used in functional (non-ulcer) dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, although additional doses may be required. Conventional doses of liquid magnesium–aluminium antacids promote ulcer healing, but less well than antisecretory drugs; proof of a relationship between healing and neutralising capacity is lacking. Liquid preparations are more effective than tablet preparations. Liquid preparations contain more than one antacid may be the same as simpler preparations. Complexes such as hydrotalcite confer no special advantage. Liquid preparations containing thickening agents do not appear to be a risk if renal function is normal.

**Aluminium- and magnesium-containing** antacids (e.g. aluminium hydroxide p. 1052, magnesium carbonate p. 71, co-magaldrate p. 70 and magnesium trisilicate p. 71), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal. The acid-neutralising capacity of preparations that contain more than one antacid may be the same as simpler preparations. Complexes such as hydrotalcite confer no special advantage. Sodium bicarbonate p. 1038 should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. However, it retains a place in the management of urinary-tract disorders and acidosis.

**Bismuth-containing** antacids (unless chelates) are not recommended because absorbed bismuth can be neurotoxic, causing encephalopathy; they tend to be constipating.

**Calcium-containing** antacids can induce rebound acid secretion: with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis, and can precipitate the milk-alkali syndrome.

**Simeticone**

Simeticone (activated dimeticone) p. 71 is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care.

**Alginates**

Alginates taken in combination with an antacid increases the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some alginate-containing preparations form a viscous gel (‘raft’) that floats on the surface of the stomach contents, thereby reducing symptoms of reflux.

The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

**ANTACIDS, ALGINATE**

### Alginic acid

**INDICATIONS AND DOSE**

**GAVISCON INFANT® POWDER SACHETS**

Management of *gastro-oesophageal reflux disease*

- BY MOUTH
  - Child 1–23 months (body-weight up to 4.5 kg): 1 dose as required, to be mixed with feeds (or water, for breast-fed infants); maximum 6 doses per day
  - Child 1–23 months (body-weight 4.5 kg and above): 2 doses as required, to be mixed with feeds (or water, for breast-fed infants); maximum 12 doses per day

**CONTRA-INDICATIONS**

Intestinal obstruction – preterm neonates - where excessive water loss likely (e.g. fever, diarrhoea, vomiting, high room temperature)

**GAVISON INFANT® POWDER SACHETS**

- Concurrent use of preparations containing thickening agents
- **RENAL IMPAIRMENT**
  - In patients with fluid retention, avoid antacids containing large amounts of sodium.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Each half of the dual-sachet is identified as ‘one dose’.
  - To avoid errors prescribe with directions in terms of ‘dose’.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder**

**ELECTROLYTES:** May contain Sodium

<table>
<thead>
<tr>
<th>Gaviscon Infant (Forum Health Products Ltd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium alginate 87.5 mg, Sodium alginate 225 mg</td>
</tr>
<tr>
<td>DT = £4.82</td>
</tr>
</tbody>
</table>

**Sodium alginate with potassium bicarbonate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, alginic acid above.

**INDICATIONS AND DOSE**

Management of mild symptoms of *dyspepsia* and *gastro-oesophageal reflux disease*

- BY MOUTH USING CHEWABLE TABLETS
  - Child 6–11 years (under medical advice only): 1 tablet, to be chewed after meals and at bedtime
  - Child 12–17 years: 1–2 tablets, to be chewed after meals and at bedtime
  - Adult: 1–2 tablets, to be chewed after meals and at bedtime

- BY MOUTH USING ORAL SUSPENSION
  - Child 2–11 years (under medical advice only): 2.5–5 mL, to be taken after meals and at bedtime
  - Child 12–17 years: 5–10 mL, to be taken after meals and at bedtime
  - Adult: 5–10 mL, to be taken after meals and at bedtime

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of oral liquid formulations may include aniseed or peppermint.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

**ELECTROLYTES:** May contain Potassium, sodium

<table>
<thead>
<tr>
<th>Acidez Advance (Wockhardt UK Ltd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium bicarbonate 20 mg per 1 ml, Sodium alginate 100 mg per 1 ml</td>
</tr>
<tr>
<td>250 ml (6)</td>
</tr>
</tbody>
</table>
Disorders of gastric acid and ulceration

Co-magaldrox

The properties listed below are those particular to the combination only. For the properties of the components please consider, aluminium hydroxide p. 1052, magnesium hydroxide p. 59.

- **INDICATIONS AND DOSE**
  - **MAALOX®**
    - **Dyspepsia**
      - **BY MOUTH**
        - Child 14–17 years: 10–20 mL, to be taken 20–60 minutes after meals, and at bedtime or when required
        - Adult: 10–20 mL, to be taken 20–60 minutes after meals, and at bedtime or when required
      - **MUCOGEL®**
        - **Dyspepsia**
          - **BY MOUTH**
            - Child 12–17 years: 10–20 mL 3 times a day, to be taken 20–60 minutes after meals, and at bedtime, or when required
            - Adult: 10–20 mL 3 times a day, to be taken 20–60 minutes after meals, and at bedtime, or when required

- **INTERACTIONS** → Appendix 1: antacids • magnesium
- **PRESCRIBING AND DISPENSING INFORMATION**

Co-magaldrox is a mixture of aluminium hydroxide and magnesium hydroxide; the proportions are expressed in the form x/y where x and y are the strengths in milligrams per unit dose of magnesium hydroxide and aluminium hydroxide respectively.

- **MAALOX®** Maalox® suspension is low in sodium.
- **MUCOGEL®** Mucogel® suspension is low in sodium.

- **MAGNESIUM hydroxide**
  - **INDICATIONS AND DOSE**
    - **Dyspepsia**
      - **BY MOUTH**
        - Child 8–11 years: 5 mL 4 times a day as required, to be taken between meals and at bedtime
        - Child 12–17 years: 10 mL 4 times a day as required, to be taken between meals and at bedtime
        - Adult: 10 mL 4 times a day as required, to be taken between meals and at bedtime

- **CONTRA-INDICATIONS**
  - Hypophosphataemia • infants • neonates
  - **CONTRA-INDICATIONS, FURTHER INFORMATION**
    - Aluminium-containing antacids Aluminium-containing antacids should not be used in neonates and infants because accumulation may lead to increased plasma-aluminium concentrations.
    - **RENAL IMPAIRMENT**
      - **Dose adjustments** Antacids containing magnesium salts should be avoided or used at a reduced dose because there is an increased risk of toxicity.
      - In adults There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).
      - In children Aluminium-containing antacids should not be used in children with renal impairment, because accumulation may lead to increased plasma-aluminium concentrations.
    - **PRESCRIBING AND DISPENSING INFORMATION**
      - Altacite Plus® is low in Na+.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
  - **Maalox®**
    - Aluminium hydroxide 35 mg per 1 mL
    - Magnesium hydroxide 40 mg per 1 mL
    - Maalox 175mg/200mg/5ml oral suspension sugar-free | 250 mL GSK £2.33 DT + £2.33
  - **Mucogel®**
    - Mucogel oral suspension sugar-free | 500 mL GSK £2.99 DT + £2.99

**Simeticone with aluminium hydroxide and magnesium hydroxide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, simeticone p. 71, aluminium hydroxide p. 1052.

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **BY MOUTH**
      - Child 12-17 years: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required
      - Adult: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required

- **INTERACTIONS** → Appendix 1: antacids

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
  - **Maalox Plus®**
    - Simeticone 5 mg per 1 mL
    - Magnesium hydroxide 39 mg per 1 mL
    - Aluminium hydroxide gel dried 44 mg per 1 mL
    - Maalox Plus oral suspension sugar-free | 250 mL GSK £2.91
Magnesium carbonate

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **By mouth using oral suspension**
    - Adults: 10 mL 3 times a day, dose to be taken in water
  - **Contra-indications**
    - Hypophosphataemia
  - **Interactions**
    - **Antacids**
    - **Magnesium with aluminium hydroxide**
      - Avoid or used at a reduced dose
      - Evidence of benefit in infantile colic uncertain
  - **Side-effects**
    - Diarrhoea
  - **Hepatic impairment**
    - In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.
  - **Renal impairment**
    - Magnesium carbonate mixture has a high sodium content; avoid in patients with fluid retention.
    - **Dose adjustments**
      - Avoid or use at a reduced dose
      - Increased risk of toxicity.
  - **Prescribing and dispensing information**
    - When prepared extemporaneously, the BP states Magnesium Carbonate Mixture, BP consists of light magnesium carbonate 3%, sodium bicarbonate 5%, in a suitable vehicle containing aromatic cardamom tincture.
  - **Medicinal forms**
    - No licensed medicines listed.

Magnesium trisilicate

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **By mouth using chewable tablets**
    - Adults: 1–2 tablets as required
  - **Contra-indications**
    - Hypophosphataemia
  - **Interactions**
    - **Antacids**
    - **Magnesium with aluminium hydroxide**
      - Avoid or used at a reduced dose
      - Evidence of benefit in infantile colic uncertain
  - **Side-effects**
    - Diarrhoea
  - **Hepatic impairment**
    - Avoid in hepatic coma; risk of renal failure.
    - **Dose adjustments**
      - Avoid or use at a reduced dose
      - Increased risk of toxicity.
  - **Prescribing and dispensing information**
    - When prepared extemporaneously, the BP states Magnesium Trisilicate, BP consists of 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour.
  - **Medicinal forms**
    - No licensed medicines listed.

Magnesium trisilicate with magnesium carbonate and sodium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, magnesium trisilicate above, magnesium carbonate above, sodium bicarbonate p. 1038.

- **INDICATIONS AND DOSE**
  - **Dyspepsia**
    - **By mouth**
      - Child 5–11 years: 5–10 mL 3 times a day, alternatively as required, dose to be made up with water
      - Child 12–17 years: 10–20 mL 3 times a day, alternatively as required, dose to be made up with water
      - Adults: 10–20 mL 3 times a day, alternatively as required, dose to be made up with water
  - **Contra-indications**
    - Hypophosphataemia • Severe renal failure
  - **Caution**
    - Heart failure • Hypermagnesaemia • Hypertension • Metabolic alkalosis • Respiratory alkalosis
  - **Interactions**
    - Antacids • Magnesium with aluminium hydroxide and magnesium carbonate mixtures have high sodium content; avoid in patients with fluid retention.
  - **Prescribing and dispensing information**
    - When prepared extemporaneously, the BP states Magnesium Trisilicate Mixture, BP consists of 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour.
  - **Medicinal forms**
    - No licensed medicines listed.

Simeticone

(Activated dimeticone)

- **Drug action**
  - Simeticone (activated dimeticone) is an antifoaming agent.

- **Indications and dose**
  - **Dentinox®**
    - Colic/Wind pains
      - **By mouth**
        - Child 1 month–1 year: 2.5 mL, to be taken with or after each feed; may be added to bottle feed; maximum 6 doses per day
  - **Infacol®**
    - Colic/Wind pains
      - **By mouth**
        - Child 1 month–1 year: 0.5–1 mL, to be taken before feeds
  - **Prescribing and dispensing information**
    - **Dentinox®**
      - The brand name Dentinox® is also used for other preparations including teething gel.
  - **Patient and carer advice**
    - Infacol® Patients or carers should be given advice on use of the Infacol® dropper.
  - **Less suitable for prescribing**
    - Infacol® Infacol® is less suitable for prescribing (evidence of benefit in infantile colic uncertain).
  - **Dentinox®**
    - Denthin® colic drops are less suitable for prescribing (evidence of benefit in infantile colic uncertain).
  - **Medicinal forms**
    - There can be variation in the licensing of different medicines containing the same drug.

- **Oral suspension**
  - Infacol (Teva UK Ltd)
    - Simeticone 40 mg per 1 ml
      - Infacol 40 mg/ml oral suspension sugar-free | 50 ml [GSL] £2.71 DT + £2.71 sugar-free | 55 ml [GSL] £3.20 sugar-free | 85 ml [GSL] £4.66
  - Oral drops
    - Dentinox Infant (Dendron Ltd)
      - Simeticone 8.4 mg per 1 ml
      - Denthin infant colic drops | 100 mL [GSL] £1.80 DT + £1.80
  - Combinations available: Co-simalite, p. 70 • Simeticone with aluminium hydroxide and magnesium hydroxide, p. 70
4.2 Gastric and duodenal ulceration

Peptic ulceration

Overview

Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma. Healing can be promoted by general measures, Smoking cessation p. 497 and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by Helicobacter pylori.

Helicobacter pylori infection

Eradication of Helicobacter pylori reduces recurrence of gastric and duodenal ulcers and the risk of rebleeding. It also causes regression of most localized gastric mucosa associated lymphoid-tissue (MALT) lymphomas. The presence of H. pylori should be confirmed before starting eradication treatment. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of H. pylori; reinfection is rare. Antibiotic associated colitis is an uncommon risk.

For initial treatment, a one-week triple-therapy regimen that comprises a proton pump inhibitor, clarithromycin p. 538, and either amoxicillin p. 548 or metronidazole p. 542 can be used. However, if a patient has been treated with metronidazole for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin is preferred for initial therapy. If a patient has been treated with a macrolide for other infections, a regimen containing a proton pump inhibitor, amoxicillin and metronidazole is preferred for initial therapy. These regimens eradicate H. pylori in about 85% of cases. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H₂-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation, then antisecretory treatment is continued for a further 3 weeks. Treatment failure usually indicates antibacterial resistance or poor compliance. Resistance to amoxicillin is rare. However, resistance to clarithromycin and metronidazole is common and can develop during treatment.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial are licensed, but produce low rates of H. pylori eradication and are not recommended. Tinidazole p. 544 is also used occasionally for H. pylori eradication as an alternative to metronidazole; tinidazole should be combined with antisecretory drugs and other antibacterials.

Routine retesting, to confirm eradication, is not necessary unless the patient has gastric MALT lymphoma or complicated H. pylori associated peptic ulcer.

A two-week regimen comprising a proton pump inhibitor plus tetracycline p. 567, plus metronidazole can be used for eradication failure. Alternatively, the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

See under NSAID-associated ulcers for the role of H. pylori eradication therapy in patients starting or taking a NSAID. Also see Dyspepsia p. 68 for H. pylori eradication in patients with dyspepsia.

Test for Helicobacter pylori

¹³C-Urea breath test kits are available for the diagnosis of gastro-duodenal infection with Helicobacter pylori. The test involves collection of breath samples before and after ingestion of an oral solution of ¹³C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific ¹³C-Urea breath test kit for children is available (Helicobacter Test INFAI for children of the age 3–11®). However, the appropriateness of testing for H. pylori infection in children has not been established.

NSAID-associated ulcers

Gastro-intestinal bleeding and ulceration can occur with NSAID use. The risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs. Whenever possible, the NSAID should be withdrawn if an ulcer occurs.

Patients at high risk of developing gastro-intestinal complications with a NSAID include those aged over 65 years, those with a history of peptic ulcer disease or serious gastro-intestinal complication, those taking other medicines that increase the risk of gastro-intestinal side-effects, or those with serious co-morbidity (e.g. cardiovascular disease, diabetes, renal or hepatic impairment). In those at risk of ulceration, a proton pump inhibitor can be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; a H₂-receptor antagonist such as ranitidine p. 75 given at twice the usual dose or misoprostol p. 77 are alternatives. Colic and diarrhoea may limit the dose of misoprostol. Its use is most appropriate for the frail or very elderly from whom NSAIDs cannot be withdrawn. A combination of a cyclo-oxygenase-2 selective inhibitor with a proton pump inhibitor may be more appropriate for those with a history of upper gastro-intestinal bleeding or 3 or more risk factors for gastro-intestinal ulceration, but see NSAIDs and Cardiovascular Events.

NSAID use and H. pylori infection are independent risk factors for gastro-intestinal bleeding and ulceration. In patients already taking a NSAID, eradication of H. pylori is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in patients with dyspepsia or a history of gastric or duodenal ulcer, who are H. pylori positive, and who are about to start long-term treatment with a non-selective NSAID, eradication of H. pylori may reduce the overall risk of ulceration.

In a patient who has developed an ulcer, if the NSAID can be discontinued, a proton pump inhibitor usually produces the most rapid healing; alternatively, the ulcer can be treated with a H₂-receptor antagonist or misoprostol. On healing, patients should be tested for H. pylori and given eradication therapy if H. pylori is present (see also Test for Helicobacter pylori).

If treatment with a non-selective NSAID needs to continue, the following options are suitable:

- Treat ulcer with a proton pump inhibitor and on healing continue the proton pump inhibitor (dose not normally reduced because asymptomatic ulcer recurrence may occur);
- Treat ulcer with a proton pump inhibitor and on healing switch to misoprostol for maintenance therapy (colic and diarrhoea may limit the dose of misoprostol);
- Treat ulcer with a proton pump inhibitor and switch non-selective NSAID to a cyclo-oxygenase-2 selective inhibitor, but see NSAIDs and Cardiovascular Events; on healing, continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

If treatment with a cyclo-oxygenase-2 selective inhibitor needs to continue, treat ulcer with a proton pump inhibitor; on healing continuation of the proton pump inhibitor in
patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

**GASTROPROTECTIVE COMPLEXES AND CHELATORS**

### Chelates and complexes

#### Overview
Sucralfate below may act by protecting the mucosa from acid-pepsin attack in gastric and duodenal ulcers. It is a complex of aluminium hydroxide and sulfated sucrose but has minimal antacid properties.

---

#### Sucralfate

### INDICATIONS AND DOSE

**Benign gastric ulceration | Benign duodenal ulceration**

- **BY MOUTH**
  - Child 15-17 years: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day
  - Adult: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Chronic gastritis**

- **Adults:** 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Prophylaxis of stress ulceration in child under intensive care**

- **BY MOUTH**
  - Child 15-17 years: 1 g 6 times a day; maximum 8 g per day

**Prophylaxis of stress ulceration**

- **BY MOUTH**
  - Adult: 1 g 6 times a day; maximum 8 g per day

### UNLICENSED USE

- In children: Tablets not licensed for prophylaxis of stress ulceration.

### CAUTIONS

- Patients under intensive care (Important: reports of bezoar formation)

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### Recommended regimens for Helicobacter pylori eradication in adults

<table>
<thead>
<tr>
<th>Acid suppressant</th>
<th>Antibacterial</th>
<th>Price for 7-day course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anxocillin</td>
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<tr>
<td>Esomeprazole 20 mg twice daily</td>
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<tr>
<td>Lansoprazole 30 mg twice daily</td>
<td>1 g twice daily</td>
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<td>Omeprazole 20 mg twice daily</td>
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<tr>
<td>Pantoprazole 40 mg twice daily</td>
<td>1 g twice daily</td>
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<tr>
<td>Rabeprazole sodium 20 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
</tbody>
</table>

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### CAUTIONS, FURTHER INFORMATION

- Bezoar formation: Following reports of bezoar formation associated with sucralfate, caution is advised in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.

### INTERACTIONS

- Appendix 1: sucralfate

### SIDE-EFFECTS

- Common or very common: Constipation
- Uncommon: Dry mouth, nausea
- Rare or very rare: Bezoar, rash

### FREQUENCY NOT KNOWN

- Back pain, bone disorders, diarrhoea, dizziness, drowsiness, encephalopathy, flatulence, headache, vertigo

### PREGNANCY

- No evidence of harm; absorption from gastrointestinal tract negligible.

### BREAST FEEDING

- Amount probably too small to be harmful.

### RENAL IMPAIRMENT

- Use with caution; aluminium is absorbed and may accumulate.

### DIRECTIONS FOR ADMINISTRATION

- Oral suspension blocks fine-bore feeding tubes. Crushed tablets may be dispersed in water.

### PRESCRIBING AND DISPENSING INFORMATION

- Flavours of oral liquid formulations may include aniseed and caramel.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension

### Tablet

- CAUTIONARY AND ADVISORY LABELS 5
- | | |
- | Sucralfate (Imported) | |
- | Sucralfate 1 gram | 1 g tablets | 100 tablet |
- | Carafate 1 g tablets | 100 tablet |

### H2-RECEPTOR ANTAGONISTS

#### H2-receptor antagonists

##### Overview

Histamine H2-receptor antagonists heal gastric and duodenal ulcers by reducing gastric acid output as a result of histamine H2-receptor blockade; they are also used to relieve symptoms of gastro-oesophageal reflux disease. H2-receptor antagonists should not normally be used for Zollinger-Ellison syndrome because proton pump inhibitors are more effective.
Maintenance treatment with low doses for the prevention of peptic ulcer disease has largely been replaced in Helicobacter pylori positive patients by eradication regimens.

In adults, H₂-receptor antagonists are used for the treatment of functional dyspepsia and may be used for the treatment of uninvestigated dyspepsia without alarm features. H₂-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal).

Treatment with a H₂-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from gastroduodenal erosions in hepatic coma, and possibly in other conditions requiring intensive care. H₂-receptor antagonists also reduce the risk of acid aspiration in obstetric patients at delivery (Mendelson's syndrome).

### H₂-receptor antagonists

#### CAUTIONS

- Signs and symptoms of gastric cancer (in adults)

#### CAUTIONS, FURTHER INFORMATION

- Gastric cancer
- In adults H₂-receptor antagonists might mask symptoms of gastric cancer; particular care is required in patients presenting with ‘alarm features’ in such cases gastric malignancy should be ruled out before treatment.

#### SIDE-EFFECTS

- Common or very common Constipation; diarrhoea; dizziness; fatigue; headache; myalgia; skin reactions
- Uncommon Confusion; depression; erectile dysfunction; gynaecomastia; hallucination; hepatic disorders; leucopenia; nausea; tachycardia
- Rare or very rare Agranulocytosis; alopecia; arthralgia; atrioventricular block; fever; galactorrhoea; pancytopenia; thrombocytopenia; vasculitis

### Cimetidine

#### INDICATIONS AND DOSE

- **Benign duodenal ulceration**
  - **BY MOUTH**
  - Adult: 400 mg twice daily for at least 4 weeks, to be taken with breakfast and at night, alternatively 800 mg once daily for at least 4 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg once daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

- **Benign gastric ulceration**
  - **BY MOUTH**
  - Adult: 400 mg twice daily for 6 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 6 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg once daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

- **NSAID-associated ulceration**
  - **BY MOUTH**
  - Adult: 400 mg twice daily for 8 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 8 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

- **Reflux oesophagitis**
  - **BY MOUTH**
  - Adult: 400 mg 4 times a day for 4–8 weeks

### Prophylaxis of stress ulceration

- **BY MOUTH**
  - Adult: 200–400 mg every 4–6 hours

### Gastric acid reduction in obstetrics

- **BY MOUTH**
  - Adult: Initially 400 mg, to be administered at start of labour, then increased if necessary up to 400 mg every 4 hours, do not use syrup in prophylaxis of acid aspiration; maximum 2.4 g per day

### Gastric acid reduction during surgical procedures

- **BY MOUTH**
  - Adult: 400 mg, to be given 90–120 minutes before induction of general anaesthesia

### Short-bowel syndrome

- **BY MOUTH**
  - Adult: 400 mg twice daily, adjusted according to response, to be taken with breakfast and at bedtime

### To reduce degradation of pancreatic enzyme supplements

- **BY MOUTH**
  - Adult: 0.8–1.6 g daily in 4 divided doses, dose to be taken 1–1.5 hours before meals

#### INTERACTIONS

- → Appendix 1: H₂ receptor antagonists

#### SIDE-EFFECTS

- Rare or very rare Anaphylactic reaction; aplastic anaemia; nephritis tubulointerstitial; pancreatitis; sinus bradycardia

#### PREGNANCY

- Manufacturer advises avoid unless essential.

#### BREAST FEEDING

- Significant amount present in milk—not known to be harmful but manufacturer advises avoid.

#### HEPATIC IMPAIRMENT

- Increased risk of confusion.

#### Dose adjustments

- Reduce dose

#### RENAL IMPAIRMENT

- Occasional risk of confusion.

#### Dose adjustments

- Reduce dose to 200 mg 4 times daily if eGFR 30–50 mL/minute/1.73 m².
- Reduce dose to 200 mg 3 times daily if eGFR 15–30 mL/minute/1.73 m².
- Reduce dose to 200 mg twice daily if eGFR less than 15 mL/minute/1.73 m².

#### EXCEPTIONS TO LEGAL CATEGORY

- Cimetidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity (max. single dose 200 mg, max. daily dose 800 mg), and for the prophylactic management of nocturnal heartburn (single night-time dose 100 mg).

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

#### Oral solution

- EXCIPIENTS: May contain Propylene glycol
- **Cimetidine (Non-proprietary)**
- Cimetidine 40 mg per 1 ml Cimetidine 200mg/5ml oral solution sugar free sugar-free | 300 ml | £14.24–£14.25 DT = £14.25
- Tagamet (Essential Pharma Ltd) Cimetidine 40 mg per 1 ml Tagamet 200mg/5ml syrup | 600 ml | £28.49 DT = £28.49

#### Tablet

- **Cimetidine (Non-proprietary)**
- Cimetidine 200 mg Cimetidine 200mg tablets | 60 tablet | £45.59 DT = £18.15
- Cimetidine 400 mg Cimetidine 400mg tablets | 60 tablet | £120.00
- Cimetidine 800 mg Cimetidine 800mg tablets | 30 tablet | £15.91
- Tagamet (Chenidex Pharma Ltd) Cimetidine 400 mg Tagamet 400mg tablets | 60 tablet | £15.48 DT = £15.48
- Cimetidine 800 mg Tagamet 800mg tablets | 30 tablet | £22.62 DT = £15.91
- Cimetidine 800 mg Tagamet 800mg tablets | 30 tablet | £22.62 DT = £15.48
**Famotidine**

### INDICATIONS AND DOSE

**Gastric and duodenal ulceration**
- **Treatment of benign gastric and duodenal ulceration**
  - **BY MOUTH**
  - Adult: 40 mg once daily for 4–8 weeks, dose to be taken at night

**Maintenance treatment of duodenal ulceration**
- **BY MOUTH**
- Adult: 20 mg once daily, dose to be taken at night

**Reflux oesophagitis**
- **BY MOUTH**
- Adult: 20–40 mg twice daily for 6–12 weeks; maintenance 20 mg twice daily

### INTERACTIONS
- Appendix 1: H2 receptor antagonists

### SIDE-EFFECTS
- Uncommon: Appetite decreased, dry mouth, taste altered, vomiting
- Rare or very rare: Anxiety, chest tightness, drowsiness, insomnia, interstitial pneumonia, libido decreased, muscle cramps, neutropenia, paraesthesia, psychiatric disorder, seizures, severe cutaneous adverse reactions (SCARs)

### PREGNANCY
- Manufacturer advises avoid unless potential benefit outweighs risk.

### BREAST FEEDING
- Present in milk—not known to be harmful but manufacturer advises avoid.

### RENAL IMPAIRMENT
- Seizures reported very rarely.
- **Dose adjustments** Use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 mL/minute/1.73 m².

### EXCEPTIONS TO LEGAL CATEGORY
- Ranitidine can be sold to the public for the prevention and treatment of symptoms of food-related heartburn and meal-induced indigestion in adults and children over 16 years; max. single dose 75 mg, max. daily dose 150 mg for max. 14 days.

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

#### Capsule
- **Nizatidine (Non-proprietary)**
  - Nizatidine 150 mg: Nizatidine 150 mg capsules | 30 capsule
    - £12.20 DT = £3.90
  - Nizatidine 300 mg: Nizatidine 300 mg capsules | 30 capsule
    - £15.43 DT = £5.14

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**Ranitidine**

### INDICATIONS AND DOSE

**Benign gastric ulceration | Duodenal ulceration**
- **BY MOUTH**
- Child 1-5 months: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
- Child 6 months–2 years: 2–4 mg/kg twice daily
- Child 3–11 years: 2–4 mg/kg twice daily (max. per dose 150 mg)
- Child 12–17 years: 150 mg twice daily, alternatively 300 mg once daily, dose to be taken at night
- Adult: 150 mg twice daily for 4–8 weeks, alternatively 300 mg once daily for 4–8 weeks, dose to be taken at night

**Chronic episodic dyspepsia**
- **BY MOUTH**
- Adult: 150 mg twice daily for 6 weeks, alternatively 300 mg once daily for 6 weeks, dose to be taken at night

**NSAID-associated gastric ulceration**
- **BY MOUTH**
- Adult: 150 mg twice daily for up to 8 weeks, alternatively 300 mg once daily for up to 8 weeks, dose to be taken at night

**NSAID-associated duodenal ulcer**
- **BY MOUTH**
- Adult: 300 mg twice daily for 4 weeks, to achieve a higher healing rate

**Prophylaxis of NSAID-associated gastric ulcer | Prophylaxis of NSAID-associated duodenal ulcer**
- **BY MOUTH**
- Adult: 300 mg twice daily

**Gastro-oesophageal reflux disease**
- **BY MOUTH**
- Adult: 150 mg twice daily for up to 8 weeks or if necessary 12 weeks, alternatively 300 mg once daily for up to 8 weeks or if necessary 12 weeks, dose to be taken at night

**Moderate to severe gastro-oesophageal reflux disease**
- **BY MOUTH**
- Adult: 600 mg daily in 2–4 divided doses for up to 12 weeks

**Long-term treatment of healed gastro-oesophageal reflux disease**
- **BY MOUTH**
- Adult: 150 mg twice daily
Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics

- **BY MOUTH**
- Adult: 150 mg, dose to be given at onset of labour, then 150 mg every 6 hours

Gastric acid reduction (prophylaxis of acid aspiration) in surgical procedures

- **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 mg, to be given 45–60 minutes before induction of anaesthesia, intravenous injection diluted to 20 mL and given over at least 2 minutes, alternatively (by mouth) 150 mg, to be given 2 hours before induction of anaesthesia and also when possible on the preceding evening

**Prophylaxis of stress ulceration**

- **INITIALLY BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 mg every 8 hours, dose to be diluted to 20 mL and given over at least 2 minutes, then (by mouth) 150 mg twice daily, may be given when oral feeding commences

**Reflux oesophagitis and other conditions where gastric acid reduction is beneficial**

- **BY MOUTH**
  - Child 1–5 months: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
  - Child 6 months–2 years: 2–4 mg/kg twice daily
  - Child 3–11 years: 2–4 mg/kg twice daily (max. per dose 150 mg); increased to up to 5 mg/kg twice daily (max. per dose 300 mg), dose increase for severe gastro-oesophageal disease
  - Child 12-17 years: 150 mg twice daily, alternatively 300 mg once daily, dose to be taken at night, then increased if necessary to 300 mg twice daily for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease, alternatively increased if necessary to 150 mg 4 times a day for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease

**Conditions where reduction of gastric acidity is beneficial and oral route not available**

- **BY INTRAMUSCULAR INJECTION**
- Adult: 50 mg every 6–8 hours
- By slow intravenous injection
- Adult: 50 mg, dose to be diluted to 20 mL and given over at least 2 minutes; may be repeated every 6–8 hours

**UNLICENSED USE**

- In children Oral preparations not licensed for use in children under 3 years.
- In adults Doses given for prophylaxis of NSAID-associated gastric or duodenal ulcer, and prophylaxis of stress ulceration, are not licensed.

**INTERACTIONS**

- Appendix 1: H2 receptor antagonists

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Rare or very rare Bone marrow depression, bradycardia, breath conditions, dyskinesia, nephritis acute interstitial, pancreatitis acute, vision blurred
- Frequency not known Dyspepsia

**SPECIFIC SIDE-EFFECTS**

- Rare or very rare
  - With parenteral use Anaphylactic shock, cardiac arrest
- **PREGNANCY** Manufacturer advises avoid unless essential, but not known to be harmful.
- **BREAST FEEDING** Significant amount present in milk, but not known to be harmful.
- **RENAL IMPAIRMENT**
  - Dose adjustments
  - In adults Use half normal dose if eGFR less than 50 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion (Zantac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%.

**PATIENT AND CARER ADVICE**

- In fat malabsorption syndrome, give oral doses 1–2 hours before food to enhance effects of pancreatic enzyme replacement.
- Medicines for Children leaflet: Ranitidine for acid reflux
- www.medicinesforchildren.org.uk/ranitidine-acid-reflux

**EXCEPTIONS TO LEGAL CATEGORY**

- Ranitidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink (max. single dose 75 mg, max. daily dose 300 mg).

**MEDIcular FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, infusion

**Tablet**

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Ranitidine 150 mg tablets 60 tablet (£0.07) £2.12 DT = £1.07
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Ranitidine 300 mg tablets 30 tablet (£0.07) £2.12 DT = £1.08
  - Zantac (Omega Pharma Ltd, GlaxoSmithKline UK Ltd) Ranitidine (as Ranitidine hydrochloride) 75 mg Zantac 75 tablets 24 tablet (£0.16) 48 tablet (£0.75 DT = £0.77
  - Ranitidine (as Ranitidine hydrochloride) 150 mg Zantac 150 mg tablets 60 tablet (£0.09) £1.30 DT = £1.07
  - Ranitidine (as Ranitidine hydrochloride) 300 mg Zantac 300 mg tablets 30 tablet (£0.10) £1.30 DT = £1.08

**Solution for injection**

- **Ranitidine (Non-proprietary)**
  - Ranitidine (as Ranitidine hydrochloride) 25 mg per 1 mL Ranitidine 50 mg/2 mL solution for injection ampoules 5 ampoule (£0.08) £2.65–£5.00 DT = £2.96
  - Zantac (GlaxoSmithKline UK Ltd) Ranitidine (as Ranitidine hydrochloride) 25 mg per 1 mL Zantac 50 mg/2 mL solution for injection ampoules 5 ampoule (£0.08) £2.82 DT = £2.96

**Effervescent tablet**

- CAUTIONARY AND ADVISORY LABELS
  - 13 ELECTROLYTES: May contain Sodium
  - **Ranitidine (Non-proprietary)**
    - Ranitidine (as Ranitidine hydrochloride) 150 mg Ranitidine 150 mg effervescent tablets 60 tablet (£0.08) £3.50 DT = £3.49
    - Ranitidine (as Ranitidine hydrochloride) 300 mg Ranitidine 300 mg effervescent tablets 30 tablet (£0.08) £3.50 DT = £3.49

**Oral solution**

- EXCIPIENTS: May contain Alcohol
  - **Ranitidine (Non-proprietary)**
    - Ranitidine (as Ranitidine hydrochloride) 15 mg per 1 mL Ranitidine 75 mg/5 mL oral solution sugar free 500 mL (£0.07) £2.07–£2.43 DT = £2.15
    - Ranitidine (as Ranitidine hydrochloride) 30 mg per 1 mL Ranitidine 150 mg/5 mL oral solution sugar free 500 mL (£0.07) £2.15 DT = £2.07
  - Zantac (GlaxoSmithKline UK Ltd) Ranitidine (as Ranitidine hydrochloride) 15 mg per 1 mL Zantac 150 mg/10 mL syrup sugar-free 300 mL (£0.08) £2.07 DT = £2.00

www.getintopharma.com
Misoprostol

**DRUG ACTION** Misoprostol is a synthetic prostaglandin analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers.

**INDICATIONS AND DOSE**

**CYTOTEC ®**

Benign gastric ulcer | Benign duodenal ulcer | NSAID-induced peptic ulcer

- **BY MOUTH**
  - Adult: 200 micrograms 2–4 times a day
  - Adult: 400 micrograms twice daily, alternatively 200 micrograms 4 times a day continued for at least 4 weeks or may be continued for up to 8 weeks if required, dose to be taken with breakfast (or main meals) and at bedtime

**Prophylaxis of NSAID-induced peptic ulcer**

- **BY MOUTH**
  - Adult: 200 micrograms 2–4 times a day

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common: Nausea, rash, vomiting
- Uncommon: Uterine rupture

**SPECIFIC SIDE-EFFECTS**

- Common or very common: Constipation, diarrhoea, dizziness, flatulence, gastrointestinal discomfort, headache
- Uncommon: Fever, haemorrhage, menstrual cycle irregularities, postmenopausal haemorrhage, uterine cramps
- Frequency not known: Chills

**SIDE-EFFECTS, FURTHER INFORMATION** Diarrhoea may occasionally be severe and require withdrawal, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids.

**CONCEPTION AND CONCEPTION**

Manufacturer advises do not use in women of childbearing potential unless pregnancy has been excluded; patients must use effective contraception during treatment, and be informed of the risks of taking misoprostol if pregnant.

**PREGNANCY**

Manufacturer advises avoid—induces uterine contractions, and associated with abortion and birth defects; teratogenic in first trimester.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk, and may cause diarrhoea in nursing infants. Tertiary sources state present in milk but amount probably too small to be harmful; to further reduce risk following termination of pregnancy, consider interrupting breastfeeding for 5 hours after a dose.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks. Manufacturer advises patients should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**MEIYODELLE ® VAGINAL DELIVERY SYSTEM**

All Wales Medicines Strategy Group (AWMSG) decisions

AWMSG No. 3627

The All Wales Medicines Strategy Group has advised (March 2018) that misoprostol (Myoselle ®) is recommended as an option for use within NHS Wales for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

- **Cytosex (Pfizer Ltd)**
  - Misoprostol 200 microgram Cytosex 200microgram tablets | 60 tablet pack £10.03 BT + £1.03

## PROSTAGLANDIN ANALOGUES AND PROSTAMIDES

GASTROPROTECTIVE

**PROSTAGLANDINS, PROSTAGLANDIN ANALOGUES AND CYTOTEC ®**

Promoting healing of gastric and duodenal ulcers.

Misoprostol is a synthetic prostaglandin analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers. It is a prostaglandin-E1 analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers.

21-Feb-2018

**Overview**

Proton pump inhibitors are effective short-term treatments for gastric and duodenal ulcers; they are also used in combination with antibiotics for the eradication of Helicobacter pylori (see specific regimens). Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery. Proton pump inhibitors can be used for the treatment of dyspepsia and gastro-oesophageal reflux disease.

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers. In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur. A proton pump inhibitor can be used to reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis. They can also be used to control excessive secretion of gastric acid in Zollinger–Ellison syndrome; high doses are often required.

**DRUG ACTION** Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen–potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell.

**IMPORTANT SAFETY INFORMATION**

**MHRA ADVICE: PROTON PUMP INHIBITORS (PPIs): VERY LOW RISK OF SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (SEPTEMBER 2015)**

Very infrequent cases of subacute cutaneous lupus erythematosus (S克莱) have been reported in patients taking PPIs. Drug-induced S克莱 can occur weeks, months or even years after exposure to the drug.

If a patient treated with a PPI develops lesions—especially in sun-exposed areas of the skin—and it is accompanied by arthralgia:

- Advise them to avoid exposing the skin to sunlight;
- Consider S克莱 as a possible diagnosis;
- Consider discontinuing PPI treatment unless it is imperative for a serious acid-related condition; a patient who develops S克莱 with a particular PPI may be at risk of the same reaction with another;
- In most cases, symptoms resolve on PPI withdrawal; topical or systemic steroids might be necessary for treatment of S克莱 only if there are no signs of remission after a few weeks or months.

**CAUTIONS**

Can increase the risk of fractures (particularly when used at high doses for over a year in the elderly) — may increase the risk of gastro-intestinal infections (including Clostridium difficile infection) — may mask the symptoms of gastric cancer (in adults) — patients at risk of osteoporosis.
**CAUTIONS, FURTHER INFORMATION**
- Risk of osteoporosis Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D, and if necessary, receive other preventative therapy.
- Gastric cancer
- In adults Particular care is required in those presenting with ‘alarm features’, in such cases gastric malignancy should be ruled out before treatment.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - constipation - diarrhoea - dizziness - dry mouth - gastrointestinal disorders - headache - insomnia - nausea - skin reactions - vomiting
- **Uncommon** Arthralgia - bone fractures - confusion - depression - drowsiness - leucopenia - malaise - myalgia - paraesthesia - peripheral oedema - thrombocytopenia - vertigo - vision disorders
- **Rare or very rare** Agranulocytosis - alopecia - gynaecomastia - hallucination - hepatic disorders - hyperhidrosis - hyponatraemia - nephritis - tubulointerstitial - pancytopenia - photosensitivity reaction - severe cutaneous adverse reactions (SCARs) - stomatitis - taste altered
- **Frequency not known** Hypomagnesaemia (more common after 1 year of treatment, but sometimes after 3 months of treatment) - subacute cutaneous lupus erythematosus

**MONITORING REQUIREMENTS** Measurement of serum-magnesium concentrations should be considered before and during prolonged treatment with a proton pump inhibitor, especially when used with other drugs that cause hypomagnesaemia or with digoxin.

**PRESCRIBING AND DISPENSING INFORMATION** A proton pump inhibitor should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.

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### Esomeprazole

- **INDICATIONS AND DOSE**
  - **NSAID-associated gastric ulcer**
    - **BY MOUTH**
      - Adult: 20 mg once daily for 4–8 weeks
      - Adult: 20 mg daily continue until oral administration possible, injection to be given over at least 3 minutes
  - **Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment**
    - **BY MOUTH**
      - Adult: 20 mg daily
  - **Prophylaxis of NSAID-associated gastric or duodenal ulcer**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 20 mg daily continue until oral administration possible, injection to be given over at least 3 minutes
  - **Gastro-oesophageal reflux disease (in the presence of erosive reflux oesophagitis)**
    - **BY MOUTH**
      - Child 1–11 years (body-weight 10–19 kg): 10 mg once daily for 8 weeks
      - Child 1–11 years (body-weight 20 kg and above): 10–20 mg once daily for 8 weeks
      - Child 12–17 years: Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily
      - Adult: Initially 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily

- **INTERACTIONS** → Appendix 1: proton pump inhibitors
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Uncommon** Encephalopathy
    - **Rare or very rare** Aggression - agitation - bronchospasm - increased risk of infection - muscle weakness
  - **SPECIFIC SIDE-EFFECTS**
    - **Rare or very rare**
      - With parenteral use Renal failure
      - With parenteral use Electrolyte imbalance - vitamin B12 deficiency
  - **PREGNANCY** Manufacturer advises caution—no information available.
  - **BREAST FEEDING** Manufacturer advises avoid—no information available.
  - **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.
  - **Dose adjustments** With oral use in adults Manufacturer advises max. 20 mg daily in severe impairment.
    - With intravenous use in adults Manufacturer advises for gastro-oesophageal reflux disease, max. 20 mg daily in severe impairment. Manufacturer advises for bleeding ulcers, by intravenous infusion, initially 80 mg, then 4 mg/hour for 72 hours in severe impairment.
    - In children Manufacturer advises in children 1–11 years, max. 10 mg daily in severe impairment. Manufacturer advises in children 12–17 years, max. 20 mg daily in severe impairment.
  - **RENAAL IMPAIRMENT** Manufacturer advises caution in severe renal insufficiency.
  - **DIRECTIONS FOR ADMINISTRATION**
    - With intravenous use in adults For intravenous infusion (Nexium®), give continuously or intermittently in Sodium Chloride 0.9%; reconstitute 40–80 mg with up to 100 ml infusion fluid; for intermittent infusion, give requisite amounts.
dose over 10–30 minutes; stable for 12 hours in Sodium Chloride 0.9%.

- With oral use: Do not chew or crush capsules; swallow whole or mix capsule contents in water and drink within 30 minutes. Do not chew or chew tablets; swallow whole or disperse in water and drink within 30 minutes. Disperse the contents of each sachet of gastro-resistant granules in approx. 15 mL water. Stir and leave to thicken for a few minutes; stir again before administration and use within 30 minutes; rinse container with 15 mL water to obtain full dose. For administration through a gastric tube, consult product literature.

- **PATIENT AND CARER ADVICE**

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

## Gastro-resistant capsule

- **Esomeprazole (Non-proprietary)**
  - Esomeprazole as Esomeprazole magnesium dihydrate 20 mg Esomeprazole 20mg gastro-resistant capsules 28 capsule [POM] £12.95 DT + £1.86
  - Esomeprazole as Esomeprazole magnesium dihydrate 20 mg Esomeprazole 40mg gastro-resistant capsules 28 capsule [POM] £11.36 DT + £2.27

- **Emozul (Consilient Health Ltd)**
  - Esomeprazole as Esomeprazole magnesium dihydrate 20 mg Emozul 20mg gastro-resistant capsules 28 capsule [POM] £2.18 DT + £1.86

- **Ventra (Ethypharm UK Ltd)**
  - Esomeprazole as Esomeprazole magnesium dihydrate 20 mg Ventra 20mg gastro-resistant capsules 28 capsule [POM] £2.78 DT + £2.27

## Gastro-resistant tablet

- **Esomeprazole (Non-proprietary)**
  - Esomeprazole as Esomeprazole magnesium trihydrate 20 mg Esomeprazole 20mg gastro-resistant tablets 28 tablet [POM] £18.50 DT + £2.15
  - Esomeprazole as Esomeprazole magnesium trihydrate 40 mg Esomeprazole 40mg gastro-resistant tablets 28 tablet [POM] £3.76 DT + £2.83

- **Nexium (AstraZeneca UK Ltd, Pfizer Consumer Healthcare Ltd)**
  - Esomeprazole as Esomeprazole magnesium trihydrate 20 mg Nexium 20mg gastro-resistant tablets 28 tablet [POM] £16.50 DT + £2.15
  - Esomeprazole as Esomeprazole magnesium trihydrate 40 mg Nexium 40mg gastro-resistant tablets 28 tablet [POM] £2.97 DT + £2.27

## Powder for solution for injection

- **Esomeprazole (Non-proprietary)**
  - Esomeprazole as Esomeprazole sodium 40 mg Esomeprazole 40mg powder for solution for injection vials 1 vial [POM] £3.07–3.13 (Hospital only)
  - **Nexium (AstraZeneca UK Ltd)**
    - Esomeprazole as Esomeprazole sodium 40 mg Nexium L.V. 40mg powder for solution for injection vials 1 vial [POM] £4.25 (Hospital only)

## Gastro-resistant granules

- **CAUTIONARY AND ADVISORY LABELS 25**

- **Nexium (AstraZeneca UK Ltd)**
  - Esomeprazole as Esomeprazole magnesium trihydrate 10 mg Nexium 10mg gastro-resistant granules sachets 28 sachet [POM] £25.19 DT + £25.19

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**Lansoprazole**

### INDICATIONS AND DOSE

**Helicobacter pylori** eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole

- **BY MOUTH**
  - Adult: 30 mg twice daily

**Benign gastric ulcer**

- **BY MOUTH**
  - Adult: 30 mg once daily for 8 weeks, dose to be taken in the morning

**Duodenal ulcer**

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, dose to be taken in the morning; maintenance 15 mg once daily

**NSAID-associated duodenal ulcer**

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed

**Prophylaxis of NSAID-associated duodenal ulcer**

- **Prophylaxis of NSAID-associated gastric ulcer**

- **BY MOUTH**
  - Adult: 15–30 mg once daily

**Zollinger–Ellison syndrome (and other hypersecretory conditions)**

- **BY MOUTH**
  - Adult: Initially 60 mg once daily, adjusted according to response, daily doses of 120 mg or more given in two divided doses

**Gastro-oesophageal reflux disease**

- **BY MOUTH**
  - Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg once daily, doses to be taken in the morning

**Severe oesophagitis**

- **BY MOUTH**
  - Adult: 30 mg once daily for 8 weeks, continue as maintenance treatment if appropriate

**Severe oesophagitis, refractory to initial treatment**

- **BY MOUTH**
  - Adult: 30 mg twice daily

**Acid-related dyspepsia**

- **BY MOUTH**
  - Adult: 15–30 mg once daily for 2–4 weeks, doses to be taken in the morning

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**UNLICENSED USE** Lansoprazole doses in BNF may differ from those in product literature. Not licensed at 30 mg twice daily for severe oesophagitis refractory to initial treatment.

**INTERACTIONS** Appendix 1: proton pump inhibitors

**SIDE-EFFECTS**

- **Common or very common** Dry throat · fatigue
- **Uncommon** Eosinophilia · oedema
- **Rare or very rare** Anaemia · angioedema · appetite decreased · erectile dysfunction · fever · glossitis · oesophageal candidiasis · pancreatitis · restlessness · tremor

**PREGNANCY** Manufacturer advises avoid.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).

**Dose adjustments** Manufacturer advises dose reduction of 50% in moderate to severe impairment.
Disorders of gastric acid and ulceration

**Gastro-intestinal system**

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder.

**Gastro-resistant capsule**

- Lansoprazole (Non-proprietary)
  - Lansoprazole 15 mg Lansoprazole 15 mg gastro-resistant capsules | 28 capsule [POM] £22.93 DT = £0.76
  - Lansoprazole 30 mg Lansoprazole 30 mg gastro-resistant capsules | 28 capsule [POM] £23.63 DT = £0.81

**Orodispersible tablet**

- Lansoprazole (Non-proprietary)
  - Lansoprazole 15 mg Lansoprazole 15 mg orodispersible tablets | 28 tablet [POM] £2.90 DT = £0.29
  - Lansoprazole 30 mg Lansoprazole 30 mg orodispersible tablets | 28 tablet [POM] £6.99 DT = £0.26

- Zoton FasTab (Pfizer Ltd)
  - Lansoprazole 15 mg Zoton FastTab 15 mg | 28 tablet [POM] £2.99 DT = £0.29
  - Lansoprazole 30 mg Zoton FastTab 30 mg | 28 tablet [POM] £5.50 DT = £0.26

**INTERACTIONS**

- Appendix: : proton pump inhibitors

**SIDE-EFFECTS**

- Rare or very rare: Aggression, agitation, bronchospasm, encephalopathy, gastrointestinal candidiasis, muscle weakness

**PREGNANCY**

- Not known to be harmful.

**HEPATIC IMPAIRMENT**

- Not more than 20 mg daily should be needed.

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**Prophylaxis in patients with a history of NSAID-associated duodenal ulcer who require continued NSAID treatment**

**Prophylaxis in patients with a history of NSAID-associated gastric ulcer who require continued NSAID treatment**

**Prophylaxis in patients with a history of NSAID-associated gastroduodenal lesions who require continued NSAID treatment**

- **BY MOUTH**
  - Adult: 20 mg once daily

**Zollinger–Ellison syndrome**

- **BY MOUTH**
  - Adult: Initially 60 mg once daily; usual dose 20–120 mg daily, total daily doses greater than 80 mg should be given in 2 divided doses
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 60 mg once daily, adjusted according to response, total daily doses greater than 60 mg should be given in 2 divided doses, injection to be given over 5 minutes, infusion to be given over 20–30 minutes

**Gastro-oesophageal reflux disease**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, continued for a further 4–8 weeks if not fully healed; maintenance 20 mg once daily

**Gastro-oesophageal reflux disease refractory to other treatment**

- **BY MOUTH**
  - Adult: 40 mg once daily for 8 weeks; maintenance 20 mg once daily

**Acid reflux disease (long-term management)**

- **BY MOUTH**
  - Adult: 10 mg once daily, increased to 20 mg once daily, dose only increased if symptoms return

**Acid-related dyspepsia**

- **BY MOUTH**
  - Adult: 10–20 mg once daily for 2–4 weeks according to response

**Treatment and prevention of benign gastric ulcers**

**Treatment and prevention of duodenal ulcers**

**Treatment and prevention of NSAID-associated ulcers**

**Treatment and prevention of gastro-oesophageal reflux disease**

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 40 mg once daily until oral administration possible, injection to be given over 5 minutes, infusion to be given over 20–30 minutes

**Major peptic ulcer bleeding (following endoscopic treatment)**

- **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: Initially 80 mg, to be given over 40–60 minutes, then (by continuous intravenous infusion) 8 mg/hour for 72 hours, subsequent dose then changed to oral therapy

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**DIRECTIONS FOR ADMINISTRATION**

- Orodispensible tablets should be placed on the tongue, allowed to disperse and swallowed, or may be swallowed whole with a glass of water. Alternatively, tablets can be dispersed in a small amount of water and administered by an oral syringe or nasogastric tube.

**PATIENT AND CARER ADVICE**

- Counselling on administration of orodispersible tablet advised.

**PROFESSION SPECIFIC INFORMATION**

- Dental practitioners’ formulary Lansoprazole capsules may be prescribed.

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**80** Disorders of gastric acid and ulceration

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**Omeprazole**

21-Mar-2018

**INDICATIONS AND DOSE**

- *Helicobacter pylori* eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole
  - **BY MOUTH**
  - Adult: 20 mg twice daily

- Benign gastric ulceration
  - **BY MOUTH**
  - Adult: 20 mg once daily for 8 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

- Duodenal ulceration
  - **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

- Prevention of relapse in gastric ulcer
  - **BY MOUTH**
  - Adult: 20 mg once daily, increased if necessary to 40 mg once daily

- Prevention of relapse in duodenal ulcer
  - **BY MOUTH**
  - Adult: 20 mg once daily, dose may range between 10–40 mg daily

**NSAID-associated duodenal ulcer**

**NSAID-associated gastric ulcer**

**NSAID-associated gastroduodenal erosions**

- **BY MOUTH**
  - Adult: 20 mg once daily for 4 weeks, continued for a further 4 weeks if not fully healed

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www.getintopharma.com
**MEDICATION FORMS**

With oral use: Omeprazole (Non-proprietary) powder for solution for infusion, Mezzopram, Losec MUPS.

Gastro-resistant omeprazole capsules may be prescribed.

**DIRECTIONS FOR ADMINISTRATION**

- **For administration by mouth, swallow whole, or disperse Losec MUPS® tablets in water, or mix capsule contents or Losec MUPS® tablets with fruit juice or yoghurt. Preparations consisting of an e/t capsule within a tablet should not be opened.**
  - With intravenous use For intravenous infusion (Losec®), give intermittently or continuously in Glucose 5% or Sodium chloride 0.9%; reconstitute each 40 mg vial with infusion fluid and dilute to 100 mL; for intermittent infusion give 40 mg over 20–30 minutes; stable for 3 hours in glucose 5% or 12 hours in sodium chloride 0.9%.

**PATIENT AND CARER ADVICE**

- **With oral use** Counselling on administration advised.

**PROFESSION SPECIFIC INFORMATION**

- Dental practitioners’ formulary
- Gastro-resistant omeprazole capsules may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**

- With oral use Omeprazole 10 mg tablets can be sold to the public for the short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks, and a pack size of 28 tablets.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Gastro-resistant capsule

- **Omeprazole (Non-proprietary)**
  - Omeprazole 10 mg Omeprazole 10 mg gastro-resistant capsules 28 capsule (P&amp;G) £3.30 DT = £0.82
  - Omeprazole 20 mg Omeprazole 20 mg gastro-resistant capsules 28 capsule (P&amp;G) £3.86 DT = £0.83
  - Omeprazole 40 mg Omeprazole 40 mg gastro-resistant capsules 7 capsule (P&amp;G) £6.96 DT = £0.92 | 28 capsule (P&amp;G) £22.44 – £17.92
  - **Losec** (AstraZeneca UK Ltd)
    - Omeprazole 10 mg Losec 10 mg gastro-resistant capsules 28 capsule (P&amp;G) £1.16 DT = £0.82
  - Omeprazole 20 mg Losec 20 mg gastro-resistant capsules 28 capsule (P&amp;G) £1.70 DT = £0.83
  - Omeprazole 40 mg Losec 40 mg gastro-resistant capsules 7 capsule (P&amp;G) £3.35 DT = £0.62
  - **Mepredac** (Discovery Pharmaceuticals)
    - Omeprazole 10 mg Mepredac 10 mg gastro-resistant capsules 28 capsule (P&amp;G) £0.68 DT = £0.82
  - Omeprazole 20 mg Mepredac 20 mg gastro-resistant capsules 28 capsule (P&amp;G) £0.70 DT = £0.83

Gastro-resistant tablet

- **Omeprazole (Non-proprietary)**
  - Omeprazole 10 mg Omeprazole 10 mg gastro-resistant tablets 28 tablet (P&amp;G) £18.91 DT = £7.90
  - Omeprazole 20 mg Omeprazole 20 mg gastro-resistant tablets 28 tablet (P&amp;G) £28.56 DT = £5.97
  - Omeprazole 40 mg Omeprazole 40 mg gastro-resistant tablets 7 tablet (P&amp;G) £14.28 DT = £2.17
  - **Losec MUPS** (AstraZeneca UK Ltd)
    - Omeprazole (as Omeprazole magnesium) 10 mg Losec MUPS 10 mg gastro-resistant tablets 28 tablet (P&amp;G) £3.30 DT = £0.30
  - Omeprazole (as Omeprazole magnesium) 20 mg Losec MUPS 20 mg gastro-resistant tablets 28 tablet (P&amp;G) £3.92 DT = £0.32
  - Omeprazole (as Omeprazole magnesium) 40 mg Losec MUPS 40 mg gastro-resistant tablets 7 tablet (P&amp;G) £6.96 DT = £0.96
  - **Mezprazol** (Sandoz Ltd)
    - Omeprazole (as Omeprazole magnesium) 10 mg Mezprazol 10 mg dispersible gastro-resistant tablets 28 tablet (P&amp;G) £6.58 DT = £0.30
  - Omeprazole (as Omeprazole magnesium) 20 mg Mezprazol 20 mg dispersible gastro-resistant tablets 28 tablet (P&amp;G) £9.86 DT = £11.92
  - Omeprazole (as Omeprazole magnesium) 40 mg Mezprazol 40 mg dispersible gastro-resistant tablets 7 tablet (P&amp;G) £4.93 DT = £6.96

Powder for solution for infusion

- **Omeprazole (Non-proprietary)**
  - Omeprazole (as Omeprazole sodium) 40 mg Omeprazole 40 mg powder for solution for infusion vials | 5 vial (P&amp;G) £26.00 – £32.45 DT + £26.00 (Hospital only)

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**Pantoprazole**

- **INDICATIONS AND DOSE**

  * Helicobacter pylori eradication in combination with amoxicillin and clarithromycin; or in combination with clarithromycin and metronidazole*
  
  - **BY MOUTH**
    - Adult: 40 mg twice daily
  
  * Benign gastric ulcer*
  
  - **BY MOUTH**
    - Adult: 40 mg daily for 8 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases

**Gastric ulcer**

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Duodenal ulcer**

- **BY MOUTH**
  - Adult: 40 mg daily for 4 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment**

- **Prophylaxis of NSAID-associated duodenal ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment**
  
  - **BY MOUTH**
    - Adult: 20 mg daily

**Gastro-oesophageal reflux disease**

- **BY MOUTH**
  - Adult: 20–80 mg daily for 4 weeks, continued for further 4 weeks if not fully healed, dose to be taken in the morning; maintenance 20 mg daily and increased to 40 mg daily, increased only if symptoms return
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

**Zollinger–Ellison syndrome (and other hypersecretory conditions)**

- **BY MOUTH**
  - Adult: Initially 80 mg daily (max. dose 80 mg), adjusted according to response
  - Elderly: 40 mg daily
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 80 mg, alternatively 160 mg in 2 divided doses, if rapid acid control required, then 80 mg once daily (max. dose 80 mg), adjusted according to response

**INTERACTIONS**

- Appendix 1: proton pump inhibitors

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Uncommon: Asthenia - gastrointestinal discomfort - sleep disorder
- Rare or very rare: Angioedema - hyperlipidaemia - weight change

**SPECIFIC SIDE-EFFECTS**

- With intravenous use: Electrolyte imbalance - muscle spasms

**PREGNANCY**

- Manufacturer advises avoid unless potential benefit outweighs risk—fetotoxic in animals.

**BREAST FEEDING**

- Manufacturer advises avoid unless potential benefit outweighs risk—small amount present in milk.

**HEPATIC IMPAIRMENT**

Dose adjustments: Max. 20 mg daily in severe impairment and cirrhosis.
82 Disorders of gastric acid and ulceration

**Rabeprazole sodium**

**INDICATIONS AND DOSE**

- **Benign gastric ulcer**
  - **BY MOUTH**
  - Adult: 20 mg daily for 8 weeks, dose to be taken in the morning

- **Duodenal ulcer**
  - **BY MOUTH**
  - Adult: 20 mg daily for 4 weeks, dose to be taken in the morning

- **Gastro-oesophageal reflux disease**
  - **BY MOUTH**
  - Adult: 20 mg once daily for 4-8 weeks; maintenance 10-20 mg daily

- **Gastro-oesophageal reflux disease (symptomatic treatment in the absence of oesophagitis)**
  - **BY MOUTH**
  - Adult: 10 mg daily for up to 4 weeks, then 10 mg daily if required

- **Severe oesophagitis**
  - **BY MOUTH**
  - Adult: 20 mg once daily for 8 weeks, continue as maintenance treatment if appropriate

- **Severe oesophagitis, refractory to initial treatment**
  - **BY MOUTH**
  - Adult: 20 mg twice daily

- **Zollinger-Ellison syndrome**
  - **BY MOUTH**
  - Adult: Initially 60 mg once daily, adjusted according to response, doses above 100 mg daily given in 2 divided doses; maximum 120 mg per day

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**Helicobacter pylori eradication in combination with amoxicillin or metronidazole and clarithromycin**

- **BY MOUTH**
  - Adult: 20 mg twice daily

**SIDE-EFFECTS**

- **Common or very common** Asthenia - cough - increased risk of infection - influenza like illness - pain
- **Uncommon** Burping - dyspepsia - leg cramps - nervousness
- **Rare or very rare** Appetite decreased - hepatic encephalopathy - leucocytosis - neutropenia - weight increased
- **Frequency not known** Chest pain - chills - fever

**PREGNANCY**

- Manufacturer advises avoid—no information available.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Gastro-resistant tablet**

- **Pantoprazole (as Pantoprazole sodium sesquihydrate)**
  - **20 mg** Pantoprazole 20mg gastro-resistant tablets | 28 tablet | £11.83 DT = £0.90
  - **40 mg** Pantoprazole 40mg gastro-resistant tablets | 28 tablet | £20.57 DT = £0.65

**Powder for solution for injection**

- **Pantoprazole (as Pantoprazole sodium sesquihydrate)**
  - **40 mg** Pantoprazole 40mg powder for solution for injection vials | 1 vial | £5.00 DT = £0.50 | 5 vial | £22.50 DT = £2.70
  - **Pantoprazole (as Pantoprazole sodium sesquihydrate)**
  - **5 mg** Pantoprazole 5mg gastro-resistant tablets | 28 tablet | £13.04 DT = £0.50

**Medicines for the treatment of gastro-oesophageal reflux disease**

4.3 **Gastro-oesophageal reflux disease**

**Gastro-oesophageal reflux disease**

**Management**

Gastro-oesophageal reflux disease (including non-erosive gastro-oesophageal reflux and erosive oesophagitis) is associated with heartburn, acid regurgitation, and sometimes, difficulty in swallowing (dysphagia); oesophageal inflammation (oesophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-oesophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response. The extent of healing depends on the severity of the disease, the treatment chosen, and the duration of therapy.

Patients with gastro-oesophageal reflux disease should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, Smoking cessation p. 497, and raising the head of the bed.

For mild symptoms of gastro-oesophageal reflux disease, initial management may include the use of **antacids and alginites**. Alginate-containing antacids can form a ‘raft’ that floats on the surface of the stomach contents to reduce reflux and protect the oesophageal mucosa. **Histamine H₂-receptor antagonists** may relieve symptoms and permit...
reduction in antacid consumption. However, proton pump inhibitors provide more effective relief of symptoms than H₂-receptor antagonists. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by giving treatment intermittently).

For severe symptoms of gastro-oesophageal reflux disease or for patients with a proven or severe pathology (e.g. oesophagitis, oesophageal ulceration, oesophagopharyngeal reflux, Barrett’s oesophagus), initial management involves the use of a proton pump inhibitor; patients need to be reassessed if symptoms persist despite treatment for 4–6 weeks with a proton pump inhibitor. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by reducing the dose of the proton pump inhibitor or by giving it intermittently, or by substituting treatment with a histamine H₂-receptor antagonist).

However, for endoscopically confirmed erosive, ulcerative, or strictureing disease, or Barrett’s oesophagus, treatment with a proton pump inhibitor usually needs to be maintained at the minimum effective dose.

### Pregnancy

If dietary and lifestyle changes fail to control gastro-oesophageal reflux disease in pregnancy, an antacid or an alginate can be used. If this is ineffective, ranitidine p. 75 can be tried. Omeprazole p. 80 is reserved for women with severe or complicated reflux disease.

### Gastro-oesophageal reflux disease in children

Gastro-oesophageal reflux disease is common in infancy but most symptoms resolve without treatment between 12 and 18 months of age. In infants, mild or moderate reflux without complications can be managed initially by changing the frequency and volume of feed; a feed thickener or thickened formula feed can be used (with advice of a dietician). If necessary, a suitable alginate-containing preparation can be used instead of thickened feeds. For older children, life-style changes similar to those for adults may be helpful followed if necessary by treatment with an alginate-containing preparation.

Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital; an H₂-receptor antagonist may be needed to reduce acid secretion. If the oesophagitis is resistant to H₂-receptor blockade, the proton pump inhibitor omeprazole can be tried.

### Other drugs used for Gastro-oesophageal reflux disease

- Cimetidine, p. 74 - Esomeprazole, p. 78 - Famotidine, p. 75 - Lansoprazole, p. 76 - Nizatidine, p. 75 - Pantoprazole, p. 81 - Ranitidine sodium, p. 82

### 4.4 Helicobacter pylori diagnosis

#### DIAGNOSTIC AGENTS

**Urea (13C)**

- **INDICATIONS AND DOSE**
  - Diagnosis of gastro-duodenal Helicobacter pylori infection
    - **BY MOUTH**
    - Adult: (consult product literature)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Soluble tablet**
  - **Pylobactell** (Torbet Laboratories Ltd)
    - Urea [13-C] 100 mg Pylobactell breath test kit | 1 kit | £20.75
    - DT = £20.75
  - **Urea [13-C] 45 mg** Helicobacter Test INFAl for children breath test kit sugar-free | 1 kit | £19.10
    - DT = £19.10
  - **Urea [13-C] 75 mg** Helicobacter Test INFAl breath test kit sugar-free | 1 kit | £21.70
    - DT = £21.70
5 Food allergy

Food allergy

Description of condition
Food allergy is an adverse immune response to a food, commonly associated with cutaneous and gastro-intestinal reactions, and less frequently associated with respiratory reactions and anaphylaxis. It is distinct from food intolerance which is non-immunological. Cow’s milk, hen’s eggs, soy, wheat, peanuts, tree nuts, fish, and shellfish are the most common allergens. Cross-reactivity between similar foods can occur (e.g. allergy to other mammalian milk in patients with cow’s milk allergy).

Management of food allergy

Allergy caused by specific foods should be managed by strict avoidance of the causal food. Sodium cromoglicate p. 270 is licensed as an adjunct to dietary avoidance in patients with food allergy. Educating patients about appropriate nutrition, food preparation, and the risks of accidental exposure is recommended, such as food and drinks to avoid, ensuring adequate nutritional intake, and interpreting food labels.

Drug treatment

There is low quality evidence to support the use of antihistamines to treat acute, non-life-threatening symptoms (such as flushing and urticaria) if accidental ingestion of allergenic food has occurred (see Antihistamines, under Antihistamines, allergen immunotherapy and allergic emergencies p. 277). Chlorphenamine maleate p. 283 is licensed for the symptomatic control of food allergy. In case of food-induced anaphylaxis, adrenaline/epinephrine p. 222 is the first-line immediate treatment (see also Allergic emergencies, under Antihistamines, allergen immunotherapy and allergic emergencies p. 277). Patients who are at risk of anaphylaxis should be trained to use self-injectable adrenaline/epinephrine.

6 Gastro-intestinal smooth muscle spasm

Antispasmodics

Antimuscarinics

The intestinal smooth muscle relaxant properties of antimuscarinic and other antispasmodic drugs may be useful in irritable bowel syndrome.

Antimuscarinics (formerly termed ‘anticholinergics’) reduce intestinal motility. They can be used for the management of irritable bowel syndrome.

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines atropine sulfate p. 1166 and dicycloverine hydrochloride below and the quaternary ammonium compounds propantheline bromide p. 86 and hyoscyamine butylbromide p. 85. The quaternary ammonium compounds are less lipid soluble than atropine sulfate and are less likely to cross the blood–brain barrier; they are also less well absorbed from the gastro-intestinal tract.
### Dicycloverine hydrochloride with aluminium hydroxide, magnesium oxide and simeticone

The properties listed below are those particular to the combination only. For the properties of the components please consider, dicycloverine hydrochloride p. 84, aluminium hydroxide p. 1052, simeticone p. 71.

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm</td>
<td></td>
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<tr>
<td><strong>BY MOUTH</strong></td>
<td></td>
</tr>
<tr>
<td>Child 12-17 years: 10–20 mL every 4 hours as required</td>
<td></td>
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<tr>
<td>Adult: 10–20 mL every 4 hours as required</td>
<td></td>
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<tr>
<td><strong>INTERACTIONS</strong></td>
<td></td>
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<tr>
<td>▶ Appendix 1: antacids - dicycloverine</td>
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<tr>
<td><strong>SIDE-EFFECTS</strong></td>
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<tr>
<td>Anticholinergic syndrome</td>
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<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
<td></td>
</tr>
<tr>
<td>Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm</td>
<td></td>
</tr>
<tr>
<td><strong>BY MOUTH</strong></td>
<td></td>
</tr>
<tr>
<td>Child 12-17 years: 20 mg 4 times a day</td>
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<tr>
<td>Adult: 20 mg 4 times a day</td>
<td></td>
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<tr>
<td><strong>IRRITABLE BOWEL SYNDROME</strong></td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Adult: 10 mg 3 times a day; increased if necessary up to 20 mg 4 times a day</td>
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<tr>
<td><strong>ACUTE SPASM</strong></td>
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<td><strong>SPASM IN DIAGNOSTIC PROCEDURES</strong></td>
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<td>Initially by intramuscular injection, or by slow intravenous injection</td>
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<tr>
<td>Adult: 20 mg, then (by intramuscular injection or by slow intravenous injection) 20 mg after 30 minutes if required, dose may be repeated more frequently in endoscopy; maximum 100 mg per day</td>
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<tr>
<td><strong>EXCESSIVE RESPIRATORY SECRETIONS IN PALLIATIVE CARE</strong></td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Child 1 month–1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)</td>
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<tr>
<td>Child 2–4 years: 5 mg 3–4 times a day</td>
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<tr>
<td>Child 5–11 years: 10 mg 3–4 times a day</td>
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<tr>
<td>Child 2–4 years: 10 mg 3–4 times a day</td>
<td></td>
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<tr>
<td><strong>BY INTRAVENOUS INJECTION</strong></td>
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<tr>
<td>Child 1 month–4 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)</td>
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<tr>
<td>Child 5–11 years: 5–10 mg 3–4 times a day</td>
<td></td>
</tr>
<tr>
<td>Child 5–11 years: 10–20 mg 3–4 times a day</td>
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<tr>
<td><strong>BY SUBCUTANEOUS INJECTION</strong></td>
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<tr>
<td>Adult: 20 mg every 4 hours if required, adjusted according to response to up to 20 mg every 1 hour</td>
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<tr>
<td><strong>BOWEL COLIC IN PALLIATIVE CARE</strong></td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Child 1 month–1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)</td>
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</tbody>
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### Hyoscine butylbromide

**INDICATIONS AND DOSE**

Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm

- **ORAL SUSPENSION**
  - Kolantion (Peckforton Pharmaceuticals Ltd)
    - Dicycloverine hydrochloride 500 microgram per 1 mL, Simeticone 4 mg per 1 mL, Magnesium oxide light 20 mg per 1 mL, aluminium hydroxide dried 40 mg per 1 mL
    - Kolantion gel sugar-free 100 mL £4.00 sugar-free 500 mL £6.00

**PALLIATIVE CARE**

- **Hyoscine butylbromide in palliative care,** see
  - www.medicinescomplete.com/#/content/palliative/hyoscine-butylbromide

**IMPORTANT SAFETY INFORMATION**

MHRA CHM ADVICE: HYOSCINE BUTYLBROMIDE (BUSCOPAN®)

- **INJECTION: RISK OF SERIOUS ADVERSE EFFECTS IN PATIENTS WITH UNDERLYING CARDIAC DISEASE (FEBRUARY 2017)**

The MHRA advises that hyoscine butylbromide injection can cause serious adverse effects including tachycardia, hypotension, and anaphylaxis; several reports have noted that anaphylaxis is more likely to be fatal in patients with underlying coronary heart disease.

Hyoscine butylbromide injection is contra-indicated in patients with tachycardia and should be used with caution in patients with cardiac disease; the MHRA recommends that these patients are monitored and that resuscitation equipment and trained personnel are readily available.

**CONTRA-INDICATIONS**

- With intramuscular use or intravenous use
  - Tachycardia

**SIDE-EFFECTS**

- General side-effects
  - Dyspnœa
  - Specific side-effects
  - With parenteral use
  - Mydriasis

**PREGNANCY**

Manufacturer advises avoid.

**BREAST FEEDING**

Amount too small to be harmful.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use in children
  - For administration by mouth, injection solution may be used; content of ampoule may be stored in a refrigerator for up to 24 hours after opening.
  - With intravenous use in children
    - For intravenous injection, may be diluted with Glucose 5% or Sodium Chloride 0.9%; give over at least 1 minute.

**PRESCRIBING AND DISPENSING INFORMATION**

- Palliative care For further information on the use of hyoscine butylbromide in palliative care, see www.medicinescomplete.com/#/content/palliative/hyoscine-butylbromide.

**EXCEPTIONS TO LEGAL CATEGORY**

Hyoscine butylbromide tablets can be sold to the public for medically confirmed irritable bowel syndrome, provided single dose does not exceed 20 mg, daily dose does not exceed 80 mg, and pack does not contain a total of more than 240 mg.

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**BNF 78**

**Gastro-intestinal smooth muscle spasm**

- Child 2–4 years: 5 mg 3–4 times a day
- Child 5–11 years: 10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day
- Child 1 month–4 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- Child 5–11 years: 5–10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day
- Child 1 month–1 year: 10 mg 3–4 times a day
- Child 1 month–1 year: 5 mg 3–4 times a day
- Child 2–4 years: 10 mg 3–4 times a day
- Child 5–11 years: 20 mg 3–4 times a day
- Child 12–17 years: 50–100 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- By intramuscular injection, or by intravenous injection
- Child 1 month–4 years: 100 micrograms/kg 3–4 times a day
- Child 5–11 years: 200–500 micrograms/kg 3–4 times a day
- Child 12–17 years: 100–200 micrograms/kg 3–4 times a day
- By subcutaneous injection
- Adult: 20 mg every 4 hours if required, adjusted according to response to up to 20 mg every 1 hour
- By subcutaneous infusion
- Adult: 20–120 mg/24 hours

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**www.getintopharma.com**
86 Gastro-intestinal smooth muscle spasm

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Solution for injection**
- Buscopan (Sanofi)
- Hyoscine butylbromide 20 mg per 1 ml Buscopan 20mg/1ml solution for injection ampoules | 10 ampoule [Pos] £2.92 DT = £2.92

**Tablet**
- Buscopan (Sanofi)
- Hyoscine butylbromide 10 mg Buscopan 10mg tablets | 56 tablet [Pos] £3.00 DT = £3.00

**Propantheline bromide**

**INDICATIONS AND DOSE**

Adult enuresis | Hyperhidrosis | Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- **BY MOUTH**
  - Adult: 15 mg 3 times a day, dose to be taken at least one hour before food and 30 mg, dose to be taken at bedtime; maximum 120 mg per day

**INTERACTIONS** → Appendix 1: propantheline

**SIDE-EFFECTS** Arrhythmias - bronchial secretion decreased - mydriasis

**PREGNANCY** Manufacturer advises avoid unless essential—no information available.

**BREAST FEEDING** May suppress lactation.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAI IMPAIRMENT** Manufacturer advises caution.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet** CAUTIONARY AND ADVISORY LABELS 23
- Pro-Banthine (Kyowa Kirin Ltd)
  - Propantheline bromide 15 mg Pro-Banthine 15mg tablets | 112 tablet [Pos] £20.74 DT = £20.74

**ANTISPASMODICS**

**Alverine citrate**

**INDICATIONS AND DOSE**

Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm | Dysmenorrhoea

- **BY MOUTH**
  - Child 12-17 years: 60–120 mg 1–3 times a day
  - Adult: 60–120 mg 1–3 times a day

**CONTRA-INDICATIONS** Intestinal obstruction - paralytic ileus

**SIDE-EFFECTS** Dizziness - dyspnoea - headache - jaundice (reversible on discontinuation) - nausea - skin reactions - wheezing

**PREGNANCY** Manufacturer advises avoid—limited information available

**BREAST FEEDING** Manufacturer advises avoid—limited information available

**PATIENT AND CARER ADVICE** Driving and skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving).

**Mebeverine hydrochloride** 12-Feb-2019

**INDICATIONS AND DOSE**

Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 10-17 years: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals
  - Adult: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals

**Irritable bowel syndrome**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 12-17 years: 200 mg twice daily
  - Adult: 200 mg twice daily

**UNLICENSED USE** Tablets and modified-release capsules not licensed for use in children.

**CONTRA-INDICATIONS** Paralytic ileus

**SIDE-EFFECTS** Angioedema - face oedema - skin reactions

**PREGNANCY** Not known to be harmful—manufacturers advise avoid.

**BREAST FEEDING** Manufacturers advise avoid—no information available.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on the timing of administration of mebeverine hydrochloride tablets and oral suspension. Medicines for Children leaflet: Mebeverine for intestinal spasms www.medicinesforchildren.org.uk/mebeverine-intestinal-spasms

**EXCEPTIONS TO LEGAL CATEGORY**

- In adults Mebeverine hydrochloride can be sold to the public for symptomatic relief of irritable bowel syndrome provided that max. single dose is 135 mg and max. daily dose is 405 mg; for uses other than symptomatic relief of irritable bowel syndrome provided that max. single dose is 100 mg and max. daily dose is 300 mg.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Oral suspension**
- Mebeverine hydrochloride (Non-proprietary)
  - Mebeverine hydrochloride (as Mebeverine pamoate) 10 mg per 1 ml Mebeverine 50mg/5ml oral suspension sugar free-sugar-free | 300 ml [Pos] £187.00 DT = £187.00

**Modified-release capsule**

CAUTIONARY AND ADVISORY LABELS 25
- Mebeverine hydrochloride (Non-proprietary)
  - Mebeverine hydrochloride 200 mg Mebeverine 200mg modified-release capsules | 60 capsule [Pos] £8.31 DT = £8.29
stones in the gallbladder or in the bile duct, and the symptoms and complications that they may cause. The majority of patients with gallstones remain asymptomatic. When the stones irritate the gallbladder or block part of the biliary system, the patient can experience symptoms such as pain, or infection and inflammation that if left untreated, can lead to severe complications such as biliary colic, acute cholecystitis, cholangitis, pancreatitis, and obstructive jaundice.

Non-drug treatment

Asymptomatic gallbladder stones do not need to be treated unless symptoms develop. The definitive treatment of symptomatic gallstones (and all bile duct stones) is surgical removal by laparoscopic cholecystectomy.

Drug treatment

Analgesia should be offered to control pain symptoms. Paracetamol p. 444 or a nonsteroidal anti-inflammatory drug (see Non-steroidal anti-inflammatory drugs p. 1130) is recommended for intermittent mild-to-moderate pain. Intramuscular diclofenac sodium p. 1135 can be given for severe pain or, if not suitable, an intramuscular opioid (such as morphine p. 463 or pethidine hydrochloride p. 470).

Although ursodeoxycholic acid p. 89 has been used for the management of gallstone disease, there is no evidence to support its use.

Useful Resources


### Inborn errors of primary bile acid synthesis

#### Description of condition

Inborn errors of primary bile acid synthesis are a group of diseases in which the liver does not produce enough primary bile acids due to enzyme deficiencies. These acids are the main components of the bile, and include cholic acid and chenodeoxycholic acid.

**Treatment**

Cholic acid p. 88 is licensed for the treatment of inborn errors in primary bile acid synthesis due to an inborn deficiency of two specific liver enzymes. It acts by replacing some of the missing bile acids, therefore relieving the symptoms of the disease.

Chenodeoxycholic acid p. 88 is licensed for the treatment of inborn errors of primary bile acid synthesis due to a deficiency of one specific enzyme in the bile acid synthesis pathway when presenting as cerebrotendinous xanthomatosis. Ursodeoxycholic acid p. 89 [unlicensed indication] has been used to treat inborn errors of primary bile acid synthesis, but there is an absence of evidence to recommend its use.

### Primary biliary cholangitis

#### Description of condition

Primary biliary cholangitis (or primary biliary cirrhosis) is a chronic cholestatic disease which develops due to progressive destruction of small and intermediate bile ducts...
Liver disorders and related conditions

Bile acids

Chenodeoxycholic acid

**INDICATIONS AND DOSE**

Cerebrotendinous xanthomatosis (specialist use only)

- **BY MOUTH**
  - Adult: Initially 750 mg daily in 3 divided doses, increased if necessary up to 1000 mg daily in divided doses

- **CONTRA-INDICATIONS** Non-functioning gall bladder - radio-opaque stones

- **INTERACTIONS** → Appendix 1: chenodeoxycholic acid

- **SIDE-EFFECTS** Constipation

- **PREGNANCY** Manufacturer advises avoid - fetotoxicity reported in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises monitor - no information available.

- **RENAL IMPAIRMENT** Manufacturer advises monitor - no information available.

- **MONITORING REQUIREMENTS** Manufacturer advises monitor serum cholesterol and/or urine bile alcohols every 3 months during the initiation of therapy and dose adjustment, and then at least annually; liver function should also be monitored during initiation of therapy and then at least annually; additional or more frequent investigations may need to be undertaken to monitor therapy during periods of fast growth or concomitant disease.

- **DIRECTIONS FOR ADMINISTRATION** For administration by mouth in patients who are unable to swallow capsules and/or need to take a dose below 250 mg, manufacturer advises add capsule contents to sodium bicarbonate solution 8.4%—for further information, consult product literature.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  - Chenodeoxycholic acid (non-proprietary) ▼
    - Chenodeoxycholic acid 250 mg: Chenodeoxycholic acid 250 mg capsules | 100 capsule [POD] £14,000.00

Cholic acid

**DRUG ACTION** Cholic acid is the predominant primary bile acid in humans, which can be used to provide a source of bile acid in patients with inborn deficiencies in bile acid synthesis.

**INDICATIONS AND DOSE**

Inborn errors of primary bile acid synthesis (initiated by a specialist)

- **BY MOUTH**
  - Adult: Usual dose 5–15 mg/kg daily; increased in steps of 50 mg daily in divided doses if required, dose to be given with food at the same time each day; Usual maximum 500 mg/24 hours

- **INTERACTIONS** → Appendix 1: cholic acid

- **SIDE-EFFECTS** Cholelithiasis (long term use) - diarrhoea - pruritus

- **PREGNANCY** Limited data available—not known to be harmful, manufacturer advises continue treatment. Monitoring: Manufacturer advises monitor patient parameters more frequently in pregnancy.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution and stop treatment if there are signs of severe hepatic failure—limited information available (no experience with impairment from causes not related to inborn errors of primary bile acid synthesis).

  - **Dose adjustments** Manufacturer advises adjust dose as the degree of impairment improves during treatment.

- **MONITORING REQUIREMENTS** Manufacturer advises monitor serum and/or urine bile-acid concentrations every 3 months for the first year, then every 6 months for three years, then annually; monitor liver function tests at the same or greater frequency.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises capsules may be opened and the content added to infant formula, juice, fruit compote, or yoghurt for administration.

- **PATIENT AND CARER ADVICE** Counselling advised on administration.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  - CAUTIONARY AND ADVISORY LABELS 25
    - Cholic acid 250 mg: Orphacol (Laboratoires CTRS) ▼
      - Cholic acid 50 mg Orphacol 50 mg capsules | 30 capsule [POD] £1,860.00
      - Cholic acid 250 mg: Orphacol 250 mg capsules | 30 capsule [POD] £6,520.00

Obeticholic acid

**DRUG ACTION** Obeticholic acid is a selective farnesoid X receptor agonist, which decreases circulating bile acid.

**INDICATIONS AND DOSE**

Primary biliary cholangitis in combination with ursodeoxycholic acid when response to ursodeoxycholic acid has been inadequate, or as monotherapy in patients intolerant of ursodeoxycholic acid

- **BY MOUTH**
  - Adult: Initially 5 mg once daily for 5 months, then increased to 10 mg once daily if necessary and if tolerated, for dose adjustments due to severe pruritus, consult product literature

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: OBETICHLIC ACID (OCALIVA®): RISK OF SERIOUS LIVER INJURY IN PATIENTS WITH PRE-EXISTING MODERATE OR SEVERE HEPATIC IMPAIRMENT; REMINDER TO ADJUST DOSING ACCORDING TO LIVER FUNCTION MONITORING (APRIL 2018)

The MHRA is aware of reports of serious liver injuries and deaths in patients with primary biliary cholangitis with pre-existing moderate or severe liver impairment who were not adequately dose-adjusted. Follow dose reduction and monitoring advice in these patients to
reduce the risk of serious liver injury; for further information, see Hepatic impairment and Monitoring.

- CONTRA-INDICATIONS Complete biliary obstruction
- INTERACTIONS Appendix 1: obeticholic acid
- SIDE-EFFECTS Common or very common Arthralgia - constipation - dizziness - fatigue - fever - gastrointestinal discomfort - oropharyngeal pain - palpitations - peripheral oedema - skin reactions
- Frequency not known Hepatic failure
- PREGNANCY Dose adjustments No evidence of harm but manufacturer advises avoid.
- BREAST FEEDING Not known to be harmful but manufacturer advises avoid.
- HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment or decompensated cirrhosis (risk of increased exposure).
- Dose adjustments Manufacturer advises initial dose reduction to 5 mg once weekly in moderate to severe impairment or decompensated cirrhosis; titrate dose according to alkaline phosphatase and/or total bilirubin level—consult product literature.
- MONITORING REQUIREMENTS Manufacturer advises hepatic status before treatment initiation and then monitor for progression of primary biliary cholangitis with laboratory and clinical assessment to evaluate the need for dose reduction; patients at an increased risk of hepatic decompensation, including those with laboratory evidence of worsening liver function and/or progression to cirrhosis, should be monitored more closely.
- NATIONAL FUNDING/ACCESS DECISIONS
  - NICE decisions
    - Obeticholic acid for treating primary biliary cholangitis (April 2017) NICE T4443
    - Obeticholic acid (Ocaliva®) is recommended as an option for treating primary biliary cholangitis, in combination with ursodeoxycholic acid when response to ursodeoxycholic acid is inadequate, or as monotherapy when ursodeoxycholic acid is not tolerated and only if the manufacturer provides obeticholic acid with the discount agreed in the patient access scheme. Response to obeticholic acid should be assessed after 12 months and treatment continued only if there is evidence of clinical benefit.
    - www.nice.org.uk/guidance/t4443
  - Scottish Medicines Consortium (SMC) decisions
    - The Scottish Medicines Consortium has advised (June 2017) that ursodeoxycholic acid (Ocaliva®) is accepted for use within NHS Scotland for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid when response to ursodeoxycholic acid is inadequate, or as monotherapy when ursodeoxycholic acid is not tolerated. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.
- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral suspension**

| CAUTIONARY AND ADVISORY LABELS | 21 |
| Ursosfalk (Dr. Falk Pharma UK Ltd) | Ursodeoxycholic acid 50 mg per 1 ml | Usosfalk 250mg/5ml oral suspension sugar-free | 250 ml | £26.98 DT = £26.98 |

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 21 |
| Ursodeoxycholic acid (Non-proprietary) | Ursodeoxycholic acid 150 mg | Ursodeoxycholic acid 150mg tablets | 60 tablet | £19.02 DT = £19.02 |
| Ursodeoxycholic acid 300 mg | Ursodeoxycholic acid 300mg tablets | 60 tablet | £41.63–£62.32 DT = £33.08 |
| Cholursal (HF HealthCare Products Ltd) | Ursodeoxycholic acid 250 mg | Cholursal 250mg tablets | 60 tablet | £15.25 DT = £15.25 |
| Ursodeoxycholic acid 500 mg | Cholursal 500mg tablets | 60 tablet | £24.00 DT = £24.00 |
| Destolt (Norgine Pharmaceuticals Ltd) | Ursodeoxycholic acid 150 mg | Destolt 150mg tablets | 60 tablet | £18.39 DT = £18.02 |
| Ursosfalk (Dr. Falk Pharma UK Ltd) | Ursodeoxycholic acid 300 mg | Ursosfalk 300mg tablets | 100 tablet | £80.00 DT = £80.00 |
| Ursosnur (PRO.MED.CS Praha a.s.) | Ursodeoxycholic acid 500 mg | Ursosnur 500mg tablets | 60 tablet | £45.00 DT = £45.00 |
| Ursosnur | Ursosnur 500mg tablets | 100 tablet | £49.00 DT = £49.00 |

**Dissolution of gallstones**

- **BY MOUTH**
  - Adult: 8–12 mg/kg once daily, dose to be taken at bedtime, alternatively 8–12 mg/kg daily in 2 divided doses for up to 2 years; treatment is continued for 3–4 months after stones dissolve

**Primary biliary cirrhosis**

- **BY MOUTH**
  - Adult: 12–16 mg/kg daily in 3 divided doses for 3 months, then 12–16 mg/kg once daily, dose to be taken at bedtime

- CONTRA-INDICATIONS Acute inflammation of the gall bladder - frequent episodes of biliary colic - inflammatory diseases and other conditions of the colon, liver or small intestine which interfere with enterohepatic circulation of bile salts - non-functioning gall bladder - radio-opaque stones
- CAUTIONS Liver disease
- INTERACTIONS Appendix 1: ursodeoxycholic acid
- SIDE-EFFECTS Common or very common Diarrhoea - pale faeces
- Rare or very rare Cholelithiasis calcification - skin reactions
- Frequency not known Nausea - vomiting
- PREGNANCY No evidence of harm but manufacturer advises avoid.
- BREAST FEEDING Not known to be harmful but manufacturer advises avoid.
- HEPATIC IMPAIRMENT Avoid in chronic liver disease (but used in primary biliary cirrhosis).
- MONITORING REQUIREMENTS In primary biliary cirrhosis, monitor liver function every 4 weeks for 3 months, then every 3 months.
- PATIENT AND CARER ADVICE Patients should be given dietary advice (including avoidance of excessive cholesterol and calories).
**Capsule**

*Obesity*

**INDICATIONS AND DOSE**

**Biliary disorders**
- **BY MOUTH**
- Adult: 1–2 capsules 3 times a day, to be taken before food

**LESS SUITABLE FOR PRESCRIBING** *Rowachol®* is less suitable for prescribing.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**

*CAUTIONARY AND ADVISORY LABELS 22*

- *Rowachol* (Meadow Laboratories Ltd)
- *Cineole 2 mg, Borneol 5 mg, Camphene 5 mg, Menthone 6 mg, (Meadow Laboratories Ltd)*
- *Terlipressin acetate 200 microgram per 1 ml* (Alliance Pharmaceuticals Ltd)
- *Glypressin 1 mg/8.5 ml solution for injection ampoules | 5 ampoule* (£)
- *Variquel (Alliance Pharmaceuticals Ltd)*
- *Terlipressin acetate 200 microgram per 1 ml* (Alliance Pharmaceuticals Ltd)

**Other drugs used for Oesophageal varices** *Vasopressin, p. 669*

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES**

**Vasopressin and analogues**

**Terlipressin acetate**

**INDICATIONS AND DOSE**

**GLYPRESSIN® INJECTION**

**Bleeding from oesophageal varices**
- **BY INTRAVENOUS INJECTION**
- Adult (body-weight up to 50 kg): Initially 2 mg every 4 hours until bleeding controlled, then reduced to 1 mg every 4 hours if required, maximum duration 48 hours
- Adult (body-weight 50 kg and above): Initially 2 mg every 4 hours until bleeding controlled, reduced if not tolerated to 1 mg every 4 hours, maximum duration 48 hours

**VARIQUEL® INJECTION**

**Bleeding from oesophageal varices**
- **BY INTRAVENOUS INJECTION**
- Adult (body-weight up to 50 kg): Initially 1 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
- Adult (body-weight 50–69 kg): Initially 1.5 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
- Adult (body-weight 70 kg and above): Initially 2 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute

**CAUTIONS**
Arrhythmia - elderly - electrolyte and fluid disturbances - heart disease - history of QT-interval prolongation - respiratory disease - septic shock - uncontrolled hypertension - vascular disease

**SIDE-EFFECTS**
- **Common or very common** Abdominal cramps - arrhythmias - diarrhoea - headache - hypertension - hypotension - pallor - peripheral ischaemia - vasoconstriction
- **Uncommon** Chest pain - cyanosis - fluid overload - heart failure - hot flush - hypotension - intestinal ischaemia - ischaemic heart disease - lymphangitis - myocardial infarction - nausea - pulmonary oedema - respiratory disorders - seizure - skin necrosis - uterine disorders - vomiting
- **Rare or very rare** Dyspnoea - hyperglycaemia - stroke

**PREGNANCY**
Avoid unless benefits outweigh risk — uterine contractions and increased intra-uterine pressure in early pregnancy, and decreased uterine blood flow reported.

**BREAST FEEDING**
Avoid unless benefits outweigh risk — no information available.

**RENAI IMPAIRMENT**
Use with caution in chronic renal failure.

**MEDITICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- *Glypressin (Ferring Pharmaceuticals Ltd)*
- *Terlipressin acetate 120 microgram per 1 ml Glypressin 1mg/8.5ml solution for injection ampoules | 5 ampoule* (£)
- *Variquel (Alliance Pharmaceuticals Ltd)*
- *Terlipressin acetate 200 microgram per 1 ml* (Alliance Pharmaceuticals Ltd)

**8 Obesity**

**Obesity**

*01-Jun-2016*

**Description of condition**

Obesity is directly linked to many health problems including cardiovascular disease, type 2 diabetes, fatty liver disease, gallstones, and gastro-oesophageal reflux disease. It is also linked to psychological and psychiatric morbidities.

In adults, obesity is generally classified as a body mass index (BMI) of > 30 kg/m², though BMI should be interpreted with caution as it is not a direct measure of adiposity, particularly in patients who are very muscular or have muscle weakness or atrophy.

Waist circumference should also be considered as it may provide an indication of total body fat and a risk of obesity-related health problems. Men with a waist circumference > 94 cm (> 90 cm for Asian men), and women with a waist circumference of > 80 cm are at increased risk of obesity-related health problems. A waist circumference of > 102 cm in men and > 88 cm in women indicates a very high risk of obesity-related health problems.

**Aims of treatment**

Management should be aimed at modest, sustainable weight loss and maintenance of a healthy weight, to reduce the risk factors associated with obesity.

**Overview**

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity. Patients should be monitored for changes in weight, as well as changes in blood pressure and blood lipids, and for other associated conditions.

An initial assessment should consider potential underlying causes (e.g. hypothyroidism) and a review of the
appropriateness of current medications which are known to cause weight gain, e.g., atypical antipsychotics, beta-adrenoceptor blocking drugs, insulin (when used in the treatment of type 2 diabetes), lithium carbonate, lithium citrate, sodium valproate, sulphonylureas, thiazolidinediones, and tricyclic antidepressants. ▶

**Lifestyle changes**

Patients should be encouraged to engage in a sustainable weight management programme which includes strategies to change behaviour, increase physical activity, and improve diet and eating behaviour. ▶

**Drug treatment**

Drug treatment should never be used as the sole element of treatment and should be used as part of an overall weight management plan. An anti-obesity drug should be considered only for those with a BMI of > 30 kg/m², in whom diet, exercise and behaviour changes fail to achieve a realistic reduction in weight. In the presence of associated risk factors, it may be appropriate to prescribe an anti-obesity drug to individuals with a BMI of > 28 kg/m². A vitamin and mineral supplement may also be considered if there is concern about inadequate micronutrient intake, particularly for vulnerable groups such as in the elderly and younger patients.

The effect of management should be monitored on a regular basis with reinforcement of supporting lifestyle advice. Rates of weight loss may be slower in patients with type 2 diabetes, so less strict goals than in those without diabetes may be appropriate.

Orlistat p. 92, is the only drug currently available in the UK that is recommended specifically for the management of obesity; it acts by reducing the absorption of dietary fat.

Orlistat is licensed for use as an adjunct in the management of obesity in patients with a BMI of > 30 kg/m², or, in individuals with a BMI of > 28 kg/m² in the presence of other risk factors. Treatment with orlistat may also be used to maintain weight loss rather than to continue to lose weight. Discontinuation of treatment with orlistat should be considered after 12 weeks if weight loss has not exceeded 5% since the start of treatment. ▶

Drugs which produce a feeling of satiety (such as methyccellulose p. 55 and sterculia p. 55 [unlicensed indications]) have been used in an attempt to control appetite, but there is little evidence for their efficacy. Various centrally acting appetite suppressants, including stimulants and serotonergic drugs (such as dexfenfluramine, fenfluramine, sibutramine, and rimonabant), have been used in the management of obesity but have been withdrawn or are no longer recommended due to serious safety concerns or their addictive potential.

**Surgery**

Bariatric surgery may be considered for patients who have a BMI of > 40 kg/m² (Obesity III, morbid obesity), or between 35–39.9 kg/m² (Obesity II) and a significant disease (such as type 2 diabetes or high blood pressure) which could be improved with weight loss, and if all appropriate non-surgical measures have been tried but clinically beneficial weight loss has not been achieved or maintained. ▶

**Useful Resources**


Other drugs used for Obesity Liraglutide, p. 699

### ANTIDEPRESSANTS > SEROTONIN AND NORADRENALINE RE- UPTAKE INHIBITORS

**Naltrexone with bupropion**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupropion hydrochloride p. 498, naltrexone hydrochloride p. 497.

**Indications and dose**

Adjunct in obesity (in conjunction with dietary measures and increased physical activity in individuals with a body mass index (BMI) of 30 kg/m² or more or in individuals with a BMI of 27 kg/m² or more in the presence of one or more weight related co-morbidity)

- **By mouth**
  - Adult 18–75 years: Initially 1 tablet daily for 7 days, then increased to 1 tablet twice daily for 7 days, then increased to 3 tablets daily in divided doses for 7 days, two tablets to be taken in the morning, and one tablet to be taken in the evening, then maintenance 2 tablets twice daily, review treatment after 16 weeks and then annually

**Dose equivalence and conversion**

- Each tablet contains 8 mg naltrexone with 90 mg bupropion.

**Contra-indications**

- Uncontrolled hypertension

**Cautionary and advisory labels**

- History of mania - hypertension

**Interactions**

- Appendix 1: bupropion - naltrexone

**Hepatic impairment**

Manufacturer advises avoid (no information available).

**Renal Impairment**

Manufacturer advises avoid in moderate-to-severe impairment—limited information available.

**Prescribing and dispensing information**

Prescribers should consult the Mysimba® Physician Prescribing Checklist provided by the manufacturer, before initiation of treatment.

**National funding/access decisions**

**NICE decisions**

- Naltrexone–bupropion for managing overweight and obesity (December 2017) NICE TA494

Naltrexone–bupropion is not recommended within its marketing authorisation for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta494

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 21, 25

- Mysimba (Orexigen Therapeutics (Ireland) Ltd)

  Naltrexone hydrochloride 8 mg, Bupropion hydrochloride 90 mg Mysimba 8mg/90mg modified-release tablets | 112 tablet BNF £73.00
92 Rectal and anal disorders

PERIPHERALLY ACTING ANTI OBESITY PRODUCTS > LIPASE INHIBITORS

Orlistat

> DRUG ACTION Orlistat, a lipase inhibitor, reduces the absorption of dietary fat.

> INDICATIONS AND DOSE

Adjunct in obesity (in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m² or more in individuals with a BMI of 28 kg/m² or more in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia)

> BY MOUTH

- Adult: 120 mg up to 3 times a day, dose to be taken immediately before, during, or up to 1 hour after each main meal, continue treatment beyond 12 weeks only if weight loss since start of treatment exceeds 5% (target for initial weight loss may be lower in patients with type 2 diabetes), if a meal is missed or contains no fat, the dose of orlistat should be omitted

> CONTRA-INDICATIONS Cholestasis · chronic malabsorption syndrome

> CAUTIONS Chronic kidney disease · may impair absorption of fat-soluble vitamins · volume depletion

CAUTIONS, FURTHER INFORMATION Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins.

> INTERACTIONS Appendix 1: orlistat

> SIDE-EFFECTS

- Common or very common Abdominal pain (may be minimised by reduced fat intake) · anxiety · diarrhoea · gastrointestinal disorders

- Frequency not known Anorectal haemorrhage · bullous dermatitis · cholelithiasis · diverticulitis · hepatitis · oxalate nephropathy · pancreatitis · renal failure

> PREGNANCY Use with caution.

> BREAST FEEDING Avoid—no information available.

> MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

- Orlistat (Non-proprietary)
  - Orlistat 120 mg Orlistat 120mg capsules | 84 capsule £35.43 DT = £26.56
  - Alli (GlaxoSmithKline Consumer Healthcare)
    - Orlistat 60 mg Alli 60mg capsules | 84 capsule £30.70 DT = £20.70
  - Orlos (Crescent Pharma Ltd)
    - Orlistat 60 mg Orlos 60mg capsules | 84 capsule £16.95 DT = £13.60
  - Xenical (Cheplapharm Arzneimittel GmbH)
    - Orlistat 120 mg Xenical 120mg capsules | 84 capsule £31.63 DT = £26.56

9 Rectal and anal disorders

Other drugs used for Rectal and anal disorders Diltiazem hydrochloride, p. 157

9.1 Anal fissures

Anal fissure

Description of condition

An anal fissure is a tear or ulcer in the lining of the anal canal, immediately within the anal margin. Clinical features of anal fissure include bleeding and persistent pain on defecation, and a linear split in the anal mucosa.

Aims of treatment

The aim of treatment is to relieve pain and promote healing of the fissure.

Drug treatment

Acute anal fissure

Initial management of acute anal fissures (present for less than 6 weeks) should focus on ensuring that stools are soft and easily passed. Bulk-forming laxatives (such as ispaghula husk p. 55) are recommended and an osmotic laxative (such as lactulose p. 56) can be considered as an alternative—see also Constipation p. 53, for further information about these laxatives. Short-term use of a topical preparation containing a local anaesthetic (such as lidocaine hydrochloride p. 103) or a simple analgesic (such as paracetamol p. 444 or ibuprofen p. 1141) may be offered for prolonged burning pain following defecation. If these measures are inadequate, the patient should be referred for specialist treatment in hospital.

Chronic anal fissure

Chronic anal fissures (present for 6 weeks or longer), and associated pain, may be treated with glyceryl trinitrate rectal ointment 0.4% or 0.2% p. 218 [unlicensed] (available from Special-order manufacturers p. 1626 or specialist importing companies). Limited evidence suggests that the strength used does not influence the effectiveness, but that the higher strength potentially increases the incidence of side-effects. Healing rates with topical glyceryl trinitrate are marginally superior to placebo, but the incidence of headache as an adverse effect is quite high (about 20–30% of patients). Recurrence of the fissure after treatment is common.

As an alternative to glyceryl trinitrate rectal ointment, chronic anal fissure may also be treated with topical diltiazem hydrochloride 2% p. 157 [unlicensed] or nifedipine 0.2–0.5% p. 162 [unlicensed] (available from Special-order manufacturers p. 1626 or specialist importing companies), which have a lower incidence of adverse effects than topical glyceryl trinitrate. Oral nifedipine [unlicensed indication] and oral diltiazem hydrochloride [unlicensed indication] may be as effective as topical treatment, but the incidence of adverse effects is likely to be higher and topical preparations are preferred.

Patients who do not respond to first-line treatment may be referred to a specialist for local injection of botulinum toxin type A [unlicensed indication].

Non-drug treatment

Surgery is an effective option for the management of chronic anal fissure in adults but is generally reserved for those who do not respond to drug treatment.
9.2 Haemorrhoids

**Haemorrhoids**

**Description of condition**

Haemorrhoids, or piles, are abnormal swellings of the vascular mucosal anal cushions around the anus. Internal haemorrhoids arise above the dentate line and are usually painless unless they become strangulated. External haemorrhoids originate below the dentate line and can be itchy or painful. Women are predisposed to developing haemorrhoids during pregnancy.

**Aims of treatment**

The aims of treatment are to reduce the symptoms (pain, bleeding and swelling), promote healing, and prevent recurrence.

**Non-drug treatment**

Stools should be kept soft and easy to pass (to minimise straining) by increasing dietary fibre and fluid intake. Advice about perianal hygiene is helpful to aid healing and reduce irritation and itching.

**Drug treatment**

If constipation is reported, it should be treated. A bulk-forming laxative can be prescribed (see Constipation p. 53).

A simple analgesic such as paracetamol p. 444 can be used for pain relief. Opioid analgesics should be avoided as they can cause constipation, and NSAIDs should be avoided if rectal bleeding is present.

Topical preparations that contain a combination of local anaesthetics, corticosteroids, astringents, lubricants, and antiseptics are available—see Related drugs below. They can offer symptomatic relief of local pain and itching but evidence does not suggest that any preparation is more effective than any other.

Topical preparations containing local anaesthetics (lidocaine, benzocaine, cinchocaine and pramocaine) should only be used for a few days as they may cause sensitisation of the anal skin. Local anaesthetics can be absorbed through the rectal mucosa (with a theoretical risk of systemic side effects) and very rarely may cause increased irritation; therefore excessive application should be avoided.

Topical preparations combining corticosteroids with local anaesthetics and soothing agents are available for the management of haemorrhoids. They may ameliorate local perianal inflammation, but no data suggest that they actually reduce haemorrhoidal swelling, bleeding, or protrusion.

Topical corticosteroids are suitable for occasional short-term use (no more than 7 days) after exclusion of infections (such as perianal streptococcal infection, *herpes simplex* or perianal thrush). Long-term use of corticosteroid creams can cause ulceration or permanent damage due to thinning of the perianal skin and should be avoided.

Continuous or excessive use carries a risk of adrenal suppression and systemic corticosteroid effects. Recurrent symptoms, should be referred to secondary care for further investigation and management.

Treatments available from specialists include rubber band ligation, injection sclerotherapy (using phenol p. 95 in oil), infrared coagulation/photocoagulation, bipolar diathermy and direct-current electrotherapy, haemorrhoidectomy, stapled haemorrhoidectomy, and haemorrhoidal artery ligation.

**Pregnancy**

Bulk forming laxatives are not absorbed, and are therefore safe for use in pregnant women (see Pregnancy, under Constipation p. 53). No topical haemorrhoidal preparations are licensed for use during pregnancy.

If treatment with a topical haemorrhoidal preparation is required, a soothing preparation containing simple, soothing products (not local anaesthetics or corticosteroids) can be considered.

**Related drugs**

Topical preparations used for haemorrhoids: lidocaine hydrochloride with bismuth oxide, bismuth subgallate, hydrocortisone acetate, peru balsam and zinc oxide below, cinchocaine hydrochloride with fluocortolone caproate and fluocortolone pivalate p. 94, cinchocaine with hydrocortisone p. 94, cinchocaine with prednisolone p. 94.

### CORTICOSTEROIDS

**Benzyl benzoate with bismuth oxide, bismuth subgallate, hydrocortisone acetate, peru balsam and zinc oxide**

21-Dec-2017

**INDICATIONS AND DOSE**

**Haemorrhoids**

**Pruritus ani**

* BY RECTUM USING OINTMENT
  
  Adult: Apply twice daily for no longer than 7 days, to be applied morning and night, an additional dose should be applied after a bowel movement.

* BY RECTUM USING SUPPOSITORIES
  
  Adult: 1 suppository twice daily for no longer than 7 days, to be inserted night and morning, additional dose after a bowel movement.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

See Corticosteroids, general use p. 670.

**CAUTIONS**

Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**PRESCRIBING AND DISPENSING INFORMATION**

A proprietary brand Anusol Plus HC® (ointment and suppositories) is on sale to the public.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

* Anusol-Hc (Church & Dwight UK Ltd)
  
  Hydrocortisone acetate 2.5 mg per 1 gram, Bismuth oxide 8.75 mg per 1 gram, Benzyl benzoate 12.5 mg per 1 gram, Peru Balsam 18.75 mg per 1 gram, Bismuth subgallate 22.5 mg per 1 gram, Zinc oxide 107.5 mg per 1 gram
  
  Anusol HC ointment | 30 gram [Pax] £2.49

**Suppository**

* Anusol-Hc (Church & Dwight UK Ltd)
  
  Hydrocortisone acetate 10 mg, Bismuth oxide 24 mg, Benzyl benzoate 33 mg, Peru Balsam 49 mg, Bismuth subgallate 59 mg, Zinc oxide 296 mg
  
  Anusol HC suppositories | 12 suppository [Pax] £1.74
## Cinchocaine hydrochloride with fluocortolone caproate and fluocortolone pivalate

**21-Dec-2017**

### INDICATIONS AND DOSE

**Haemorrhoids | Pruritus ani**

- **Adult:** Apply twice daily for 5–7 days, apply 3–4 times a day if required, on the first day of treatment, then apply once daily for a few days after symptoms have cleared
- **By rectum using suppositories:**
  - Adult: Initially 1 suppository daily for 5–7 days, to be inserted after a bowel movement, then 1 suppository once daily on alternate days for 1 week

**Haemorrhoids (severe cases) | Pruritus ani (severe cases)**

- **Adult:** Initially 1 suppository 2–3 times a day for 5–7 days, then 1 suppository once daily on alternate days for 1 week

### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE:** CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

See Corticosteroids, general use p. 670.

- **Caution:** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application) – local anaesthetic component may cause sensitisation (use for short periods only — no longer than a few days)

### MEDICINAL FORMS

- **There can be variation in the licensing of different medicines containing the same drug.**
  - **Ointment**
    - **Uniproct** (Meadow Laboratories Ltd)
      - Fluocortolone pivalate 920 microgram per 1 gram, Fluocortolone caproate 950 microgram per 1 gram, Cinchocaine hydrochloride 5 mg per 1 gram
      - Ultraproct ointment | 30 gram [P08] £8.27
  - **Suppository**
    - **Uniproct** (Meadow Laboratories Ltd)
      - Fluocortolone pivalate 610 microgram, Fluocortolone caproate 630 microgram, Cinchocaine hydrochloride 1 mg
      - Ultraproct suppositories | 12 suppository [P08] £4.06

## Cinchocaine with hydrocortisone

**21-Dec-2017**

### INDICATIONS AND DOSE

**Proctosedyl Ointment**

- **Pruritus ani**
  - **Child:** Apply twice daily, to be administered morning and night and after a bowel movement. Apply externally or by rectum. Do not use for longer than 7 days
  - **Adult:** Apply twice daily, to be administered morning and night and after a bowel movement. Apply externally or by rectum. Do not use for longer than 7 days

**Proctosedyl Suppositories**

- **Pruritus ani**
  - **Child 12–17 years:** 1 suppository, insert suppository night and morning and after a bowel movement. Do not use for longer than 7 days

## Cinchocaine with prednisolone

**21-Dec-2017**

### INDICATIONS AND DOSE

- **Pruritus ani**
  - **Adult:** Apply twice daily for 5–7 days, apply 3–4 times a day on the first day if necessary, then apply once daily for a few days after symptoms have cleared
  - **By rectum using suppositories:**
  - **Adult:** 1 suppository daily for 5–7 days, to be inserted after a bowel movement
### Hydrocortisone with pramocaine

**INDICATIONS AND DOSE**

**Haemorrhoids** | **Proctitis**  
--- | ---  
**BY RECTUM USING AEROSOL SPRAY**  
**Adult:** 1 spray up to 3 times a day for no longer than 7 days without medical advice, spray once over the affected area  
**BY RECTUM USING OINTMENT**  
**Adult:** Apply several times daily, for short term use only  

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

See Corticosteroids, general use p. 670.

### Phenol

**INDICATIONS AND DOSE**

**Haemorrhoids (particularly when unprolapsed)**  
**BY SUBMUCOSAL INJECTION**  
**Adult:** 2–3 mL, dose (using phenol 5%) to be injected into the submucosal layer at the base of the pile; several injections may be given at different sites, max. total injected 10 mL at any one time  

**SIDE-EFFECTS** Abdominal sepsis · abscess · dizziness · erectile dysfunction · fever · hepatitis · increased risk of infection · injection site necrosis · ulcer · urinary disorders  

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Oily Phenol Injection, BP consists of phenol 5% in a suitable fixed oil.

**MEDICAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection  

**Solution for injection**  
**Phenol (Non-proprietary)**  
Phenol 50 mg per 1 ml Oily phenol 5% solution for injection 5ml ampoules | 10 ampoules (POM) £70.31 DT = £70.31

### Exocrine pancreatic insufficiency

**Description of condition**

Exocrine pancreatic insufficiency is characterised by reduced secretion of pancreatic enzymes into the duodenum.  

The main clinical manifestations are malabsorption and malnutrition, associated with low circulating levels of fat-soluble vitamins, amino acids, and trace elements. The main manifestations are maldigestion and malnutrition, associated with low circulating levels of micronutrients, fat-soluble vitamins and lipoproteins.

Patients also present with gastro-intestinal symptoms such as diarrhoea, abdominal cramps and steatorrhoea.

Exocrine pancreatic insufficiency can result from chronic pancreatitis, cystic fibrosis, obstructive pancreatic tumours,
Aims of treatment
The aim of treatment is to relieve gastro-intestinal symptoms and to achieve a normal nutritional status.

Drug treatment
Pancreatic enzyme replacement therapy with pancreatin below is the mainstay of treatment for exocrine pancreatic insufficiency.

Pancreatin contains the three main groups of digestive enzymes: lipase, amylase and protease. These enzymes respectively digest fats, carbohydrates and proteins into their basic components so that they can be absorbed and utilised by the body. Pancreatin should be administered with meals and snacks. The dose should be adjusted, as necessary, to the lowest effective dose according to the symptoms of malabsorption and maldigestion.

Fibrosing colonopathy has been reported in patients with cystic fibrosis taking high dose pancreatic enzyme replacement therapy (in excess of 10 000 units/kg/day of lipase). Possible risk factors are gender (in children, boys are at greater risk than girls), more severe cystic fibrosis, and concomitant use of laxatives. The peak age for developing fibrosing colonopathy is between 2 and 8 years. Manufacturers of Pancrease HL® and Nutrizym 22® recommend that the total dose of pancreatin used in patients with cystic fibrosis should not usually exceed 10 000 units/kg/day of lipase. Manufacturers of pancreatin recommend that if a patient taking pancreatin develops new abdominal symptoms (or any change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic disease, Zollinger-Ellison syndrome, and gastrointestinal or pancreatic surgical resection.

There is limited evidence that acid suppression may improve the effectiveness of pancreatin. Acid-suppressing drugs (proton pump inhibitors or H2-receptor antagonists) may be trialled in patients who continue to experience symptoms despite high doses of pancreatin.

Levels of fat-soluble vitamins and micronutrients (such as zinc and selenium) should be routinely assessed and supplementation advised whenever necessary.

Non-drug treatment
Dietary advice should be provided. Food intake should be distributed between three main meals per day, and two or three snacks. Food that is difficult to digest should be avoided, such as legumes (peas, beans, lentils) and high-fibre foods. Alcohol should be avoided completely. Reduced fat diets are not recommended.

Medium-chain triglycerides (see MCT oil, in Borderline substances), which are directly absorbed by the intestinal mucosa, were thought to be useful in some patients. However evidence has shown that MCT-enriched preparations offer no advantage over a normal balanced diet.

PANCREATIC ENZYMES

Pancreatin

INDICATIONS AND DOSE
CREON® 10000
Pancreatic insufficiency
"BY MOUTH"
Child: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
CREON® 25000
Pancreatic insufficiency
"BY MOUTH"
Child 2-17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
CREON® 40000
Pancreatic insufficiency
"BY MOUTH"
Child 2-17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)
CREON® MICRO
Pancreatic insufficiency
"BY MOUTH"
Child: Initially 100 mg, for administration advice, see Directions for administration
Adult: Initially 100 mg, for administration advice, see Directions for administration
DOSE EQUIVALENCE AND CONVERSION
For Creon® Micro: 100 mg granules = one measured spoonful (spoon supplied with product).

Dietary advice should be provided. Food intake should be distributed between three main meals per day, and two or three snacks. Food that is difficult to digest should be avoided, such as legumes (peas, beans, lentils) and high-fibre foods. Alcohol should be avoided completely. Reduced fat diets are not recommended.

Medium-chain triglycerides (see MCT oil, in Borderline substances), which are directly absorbed by the intestinal mucosa, were thought to be useful in some patients. However evidence has shown that MCT-enriched preparations offer no advantage over a normal balanced diet.

www.getintopharma.com
NUTRIZYM 22® GASTRO-RESISTANT CAPSULES

Pancreatic insufficiency
- BY MOUTH
  - Adult: Initially 1–2 capsules, dose to be taken with meals and 1 capsule as required, dose to be taken with snacks, doses should be swallowed whole or contents taken with water, or mixed with acidic fluid or soft food (then swallowed immediately without chewing)
  - Adult: Initially 1–2 capsules, dose to be taken during each meal and 1 capsule, to be taken with snacks, all doses either taken whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing)

PANCREASE HL®

Pancreatic insufficiency
- BY MOUTH
  - Child 15-17 years: Initially 1–2 capsules, dose to be taken during each meal and 1 capsule, to be taken with snacks, all doses either taken whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing)

PANCREX®

Pancreatic insufficiency
- BY MOUTH
  - Child 2-17 years: 5–10 g, to be taken just before meals, washed down or mixed with milk or water
  - Adult: 5–10 g, to be taken just before meals; washed down or mixed with milk or water

PANCREX® V

Pancreatic insufficiency
- BY MOUTH
  - Child 1-11 months: 1–2 capsules, contents of capsule to be mixed with feeds
  - Child 1-17 years: 2–6 capsules, dose to be taken with each meal either swallowed whole or sprinkled on food
  - Adult: 2–6 capsules, dose to be taken with each meal either swallowed whole or sprinkled on food

PANCREX® V POWDER

Pancreatic insufficiency
- BY MOUTH
  - Child: 0.5–2 g, to be taken before or with meals, washed down or mixed with milk or water
  - Adult: 0.5–2 g, to be taken before or with meals, washed down or mixed with milk or water

PANCREX® V TABLETS

Pancreatic insufficiency
- BY MOUTH
  - Child 2-17 years: 5–15 tablets, to be taken before meals
  - Adult: 5–15 tablets, to be taken before meals

PANCREX® V TABLETS FORTE

Pancreatic insufficiency
- BY MOUTH
  - Child 2-17 years: 6–10 tablets, to be taken before meals
  - Adult: 6–10 tablets, to be taken before meals

CONTRA-INDICATIONS

PANCREASE HL® Should not be used in children aged 15 years or less with cystic fibrosis

CAUTIONS Can irritate the perioral skin and buccal mucosa if retained in the mouth; excessive doses can cause perianal irritation

INTERACTIONS Appendix 1: pancreatin

SIDE-EFFECTS
- Common or very common Abdominal distension · constipation · nausea · vomiting
- Uncommon Skin reactions
- Frequency not known Fibrosing colonopathy
- PREGNANCY Not known to be harmful

DIRECTIONS FOR ADMINISTRATION Pancreatin is inactivated by gastric acid therefore manufacturer advises pancreatin preparations are best taken with food (or immediately before or after food). Since pancreatin is inactivated by heat, excessive heat should be avoided if preparations are mixed with liquids or food; manufacturer advises the resulting mixtures should not be kept for more than one hour and any left-over food or liquid containing pancreatin should be discarded. Enteric-coated preparations deliver a higher enzyme concentration in the duodenum (provided the capsule contents are swallowed whole without chewing). Manufacturer advises gastro-resistant granules should be mixed with slightly acidic soft food or liquid such as apple juice, and then swallowed immediately without chewing. Capsules containing enteric-coated granules can be opened and the granules administered in the same way. For infants, Creon® Micro granules can be mixed with a small amount of milk on a spoon and administered immediately—granules should not be added to the baby’s bottle. Manufacturer advises Pancrex® V powder may be administered via nasogastric tube or gastrostomy tube—consult local and national official guidelines.

PRESCRIBING AND DISPENSING INFORMATION Preparations may contain porc pancreatin—consult product literature.

HANDLING AND STORAGE Hypersensitivity reactions occur occasionally and may affect those handling the powder.

PATIENT AND CARER ADVICE Patients or carers should be given advice on administration. It is important to ensure adequate hydration at all times in patients receiving higher-strength pancreatin preparations. Medicines for Children leaflet: Pancreatin for pancreatic insufficiency www.medicinesforchildren.org.uk/pancreatin-pancreatic-insufficiency

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Gastro-resistant capsule
- Creon® (Mylan)
  - Protease 600 unit, Amylase 8000 unit, Lipase 10000 unit Creon 10000 gastro-resistant capsules £12.93
  - Protease 1000 unit, Amylase 18000 unit, Lipase 25000 unit Creon 25000 gastro-resistant capsules £28.25
  - Protease 1600 unit, Amylase 25000 unit, Lipase 40000 unit Creon 40000 gastro-resistant capsules £47.55

- Nutrizym® (Merck Serono Ltd)
  - Protease 600 unit, Amylase 8000 unit, Lipase 10000 unit Nutrizym 6000 gastro-resistant capsules £33.33

- Pancrease® (Janssen-Cilag Ltd)
  - Protease 1250 unit, Amylase 22500 unit, Lipase 25000 unit Pancrease H gastro-resistant capsules £40.38

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 5, 25

- Pancrex® (Essential Pharmaceuticals Ltd)
  - Protease 110 unit, Amylase 1700 unit, Lipase 1900 unit Pancrex V gastro-resistant tablets £38.79
  - Protease 330 unit, Amylase 5000 unit, Lipase 5600 unit Pancrex V forte gastro-resistant tablets £48.11

Gastro-resistant granules

CAUTIONARY AND ADVISORY LABELS 25

- Creon® (Mylan)
  - Protease 600 unit, Amylase 3600 unit, Lipase 5000 unit Creon Micro Pancreatin 60.12mg gastro-resistant granules 20 gram £31.50

- Pancrex® (Essential Pharmaceuticals Ltd)
  - Protease 300 unit, Amylase 4000 unit, Lipase 5000 unit Pancrex gastro-resistant granules 30 gram £57.00
**Stoma care**

**Description of condition**

A stoma is an artificial opening on the abdomen to divert the flow of faeces or urine into an external pouch located outside the body. This procedure may be temporary or permanent. Colostomy and ileostomy are the most common forms of stoma but a gastrostomy, jejunostomy, duodenostomy or caecostomy may also be performed. Understanding the type and extent of surgical intervention in each patient is crucial in managing the patient’s pharmaceutical needs correctly.

**Overview**

Prescribing for patients with stoma calls for special care due to modifications in drug delivery, resulting in a higher risk of sub-optimal absorption. The following is a brief account of some of the main points to be borne in mind.

**Enteric-coated and modified-release medicines** are unsuitable, particularly in patients with an ileostomy, as there may not be sufficient release of active ingredient. Soluble tablets, liquids, capsules or uncoated tablets are more suitable due to their quicker dissolution. When a solid-dose form such as a capsule or a tablet is given, the contents of the ostomy bag should be checked for any remnants. Preparations containing sorbitol as an excipient should be avoided, due to its laxative side effects.

**Analgesics**

Opioid analgesics may cause troublesome constipation in colostomy patients. When a non-opioid analgesic is required, paracetamol is usually suitable. Anti-inflammatory analgesics may cause gastric irritation and bleeding; faecal output should be monitored for traces of blood.

**Antacids**

The tendency to diarrhoea from magnesium salts or constipation from aluminium or calcium salts may be increased in patients with stoma.

**Antisecretory drugs**

The gastric acid secretion often increases stoma output. Proton pump inhibitors and somatostatin analogues (octreotide p. 950 and lanreotide p. 949) are often used to reduce this risk.

**Antidiarrhoeal drugs**

Loperamide hydrochloride p. 66 and codeine phosphate p. 454 reduce intestinal motility and decrease water and sodium output from an ileostomy. Loperamide hydrochloride circulates through the enterohepatic circulation, which is disrupted in patients with a short bowel; high doses of loperamide hydrochloride may be required. Codeine phosphate can be added if response with loperamide hydrochloride alone is inadequate.

**Potassium supplements**

Liquid formulations are preferred to modified-release formulations. The daily dose should be split to avoid osmotic diarrhoea.

**Care of stoma**

Patients and their carers are usually given advice about the use of cleansing agents, protective creams, lotions, deodorants, or sealants whilst in hospital, either by the surgeon or by stoma care nurses. Voluntary organisations offer help and support to patients with stoma.
Chapter 2
Cardiovascular system

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1 Arrhythmias

Overview
Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Ectopic beats
If ectopic beats are spontaneous and the patient has a normal heart, treatment is rarely required and reassurance to the patient will often suffice. If they are particularly troublesome, beta-blockers are sometimes effective and may be safer than other suppressant drugs.

Atrial fibrillation
Treatment of patients with atrial fibrillation aims to reduce symptoms and prevent complications, especially stroke. All patients with atrial fibrillation should be assessed for their risk of stroke and thromboembolism. Atrial fibrillation can be managed by either controlling the ventricular rate (‘rate control’) or by attempting to restore and maintain sinus rhythm (‘rhythm control’). At any stage if treatment fails to control symptoms, or, if symptoms reoccur after cardioversion and specialised management is required, referral should be made within 4 weeks. If drug treatment fails to control the symptoms of atrial fibrillation or is unsuitable, ablation strategies can be considered. Review anticoagulation, stroke, and bleeding risk at least annually in all patients with atrial fibrillation.

Acute presentation
All patients with life-threatening haemodynamic instability caused by new-onset atrial fibrillation should undergo emergency electrical cardioversion without delaying to achieve anticoagulation. In patients presenting acutely but without life-threatening haemodynamic instability, rate or rhythm control can be offered if the onset of arrhythmia is less than 48 hours; rate control is preferred if onset is more than 48 hours or uncertain. Consideration of pharmacological or electrical cardioversion should be based on clinical circumstances. If pharmacological cardioversion has been agreed, intravenous amiodarone hydrochloride p. 105, or alternatively flecainide acetate p. 103, can be used (amiodarone hydrochloride is preferred if there is structural heart disease). If urgent rate control is required, a beta-blocker or verapamil hydrochloride p. 164 can be given intravenously.

Cardioversion
Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an oral or intravenous antiarrhythmic drug e.g. flecainide acetate or amiodarone hydrochloride. If atrial fibrillation has been present for more than 48 hours, electrical cardioversion is preferred and should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, parenteral anticoagulation should be commenced, and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks; prior to cardioversion, offer rate control as appropriate.

Drug treatment
Rate control is the preferred first-line drug treatment strategy for atrial fibrillation except in patients with new-onset atrial fibrillation, atrial flutter suitable for an ablation strategy, atrial fibrillation with a reversible cause, or if rhythm control is more suitable based on clinical judgement. Ventricular rate can be controlled with a standard beta-blocker (not sotalol hydrochloride p. 108) or a rate-limiting calcium channel blocker such as diltiazem hydrochloride p. 157 [unlicensed indication], or verapamil hydrochloride as monotherapy. Choice of drug should be based on individual symptoms, heart rate, comorbidities, and patient preference. Digoxin p. 109 is usually only effective for controlling the ventricular rate at rest, and should therefore only be used as monotherapy in predominantly sedentary patients with non-paroxysmal atrial fibrillation. When a single drug fails to adequately control the ventricular rate, a combination of two drugs including a beta-blocker, digoxin, or diltiazem hydrochloride can be used. If symptoms are not controlled with a combination of two drugs, a rhythm-control strategy should be considered. If ventricular function is diminished, the combination of a beta-blocker (that is licensed for use in heart failure) and digoxin is preferred. Digoxin is also used when atrial fibrillation is accompanied by congestive heart failure.
If drug treatment is required to maintain sinus rhythm (‘rhythm control’) post-cardioversion, a standard beta-blocker is used. If a standard beta-blocker is not appropriate or is ineffective, consider an oral anti-arrhythmic drug such as sotalol hydrochloride, flecainide acetate, propafenone hydrochloride p. 104, or amiodarone hydrochloride; dronedarone p. 106 may be considered in paroxysmal or persistent atrial fibrillation (see NICE guidance). If necessary, amiodarone hydrochloride can be started 4 weeks before and continuing for up to 12 months after electrical cardioversion to increase success of the procedure, and to maintain sinus rhythm. Flecainide acetate or propafenone hydrochloride should be started for patients with left ventricular impairment or heart failure.

**Paroxysmal atrial fibrillation**

In symptomatic paroxysmal atrial fibrillation, ventricular rhythm is controlled with a standard beta-blocker. Alternatively, if symptoms persist or a standard beta-blocker is inappropriate, an oral anti-arrhythmic drug such as dronedarone (see NICE guidance), sotalol hydrochloride, flecainide acetate, propafenone hydrochloride, or amiodarone hydrochloride can be given (see also Paroxysmal supraventricular tachycardia and Supraventricular arrhythmias). In selected patients with infrequent episodes of symptomatic paroxysmal atrial fibrillation, sinus rhythm can be restored using the ‘pill-in-the-pocket’ approach; this involves the patient taking oral flecainide acetate or propafenone hydrochloride to self-treat an episode of atrial fibrillation when it occurs.

**Stroke prevention**

All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis; the need needs to be balanced with the patient’s risk of bleeding; a NICE guideline (NICE clinical guideline 180 (June 2014). Atrial fibrillation: The management of atrial fibrillation) recommends using the CHA2DS2VASc assessment tool for stroke risk and the HAS-BLED tool for bleeding risk prior to and during anticoagulation. Risk factors for stroke taken into account by CHA2DS2-VASc include prior ischaemic stroke, transient ischaemic attacks, or thromboembolic events, heart failure, left ventricular systolic dysfunction, vascular disease, diabetes, hypertension, females, and patients over 65 years. Patients with a very low risk of stroke (CHA2DS2-VASc score of 0 for men or 1 for women) do not require an antithrombotic for stroke prevention. Parenteral anticoagulation should be offered to patients with new-onset atrial fibrillation who are receiving subtherapeutic or no anticoagulation therapy until assessment is made, and appropriate anticoagulation is started. Oral anticoagulation should be offered to patients with confirmed diagnosis of atrial fibrillation in whom sinus rhythm has not been successfully restored within 48 hours of onset, patients who have had, or are at high risk of recurrence of atrial fibrillation such as those with structural heart disease, prolonged history of atrial fibrillation (more than 12 months), a history of failed attempts at cardioversion, and patients whom the risk of stroke outweighs the risk of bleeding. Anticoagulation treatment should not be withheld solely because of the risk of falls, and choice of treatment should be based on clinical features and patient preferences. Oral anticoagulation may be with a vitamin K antagonist (e.g. warfarin sodium p. 140, or in non-valvular atrial fibrillation with apixaban p. 125, dabigatran etexilate p. 136, edoxaban p. 126, or rivaroxaban p. 128. Anticoagulants are also indicated during cardioversion procedures. Aspirin p. 121 is less effective than warfarin sodium at preventing emboli; the modest benefit is offset by the risk of bleeding, and aspirin should not be offered as monotherapy solely for stroke prevention in atrial fibrillation. If anticoagulant treatment is contra-indicated or not tolerated, left atrial appendage occlusion can be considered.

**Atrial flutter**

Like atrial fibrillation, treatment options for atrial flutter involve either controlling the ventricular rate or attempting to restore and maintain sinus rhythm. However, atrial flutter generally responds less well to drug treatment than atrial fibrillation.

Control of the ventricular rate is usually an interim measure pending restoration of sinus rhythm. Ventricular rate can be controlled by administration of a beta-blocker, diltiazem hydrochloride p. 157 [unlicensed indication], or verapamil hydrochloride p. 164; an intravenous beta-blocker or verapamil hydrochloride is preferred for rapid control. Digoxin p. 109 can be added if rate control remains inadequate, and may be particularly useful in those with heart failure.

Conversion to sinus rhythm can be achieved by electrical cardioversion (by cardiac pacing or direct current), pharmacological cardioversion, or catheter ablation. If the duration of atrial flutter is unknown, or it has lasted for over 48 hours, cardioversion should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, percutaneous anticoagulation should be commenced and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks.

Direct current cardioversion is usually the treatment of choice when rapid conversion to sinus rhythm is necessary (e.g. when atrial flutter is associated with haemodynamic compromise); catheter ablation is preferred for the treatment of recurrent atrial flutter. There is a limited role for anti-arrhythmic drugs as their use is not always successful. Flecainide acetate p. 103 or propafenone hydrochloride p. 104 can slow atrial flutter, resulting in 1:1 conduction to the ventricles, and should therefore be prescribed in conjunction with a ventricular rate controlling drug such as a beta-blocker, diltiazem hydrochloride [unlicensed indication], or verapamil hydrochloride. Amiodarone hydrochloride p. 105 can be used when other drug treatments are contra-indicated or ineffective.

All patients should be assessed for their risk of stroke and the need for thromboprophylaxis; the choice of anticoagulant is based on the same criteria as for atrial fibrillation.

**Paroxysmal supraventricular tachycardia**

This will often terminate spontaneously or with reflex vagal stimulation such as a Valsalva manoeuvre, immersing the face in ice-cold water, or carotid sinus massage; such manoeuvres should be performed with ECG monitoring. If the effects of reflex vagal stimulation are transient or ineffective, or if the arrhythmia is causing severe symptoms, intravenous adenosine p. 107 should be given. If adenosine is ineffective or contra-indicated, intravenous verapamil hydrochloride is an alternative, but it should be avoided in patients recently treated with beta-blockers.

Failure to terminate paroxysmal supraventricular tachycardia with reflex vagal stimulation or drug treatment may suggest an arrhythmia of atrial origin, such as focal atrial tachycardia or atrial flutter.

Treatment with direct current cardioversion is needed in haemodynamically unstable patients or when the above measures have failed to restore sinus rhythm (and an alternative diagnosis has not been found).

Recurrent episodes of paroxysmal supraventricular tachycardia can be treated by catheter ablation, or prevented with drugs such as diltiazem hydrochloride, verapamil hydrochloride, beta-blockers including sotalol hydrochloride p. 108, flecainide acetate or propafenone hydrochloride.
**Arrhythmias after myocardial infarction**

In patients with a paroxysmal tachycardia or rapid irregularity of the pulse it is best not to administer an antiarrhythmic until an ECG record has been obtained. Bradycardia, particularly if complicated by hypotension, should be treated with an intravenous dose of atrotive sulfate p. 1334 the dose may be repeated if necessary. If there is a risk of asystole, or if the patient is unstable and has failed to respond to atrotive sulfate, adrenaline/epinephrine p. 222 should be given by intravenous infusion, and the dose adjusted according to response.

For further advice, refer to the most recent recommendations of the Resuscitation Council (UK) available at www.resus.org.uk.

**Ventricular tachycardia**

Pulseless ventricular tachycardia or ventricular fibrillation should be treated with immediate defibrillation (see Cardiopulmonary resuscitation).

Patients with unstable sustained ventricular tachycardia, who continue to deteriorate with signs of hypotension or reduced cardiac output, should receive direct current cardioversion to restore sinus rhythm. If this fails, intravenous amiodarone hydrochloride should be administered and direct current cardioversion repeated.

Patients with sustained ventricular tachycardia who are haemodynamically stable can be treated with intravenous anti-arrhythmic drugs. Amiodarone hydrochloride is the preferred drug. Flecainide acetate, propafenone hydrochloride, and, although less effective, lidocaine hydrochloride, and, although less effective, lidocaine hydrochloride p. 103 have all been used. If sinus rhythm is not restored, direct current cardioversion or pacing should be considered. Catheter ablation is an alternative if cessation of the arrhythmia is not urgent. Non-sustained ventricular tachycardia can be treated with a beta-blocker.

All patients presenting with ventricular tachycardia should be referred to a specialist. Following restoration of sinus rhythm, patients who remain at high risk of cardiac arrest will require maintenance therapy. Most patients will be treated with an implantable cardioverter defibrillator. Beta-blockers or sotalol hydrochloride (in place of a standard beta-blocker), or amiodarone hydrochloride (in combination with a standard beta-blocker), can be used in addition to the device in some patients; alternatively, they can be used alone when use of an implantable cardioverter defibrillator is not appropriate.

**Torsade de pointes**

**Torsade de pointes** is a form of ventricular tachycardia associated with a long QT syndrome (usually drug-induced, but other factors including hypokalaemia, severe bradycardia, and genetic predisposition are also implicated). Episodes are usually self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous infusion of magnesium sulfate p. 1051 is usually effective. A beta-blocker (but not sotalol hydrochloride) and atrial (or ventricular) pacing can be considered. Anti-arrhythmics can further prolong the QT interval, thus worsening the condition.

**Anti-arrhythmic drugs**

Anti-arrhythmic drugs can be classified clinically into those that act on supraventricular arrhythmias (e.g. verapamil hydrochloride), those that act on both supraventricular and ventricular arrhythmias (e.g. amiodarone hydrochloride), and those that act on ventricular arrhythmias (e.g. lidocaine hydrochloride).

Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

- **Class I:** membrane stabilising drugs (e.g. lidocaine, flecaïnide)
- **Class II:** beta-blockers
- **Class III:** amiodarone; sotalol (also Class II)
- **Class IV:** calcium-channel blockers (includes verapamil but not dihydropyridines)

The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaeia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

**Supraventricular arrhythmias**

Adenosine p. 107 is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia. As it has a very short duration of action (half-life only about 8 to 10 seconds, but prolonged in those taking dipyridamole p. 124), most side-effects are short lived. Unlike verapamil hydrochloride p. 164, adenosine can be used after a beta-blocker. Verapamil hydrochloride may be preferable to adenosine in asthma.

Oral administration of a cardiac glycoside (such as digoxin p. 109) slows the ventricular response in cases of atrial fibrillation and atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate. Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff- Parkinson-White syndrome).

Verapamil hydrochloride is usually effective for supraventricular tachycardias. An initial intravenous dose (important: serious beta-blocker interaction hazard) may be followed by oral treatment; hypotension may occur with large doses. It should not be used for tachyarrhythmias where the QRS complex is wide (i.e. broad complex) unless a supraventricular origin has been established beyond reasonable doubt. It is also contra-indicated in atrial fibrillation or atrial flutter associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It should not be used in children with arrhythmias without specialist advice; some supraventricular arrhythmias in childhood can be accelerated by verapamil hydrochloride with dangerous consequences.

Intravenous administration of a beta-blocker such as esmolol hydrochloride p. 154 or propranolol hydrochloride p. 150, can achieve rapid control of the ventricular rate. Drugs for both supraventricular and ventricular arrhythmias include amiodarone hydrochloride p. 105, betablockers, disopyramide p. 102, flecaïnide acetate p. 103, procainamide (available from ‘special-order’ manufacturers or specialist importing companies), and propafenone hydrochloride p. 104.

**Supraventricular and ventricular arrhythmias**

Amiodarone hydrochloride is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. It can be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It can also be used for tachyarrhythmias associated with Wolf-Parkinson-White syndrome. It should be initiated only under hospital or specialist supervision. Amiodarone hydrochloride may be given by intravenous infusion as well as by mouth, and has the advantage of causing little or no myocardial depression. Unlike oral amiodarone hydrochloride, intravenous amiodarone hydrochloride acts relatively rapidly.

Intravenous injection of amiodarone hydrochloride can be used in cardiopulmonary resuscitation for ventricular

www.getintopharma.com
Arrhythmias

Antiarrhythmics > Class IA

Disopyramide

Indications and dose
Prevention and treatment of ventricular and supraventricular arrhythmias, including after myocardial infarction / Maintenance of sinus rhythm after cardioversion

- By mouth using immediate-release medicines
  - Adult: 300–800 mg daily in divided doses
- By mouth using modified-release medicines
  - Adult: 250–375 mg every 12 hours

Contra-Indications
Bundle-branch block associated with first-degree AV block - second- and third-degree AV block or bifascicular block (unless pacemaker fitted) - severe heart failure (unless secondary to arrhythmia) - severe sinus node dysfunction

Caution
Atrial flutter or atrial tachycardia with partial block - avoid in Acute porphyrias

Interactions
Appendix 1: antiarrhythmics

Side-effects

Pregnancy
Manufacturer advises use only if potential benefit outweighs risk; may induce labour if used in third trimester.

Breastfeeding
Present in milk – use only if essential.

Hepatic Impairment
For immediate-release capsules, manufacturer advises caution (risk of increased half-life).

Renal Impairment
Avoid modified-release preparation.

Dose adjustments
Reduce dose by increasing dose interval; adjust according to response.

Monitoring Requirements
Monitor for hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or torsade de pointses (discontinue if occur).

Monitoring serum potassium.

Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Modified-release tablet
Cautionary and Advisory Labels 25
- Rythmodan Retard (Sanofi)
- Disopyramide (as Disopyramide phosphate) 250 mg Rythmodan Retard 250mg tablets | 60 tablet | £32.08 DT = £32.08

Capsule
- Disopyramide (Non-proprietary)
- Disopyramide 100 mg Disopyramide 100mg capsules | 84 capsule | £26.51 DT = £24.30
- Disopyramide 150 mg Disopyramide 150mg capsules | 84 capsule | £33.40 DT = £27.58
- Rythmodan (Sanofi)
- Disopyramide 100 mg Rythmodan 100mg capsules | 84 capsule | £14.14 DT = £24.30

Advanced Pharmacy Services
Patients with an arrhythmia may be eligible for the New Medicines Service / Medicine Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Other drugs used for Arrhythmias
- Acebutolol, p. 152
- Atenolol, p. 152
- Metoprolol tartrate, p. 154
- Nadolol, p. 149
ANTIARRHYTHMICS › CLASS IB

Lidocaine hydrochloride
(Lignocaine hydrochloride)

- INDICATIONS AND DOSE
  Cardiopulmonary resuscitation (as an alternative if amiodarone is not available)
  - BY INTRAVENOUS INJECTION
  - Adult: 1 mg/kg, do not exceed 3 mg/kg over the first hour

Ventricular arrhythmias, especially after myocardial infarction in patients without gross circulatory impairment
  - INITIALLY BY INTRAVENOUS INJECTION
  - Adult: 100 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes).
  - If an intravenous infusion is not immediately available the initial intravenous injection of 100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Ventricular arrhythmias, especially after myocardial infarction in lighter patients or those whose circulation is severely impaired
  - INITIALLY BY INTRAVENOUS INJECTION
  - Adult: Initially 50 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes).
  - If an intravenous infusion is not immediately available the initial intravenous injection of 50 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

- CONTRA-INDICATIONS
  All grades of atrioventricular block - severe myocardial depression - sino-atrial disorders

- CAUTIONS
  Acute porphyrias p. 1058 (consider infusion with glucose for its anti-porphyrinogenic effects) - congestive cardiac failure (consider lower dose) - post cardiac surgery (consider lower dose)

- INTERACTIONS ➔ Appendix 1: antiarrhythmics

- SIDE-EFFECTS
  Anxiety - arrhythmias - atrioventricular block - cardiac arrest - circulatory collapse - confusion - dizziness - drowsiness - euphoric mood - headache - hypotension (may lead to cardiac arrest) - loss of consciousness - methaemoglobinemia - muscle twitching - myocardial contractility decreased - nausea - neurological effects - nystagmus - pain - psychosis - respiratory disorders - seizure - sensation abnormal - temperature sensation altered - tinnitus - tremor - vision blurred - vomiting

- SIDE-EFFECTS, FURTHER INFORMATION
  Methaemoglobinemia
  Methylthioninium chloride is licensed for the acute symptomatic treatment of drug-induced methaemoglobinemia.

- PREGNANCY
  Crosses the placenta but not known to be harmful in animal studies — use if benefit outweighs risk.

- BREAST FEEDING
  Present in milk but amount too small to be harmful.

HEPATIC IMPAIRMENT
  Caution — increased risk of side-effects.

RENAL IMPAIRMENT
  Possible accumulation of lidocaine and active metabolite; caution in severe impairment.

- MONITORING REQUIREMENTS
  - With systemic use Monitor ECG and have resuscitation facilities available.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

  Solution for injection
  - Lidocaine hydrochloride (Non-proprietary)
    - Lidocaine hydrochloride 5 mg per 1 ml
      - Adult: 50 mg/10ml (0.5%) solution for injection ampoules | 10 ampoule (Po) £7.00
    - Lidocaine hydrochloride 10 mg per 1 ml
      - Adult: 100 mg/10ml (1%) solution for injection vials | 10 vial (V) £19.00–£22.00 DT = £22.00

  Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule (Po) £10.00–£11.00 DT = £11.00
  - Lidocaine 50mg/5ml (1%) solution for injection ampoules | 10 ampoule (Po) £2.59–£12.00 DT = £2.59
  - Lidocaine 20mg/2ml (1%) solution for injection ampoules | 10 ampoule (Po) £1.20 DT = £1.20
  - Lidocaine hydrochloride 20 mg per 1 ml
    - Adult: 100mg/5ml (2%) solution for injection ampoules | 10 ampoule (Po) £2.70–£12.00 DT = £2.70
  - Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 vial (V) £15.90–£23.00 DT = £23.00
  - Lidocaine 200mg/10ml (2%) solution for injection ampoules | 10 ampoule (Po) £14.95
  - Lidocaine 40mg/2ml (2%) solution for injection ampoules | 10 ampoule (Po) £1.10–£2.37
  - Lidocaine 40mg/20ml (2%) solution for injection ampoules | 10 ampoule (Po) £8.00–£11.40 DT = £11.40

ANTIARRHYTHMICS › CLASS IC

Flecainide acetate

- INDICATIONS AND DOSE
  Supraventricular arrhythmias
  - BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
    - Adult: Initially 50 mg twice daily, increased if necessary up to 300 mg daily
  - BY MOUTH USING MODIFIED-RELEASE MEDICINES
    - Adult: 200 mg daily
  - Ventricular arrhythmias (initiated under direction of hospital consultant)
    - BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
      - Adult: Initially 100 mg twice daily for 3–5 days, maximum 400 mg daily reserved for rapid control or in heavily built patients; for maintenance, reduce to the lowest dose that controls the arrhythmia

DOSE ADJUSTMENTS DUE TO INTERACTIONS
  - Manufacturer advises reduce dose by half with concurrent use of amiodarone.

DOSE EQUIVALENCE AND CONVERSION
  - Patients stabilised on 200 mg daily immediate-release flecainide may be transferred to modified-release medicines.

UNLICENSED USE
  Capsules and tablets: licensed for AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily). Immediate-release tablets only: licensed for symptomatic sustained ventricular tachycardia, disabling symptoms of premature ventricular
Propafenone hydrochloride

**INDICATIONS AND DOSE**

**Ventricular arrhythmias (specialist supervision in hospital) | Paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or fibrillation and paroxysmal re-entrant tachycardias involving the AV node or accessory pathway, where standard therapy ineffective or contra-indicated (specialist supervision in hospital)**

▶ **BY MOUTH**

- **Adult:** Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 3 days, reduce total daily dose for patients under 70 kg
- **Elderly:** Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 5 days, reduce total daily dose for patients under 70 kg

▶ **CONTRA-INDICATIONS**

- Atrial conduction defects (unless adequately paced)
- Brugada syndrome
- Bundle branch block (unless adequately paced)
- Cardiogenic shock (except arrhythmia induced)
- Distal block (unless adequately paced)
- Electrolyte disturbances
- Marked hypotension
- Myasthenia gravis
- Myocardial infarction
- Within last 3 months
- Second degree or greater AV block (unless adequately paced)
- Severe bradycardia
- Severe obstructive pulmonary disease (due to weak beta-blocking activity)
- Sinus node dysfunction (unless adequately paced)
- Uncontrolled congestive heart failure with left ventricular ejection fraction less than 35%

▶ **CAUTIONS**

- Elderly: great caution in mild to moderate obstructive airways disease owing to beta-blocking activity
- Heart failure: pacemaker patients: potential for conversion of paroxysmal atrial fibrillation to atrial flutter with 2:1 or 1:1 conduction block

▶ **INTERACTIONS**

→ Appendix 1: antiarrhythmics

▶ **SIDE-EFFECTS**

- **Common or very common**
  - Anxiety, confusion, dizziness, dyspnoea, fever, oedema, vision disorders
- **Uncommon**
  - Alopecia, appetite decreased, constipation, diarrhoea, flatulence, gastrointestinal discomfort, nausea, skin reactions, vomiting

▶ **FREQUENCY NOT KNOWN**

- Altered pacing threshold, atrioventricular block, cardiac arrest, chest pain, heart failure, hypotension, palpitations, QT interval prolongation

▶ **PREGNANCY**

- Used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in animal studies; infant hyperbilirubinaemia also reported.

▶ **BREAST FEEDING**

- Significant amount present in milk but not known to be harmful.

▶ **HEPATIC IMPAIRMENT**

- **Dose adjustments**
  - Avoid or reduce dose in severe impairment.

▶ **RENAL IMPAIRMENT**

- **Dose adjustments**
  - Reduce initial oral dose to max. 100 mg daily if eGFR less than 35 mL/minute/1.73 m².

▶ **MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tambocor XL</strong> (Teva UK Ltd)</td>
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<tr>
<td><strong>Flecainide acetate 200 mg</strong></td>
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**Tablet**

<table>
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[www.getintopharma.com](http://www.getintopharma.com)
ANTIARRHYTHMICS > CLASS III

Amiodarone hydrochloride

● INDICATIONS AND DOSE

Treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated (including paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, ventricular fibrillation, and tachyarrhythmias associated with Wolff-Parkinson-White syndrome) (initiated in hospital or under specialist supervision)

▶ BY MOUTH

Adult: 200 mg 3 times a day for 1 week, then reduced to 200 mg twice daily for a further week, followed by maintenance dose, usually 200 mg daily or the minimum dose required to control arrhythmia

▶ BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, to be given over 20–120 minutes with ECG monitoring, subsequent infusions given if necessary according to response; maximum 1.2 g per day

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (for cardiopulmonary resuscitation)

▶ INITIALLY BY INTRAVENOUS INJECTION

Adult: Initially 300 mg, dose to be considered after administration of adrenaline, dose should be given from a pre-filled syringe or diluted in 20 mL. Glucose 5%, then (by intravenous injection) 150 mg if required, followed by (by intravenous infusion) 900 mg/24 hours

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SOFOSBUVIR WITH DACLATASVIR; SOFOSBUVIR AND LEDIPASVIR (MAY 2015); SIMEPREVIR WITH SOFOSBUVIR (AUGUST 2015): RISK OF SEVERE BRADYCARDIA AND HEART BLOCK WHEN TAKEN WITH AMIODARONE

Avoid concomitant use unless other antiarrhythmics cannot be given.

● CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS

Avoid in severe conduction disturbances (unless pacemaker fitted) - avoid in sinus node disease (unless pacemaker fitted) - iodine sensitivity - sino-atrial heart block (except in cardiac arrest) - sinus bradycardia (except in cardiac arrest) - thyroid dysfunction

SPECIFIC CONTRA-INDICATIONS

With intravenous use - Avoid bolus injection in cardiomyopathy - avoid bolus injection in congestive heart failure - avoid in circulatory collapse - avoid in severe arterial hypertension - avoid in severe respiratory failure

● CAUTIONS

GENERAL CAUTIONS

Acute porphyrias p. 1058 - conduction disturbances (in excessive dosage) - elderly - heart failure - hypokalaemia - severe bradycardia (in excessive dosage)

SPECIFIC CAUTIONS

With intravenous use moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) - severe hepatocellular toxicity

INTERACTIONS → Appendix 1: antiarrhythmics

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Arrhythmias - hepatic disorders - hyperthyroidism - nausea - respiratory disorders - skin reactions

Rare or very rare Bronchospasm (in patients with severe respiratory failure) - headache - idiopathic intracranial hypertension - nerve disorders - SIADH

Frequency not known Angioedema - confusion - delirium - pancreatitis - severe cutaneous adverse reactions (SCARs)

SPECIFIC SIDE-EFFECTS

Common or very common

With oral use Constipation - corneal deposits - hypothyroidism - movement disorders - photosensitivity reaction - sleep disorders - taste altered - vomiting

With parenteral use Hypotension (following rapid injection)

Uncommon

With oral use Cardiac conduction disorders - dry mouth - myopathy (usually reversible on discontinuation) - peripheral neuropathy (usually reversible on discontinuation)

Rare or very rare

With oral use Alopecia - aplastic anaemia - epididymo-orchitis - erectile dysfunction - haemolytic anaemia - pulmonary haemorrhage - thrombocytopenia - vertigo

With parenteral use Hot flush - hyperhidrosis

Frequency not known

With oral use Altered smell sensation - appetite decreased - parkinsonism - vasculitis

With parenteral use Agranulocytosis - libido decreased - neutropenia

SIDE-EFFECTS, FURTHER INFORMATION

Corneal microdeposits

Patients taking amiodarone may develop corneal microdeposits ( reversible on withdrawal of treatment). However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought.

Thyroid function

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

Hepatotoxicity

Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.

Pulmonary toxicity

Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone.

PREGNANCY

Possible risk of neonatal goitre; use only if no alternative.

BREAST FEEDING

Avoid; present in milk in significant amounts; theoretical risk of neonatal hypothyroidism from release of iodine.

MONITORING REQUIREMENTS

Thyroid function tests should be performed before treatment and then every 6 months. Clinical assessment of thyroid function alone is unreliable. Thyroxine (T4) may be raised in the absence of hyperthyroidism; therefore tri-
iodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis.

- Liver function tests required before treatment and then every 6 months.
- Serum potassium concentration should be measured before treatment.
- Chest x-ray required before treatment.
- If concomitant use of amiodarone with sofosbuvir and daclatasvir, simeprevir and sofosbuvir, or sofosbuvir and ledipasvir cannot be avoided because other anti-arrhythmics are not tolerated or contra-indicated, patients should be closely monitored, particularly during the first weeks of treatment. Patients at high risk of bradycardia should be monitored continuously for 48 hours in an appropriate clinical setting after starting concomitant treatment. Patients who have stopped amiodarone within the last few months and need to start sofosbuvir and daclatasvir, simeprevir and sofosbuvir, or sofosbuvir and ledipasvir should be monitored.

- With intravenous use ECG monitoring and resuscitation facilities must be available. Monitor liver transaminases closely.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (Cordarone X®), give continuously or intermittently in Glucose 5%. Suggested initial infusion volume 250 mL given over 20–120 minutes; for repeat infusions up to 1.2 g in max. 500 mL; should not be diluted to less than 600 micrograms/mL. See cardio-pulmonary resuscitation for details of infusion in extreme emergency. Incompatible with Sodium Chloride infusion fluids; avoid equipment containing the plasticizer di-2-ethylhexphthalate (DEHP).
- With oral use For administration by mouth, tablets may be crushed and dispersed in water; injection solution should not be given orally (irritant).

**PATIENT AND CARER ADVICE** Because of the possibility of phototoxic reactions, patients should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen to protect against both long-wave ultraviolet and visible light should be used.

If taking amiodarone with concomitant sofosbuvir and daclatasvir, simeprevir and sofosbuvir, or sofosbuvir and ledipasvir, patients and their carers should be told how to recognise signs and symptoms of bradycardia and heart block and advised to seek immediate medical attention if symptoms such as shortness of breath, light-headedness, palpitations, fainting, unusual tiredness or chest pain develop.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

<table>
<thead>
<tr>
<th>MEDICATIORY AND ADVISORY LABELS: 11</th>
</tr>
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<tbody>
<tr>
<td>Amiodarone hydrochloride (Non-proprietary)</td>
</tr>
<tr>
<td>Amiodarone hydrochloride 100 mg Amiodarone 100mg tablets</td>
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<tr>
<td>Amiodarone hydrochloride 200 mg Amiodarone 200mg tablets</td>
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<tr>
<td>Cordarone X (Sanofi)</td>
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<tr>
<td>Amiodarone hydrochloride 100 mg Cordarone X 100 tablets</td>
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<td>Amiodarone hydrochloride 200 mg Cordarone X 200 tablets</td>
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**Solution for injection**

<table>
<thead>
<tr>
<th>EXCIPIENTS: May contain Benzyl alcohol</th>
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<tbody>
<tr>
<td>Amiodarone hydrochloride (Non-proprietary)</td>
</tr>
<tr>
<td>Amiodarone hydrochloride 30 mg per 1 ml Amiodarone 300mg/10ml solution for injection pre-filled syringes</td>
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</tbody>
</table>

**Dronedarone**

**DRUG ACTION** Dronedarone is a multi-channel blocking anti-arrhythmic drug.

**INDICATIONS AND DOSE**

Maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial fibrillation, when alternative treatments are unsuitable (initiated under specialist supervision)

- BY MOUTH
- Adult: 400 mg twice daily

**CONTRA-INDICATIONS**

- Atrial conduction defects - bradycardia - complete bundle branch block - distal block - existing or previous heart failure or left ventricular systolic dysfunction - haemodynamically unstable patients - liver toxicity associated with previous amiodarone use - lung toxicity associated with previous amiodarone use - permanent atrial fibrillation - prolonged QT interval - second- or third-degree AV block - sick sinus syndrome (unless pacemaker fitted) - sinus node dysfunction

**CAUTIONS**

- Coronary artery disease - correct hypokalaemia and hypomagnesaemia before starting and during treatment

**SIDE-EFFECTS**

- Common or very common Asthenia - bradycardia - congestive heart failure - diarrhoea - gastrointestinal discomfort - nausea - QT interval prolongation - skin reactions - vomiting

- Uncommon Photosensitivity reaction - respiratory disorders - taste altered

- Rare or very rare Hepatic disorders - vasculitis

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Liver injury** Liver injury including life-threatening acute liver failure reported rarely; discontinue treatment if 2 consecutive alanine aminotransferase concentrations exceed 3 times upper limit of normal.

- **Heart failure** New onset or worsening heart failure reported. If heart failure or left ventricular systolic dysfunction develops, discontinue treatment.

- **Pulmonary toxicity** Interstitial lung disease, pneumonitis and pulmonary fibrosis reported. Investigate if symptoms such as dyspnoea or dry cough develop and discontinue if confirmed.

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Ongoing monitoring should occur under specialist supervision.
- Monitor for heart failure.
- Perform ECG at least every 6 months—consider discontinuation if atrial fibrillation reoccurs.
- Measure serum creatinine before treatment and 7 days after initiation—if raised, measure again after a further 7 days and consider discontinuation if creatinine continues to rise.
Monitor liver function before treatment, 1 week and 1 month after initiation of treatment, then monthly for 6 months, then every 3 months for 6 months and periodically thereafter.

**PATIENT AND CARER ADVICE**
Heart failure Patients or their carers should be told how to recognise signs of heart failure and advised to seek prompt medical attention if symptoms such as weight gain, dependent oedema, or dyspnoea develop or worsen. Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as abdominal pain, anorexia, nausea, vomiting, fever, malaise, itching, dark urine, or jaundice develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

> NICE decisions
- Dronedarone for the treatment of non-permanent atrial fibrillation (December 2012) NICE TA197

Dronedarone is an option for the maintenance of sinus rhythm after successful cardioversion in paroxysmal or persistent atrial fibrillation which is not controlled by first-line therapy (usually including beta-blockers), and after alternative options have been considered in patients:
- who have at least 1 of the following cardiovascular risk factors: hypertension requiring drugs of at least 2 different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, or age 70 years or older and
- who do not have left ventricular systolic dysfunction nor a history of, or current, heart failure

Patients who do not meet the above criteria who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA197

> MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Multaq** (Sanofi)
  - Dronedarone (as Dronedarone hydrochloride) 400 mg Multaq 400mg tablets | 20 tablet (PST) £22.50 | 60 tablet (PST) £67.50

**ANTIARRHYTHMICS**

### Adenosine

**INDICATIONS AND DOSE**

**Rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) Used to aid to diagnosis of broad or narrow complex supraventricular tachycardias**

- **BY RAPID INTRAVENOUS INJECTION**
  - Adult: Initially 3 mg, administer into a central or large peripheral vein and give over 2 seconds, followed by 6 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required, increments should not be given if high level AV block develops at any particular dose

**SIDE-EFFECTS**

- Common or very common Abdominal discomfort - arrhythmias - atroventricular block - chest discomfort - chest pain (discontinue) - dizziness - dry mouth - dyspnoea - flushing - headache - hypotension (discontinue if severe) - pain - paraesthesia - throat discomfort
- Uncommon Asthenia - back discomfort - bradycardia (discontinue if asystole or severe bradycardia occur) - hyperhidrosis - limb discomfort - nervousness - taste metallic - Rare or very rare Drowsiness - nasal congestion - nipple tenderness - respiratory disorders - respiratory failure (discontinue) - tinnitus - tremor - urinary urgency - vision blurred

**PREGNANCY**
Large doses may produce fetal toxicity; manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**
No information available—unlikely to be present in milk owing to short half-life.

**MONITORING REQUIREMENTS**
Monitor ECG and have resuscitation facilities available.

**DIRECTIONS FOR ADMINISTRATION**
For rapid intravenous injection give over 2 seconds into central or large peripheral vein followed by rapid Sodium Chloride 0.9% flush; injection solution may be diluted with Sodium Chloride 0.9% if required.
Sotalol hydrochloride

**INDICATIONS AND DOSE**

Symptomatic non-sustained ventricular tachyarrhythmias. Prevent or postpone paroxysmal atrial fibrillation or atrial flutter, paroxysmal AV re-entrant tachycardias (both nodal and involving accessory pathways), and paroxysmal supraventricular tachycardia after cardiac surgery. Maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter.

**BY MOUTH**

Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 160–320 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days.

**LIFE-THREATENING ARRHYTHMIAS INCLUDING VENTRICULAR TACHYARRHYTHMIAS**

**BY MOUTH**

Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 160–320 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days. Higher doses of 480–640 mg daily may be required for life-threatening ventricular arrhythmias (under specialist supervision).

**IMPORTANT SAFETY INFORMATION**

Sotalol may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias. In patients taking sotalol—electrolyte disturbances, particularly hypokalaemia and hypomagnesaemia should be corrected before sotalol started and during use.

**CONTRA-INDICATIONS**

Long QT syndrome (congenital or acquired).

**CAUTIONS**

Diarrhoea (severe or prolonged).

**INTERACTIONS**

Appendix 1: beta blockers, non-selective.

**SIDE-EFFECTS**

Common or very common: Anxiety, arthralgia, chest pain, dyspepsia, fever, fatigue, hearing impairment, mood altered, muscle spasms, oedema, palpitations, sexual dysfunction, taste altered, torsade de pointes (increased risk in females).

**BREAST FEEDING**

Water soluble beta-blockers such as sotalol are present in breast milk in greater amounts than other beta blockers.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 10 mL/minute/1.73 m².

Dose adjustments: Use half normal dose if eGFR 30–60 mL/minute/1.73 m²; use one-quarter normal dose if eGFR 10–30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Measurement of corrected QT interval, and monitoring of ECG and electrolytes required; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion.

**SOLUTION FOR INJECTION**

Electrolytes: May contain Sodium.

- **Adenosine (Non-proprietary)**
  - Sotalol hydrochloride 80 mg (Cheplapharm Arzneimittel GmbH)
  - 28 tablet [DT] £1.53 / + £1.19
  - Sotalol hydrochloride 160 mg (Sanofi)
  - 28 tablet [DT] £3.75 / + £1.55
  - Sotalol hydrochloride 200 mg (Beta-Cardone Pharma)
  - 28 tablet [DT] £2.20 / + £1.40
  - Sotalol hydrochloride 40 mg (Advanz Pharma)
  - 28 tablet [DT] £0.95 / + £3.97

**BETA-ADRENOCEPTOR BLOCKERS**

**NON-SELECTIVE**

**SOTALOL HYDROCHLORIDE**

**CARBDICAL GLYOSIDES**

**Cardiac glycosides**

**Digoxin-specific antibody**

Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (see further information, under Poisoning, emergency treatment p. 1359). Digoxin-specific antibody fragments p. 1368 are indicated for the treatment of known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradycardia. Digoxin unresponsive to atropine sulphate p. 1334 and when measures beyond the withdrawal of digoxin p. 109 and correction of any electrolyte abnormalities are considered necessary.

**Digoxin**

Digoxin is most useful for controlling ventricular response in persistent and permanent atrial fibrillation and atrial flutter. Digoxin also has a role in heart failure.

For management of atrial fibrillation the maintenance dose of digoxin can usually be determined by the ventricular rate at rest, which should not usually be allowed to fall persistently below 60 beats per minute.

Digoxin is now rarely used for rapid control of heart rate (see management of supraventricular arrhythmias). Even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose. The intramuscular route is not recommended.

In patients with heart failure who are in sinus rhythm a loading dose is not required, and a satisfactory plasma-digoxin concentration can be achieved over a period of about a week.

Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea); renal function is the most important determinant of digoxin dosage.
Unwanted effects depend both on the concentration of digoxin in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease. It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because symptoms of both are similar. The plasma concentration alone cannot indicate toxicity reliably, but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Digoxin should be used with special care in the elderly, who may be particularly susceptible to digitals toxicity.

Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected. Hypokalaemia predisposes the patient to digitals toxicity; it is managed by giving a potassium-sparing diuretic or, if necessary, potassium supplementation.

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. Digoxin-specific antibody fragments are available for reversal of life-threatening overdose.

Digoxin

**Indications and dose**

- **Drug action** Digoxin is a cardiac glycoside that increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node.

- **Contraindications** Constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—but use with caution), hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but use with caution), intermittent complete heart block, myocarditis, second degree AV block, supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) (although can be used in infancy) - ventricular tachycardia or fibrillation

- **CAUTIONS** Hypercalcaemia (risk of digitalis toxicity), hypokalaemia (risk of digitalis toxicity), hypomagnesaemia (risk of digitalis toxicity), hypoxia (risk of digitalis toxicity), recent myocardial infarction, severe respiratory disease, sick sinus syndrome, thyroid disease

- **INTERACTIONS**
  - Appendix 1: digoxin

- **Side effects**
  - Common or very common Arrhythmias, cardiac conduction disorder, cerebral impairment, diarrhoea, dizziness, eosinophilia, nausea, skin reactions, vision disorders, vomiting
  - Uncommon Depression
  - Rare or very rare Appetite decreased, asthenia, confusion, gastrointestinal disorders, gynaecomastia, headache, malaise, psychosis, thrombocytopenia

**Overdose** If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management.

- **Pregnancy**
  - Dose adjustments May need dosage adjustment.

- **Breast feeding**
  - Amount too small to be harmful.

**Renal impairment**

- Dose adjustments Reduce dose.

- Monitoring Monitor plasma-digoxin concentration in renal impairment.

**Monitoring requirements**

- For plasma-digoxin concentration assay, blood should be taken at least 6 hours after a dose.

- Monitor serum electrolytes and renal function. Toxicity increased by electrolyte disturbances.

- With intravenous use Avoid rapid intravenous administration (risk of hypertension and reduced coronary flow). For intravenous infusion (Lanoxin®), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of not more than 62.5 micrograms/ml. To be given over at least 2 hours.

- With oral use. For oral administration, oral solution must not be diluted.

- **Patient and carer advice** Patient counselling is advised for digoxin elixir (use pipette).

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection

**Tablet**

- **Digoxin (Non-proprietary)**
  - Digoxin 62.5 microgram tablets (£0.09)
  - Digoxin 125 microgram tablets (£0.18)
  - Digoxin 250 microgram tablets (£0.35)

- **Lanoxin** (Aspen Pharma Trading Ltd)
  - Digoxin 62.5 microgram tablets (£0.09)
  - Lanoxin 125 microgram tablets (£0.18)

**Solution for infusion**

- **Digoxin (Non-proprietary)**
  - Digoxin 250 microgram per 1 ml (£0.70)
  - Lanoxin (Aspen Pharma Trading Ltd)
  - Lanoxin 125 microgram per 1 ml (£0.18)

- **Lanoxin** (Aspen Pharma Trading Ltd)

- **Digoxin 250 microgram per 1 ml (£3.30)**
Bleeding disorders

2 Antifibrinolytic drugs and haemostatics

Overview
Fibrin dissolution can be impaired by the administration of tranexamic acid below, which inhibits fibrinolysis. It can be used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis (e.g. in surgery, dental extraction, obstetric disorders, and traumatic hyphaema) and in the management of menorrhagia. Tranexamic acid may also be used in hereditary angioedema, epistaxis, and in thrombolytic overdose.

Desmopressin is used in the management of heavy menstrual bleeding and its use is no longer recommended.

TRANSAEMORRHAGICS

Tranexamic acid

26-Apr-2017

- INDICATIONS AND DOSE
- Local fibrinolysis
  - Adult: 1–1.5 g 2–3 times a day, alternatively 15–25 mg/kg 2–3 times a day
  - Initially by slow intravenous injection
  - Adult: 0.5–1 g 2–3 times a day, to be administered at a rate not exceeding 100 mg/minute, followed by (by continuous intravenous infusion) 25–50 mg/kg if required, dose to be given over 24 hours

- Menorrhagia
  - By mouth
  - Adult: 1 g 3 times a day for up to 4 days, to be initiated when menstruation has started; maximum 4 g per day

- Hereditary angioedema
  - By mouth
  - Adult: 1–1.5 g 2–3 times a day, for short-term prophylaxis of hereditary angioedema, tranexamic acid is started several days before planned procedures which may trigger an acute attack of hereditary angioedema (e.g. dental work) and continued for 2–5 days afterwards

- Epistaxis
  - By mouth
  - Adult: 1 g 3 times a day for 7 days

- General fibrinolysis
  - By slow intravenous injection
  - Adult: 1 g every 6–8 hours, alternatively 15 mg/kg every 6–8 hours, dose to be given at a rate not exceeding 100 mg/minute

PREVENTION AND TREATMENT OF SIGNIFICANT HEMORRHAGE FOLLOWINGTRAUMA

- Initially by slow intravenous injection
- Adult: Loading dose 1 g to be given over 10 minutes, treatment should commence within 8 hours of injury, followed by (by intravenous infusion) 1 g to be given over 8 hours

- UNLICENSED USE
  - Use of tranexamic acid by continuous intravenous infusion for treatment of local fibrinolysis is an unlicensed route of administration.
  - Not licensed for prevention and treatment of significant haemorrhage following trauma.

- CONTRA-INDICATIONS
  - Fibrinolytic conditions following disseminated intravascular coagulation (unless predominant activation of fibrinolytic system with severe bleeding).
  - History of convulsions.
  - Thromboembolic disease.

- CAUTIONS
  - Irregular menstrual bleeding (establish cause before initiating therapy).
  - Massive haematuria (avoid if risk of ureteric obstruction).
  - Patients receiving oral contraceptives (increased risk of thrombosis).

- INTERACTIONS
  - Tranexamic acid

- SIDE-EFFECTS
  - General side-effects
    - Diarrhoea (reduce dose).
    - Nausea.
    - Vomiting.
    - Allergic dermatitis.
    - Colour vision change.
    - Seizure.

  - Specific side-effects
    - Hypotension.
    - Visual impairment.

  - Pregnancy
    - No evidence of teratogenicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta.

  - Breastfeeding
    - Small amount present in milk—antifibrinolytic effect in infant unlikely.

  - Renal impairment
    - Dose adjustments.

  - Monitoring requirements
    - Regular liver function tests in long-term treatment of hereditary angioedema.

  - Directions for administration
    - For intravenous infusion
      - (Cyclokapron®), give continuously in Glucose 5% or Sodium chloride 0.9%.

- Medicinal forms
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, and solution for injection.

- Tablet
  - Tranexamic acid (Non-proprietary)
    - Tranexamic acid 500 mg tablets
      - 60 tablets (Boehringer Ingelheim) £32.10 DT + £5.42
    - Tranexamic acid 500 mg tablets
      - 60 tablets (Boehringer Ingelheim) £32.10 DT + £5.42

- Solution for injection
  - Tranexamic acid (Non-proprietary)
    - Tranexamic acid 100 mg per 1 ml
      - Tranexamic acid 500mg/5ml solution for injection ampoules
      - 5 ampoules (Boehringer Ingelheim) £7.50 DT + £7.50
      - 10 ampoules (Boehringer Ingelheim) £15.47 DT + £15.47 (Hospital only)
Etamsylate
(Ethamsylate)

**INDICATIONS AND DOSE**

**Short-term blood loss in menorrhagia**
- **BY MOUTH**
- Adult: 500 mg 4 times a day during menstruation

**CONTRA-INDICATIONS**
Acute porphyrias p. 1058

**CAUTIONS**
Exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment.

**SIDE-EFFECTS**
Diarrhoea • fever (discontinue) • headache • nausea • rash • vomiting

**BREAST FEEDING**
Present in milk—manufacturer advises avoid.

**LESS SUITABLE FOR PRESCRIBING**
Less suitable for prescribing.

**MEDICINAL FORMS**
Forms available from special-order manufacturers include: tablet, oral solution

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**2.1 Coagulation factor deficiencies**

**BLOOD AND RELATED PRODUCTS**

**Coagulation proteins**

**Dried prothrombin complex**
(Human prothrombin complex)

**INDICATIONS AND DOSE**

Treatment and peri-operative prophylaxis of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available | Treatment and peri-operative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment)
- **BY INTRAVENOUS INFUSION**
- Adult: (consult haematologist)
  - Major bleeding in patients on warfarin following phytomenadione (initiated under specialist supervision)
  - **BY INTRAVENOUS INFUSION**
  - Adult: 25–50 units/kg

**CONTRA-INDICATIONS**
Angina • history of heparin induced thrombocytopenia • recent myocardial infarction (except in life-threatening haemorrhage following overdosage of oral anticoagulants, and before induction of thromboembolic complications).

**CAUTIONS**
Disseminated intravascular coagulation • history of myocardial infarction or coronary heart disease • postoperative use • risk of thrombosis

**SIDE-EFFECTS**
Rare or very rare
- Fever • headache • hypersensitivity
- Frequency not known
- Disseminated intravascular coagulation • nephrotic syndrome • thromboembolism

**HEPATIC IMPAIRMENT**
Manufacturer advises caution (risk of thromboembolic complications).

**MONITORING**
Monitor closely in hepatic impairment (risk of thromboembolic complications).

**PRESCRIBING AND DISPENSING INFORMATION**

Dried prothrombin complex is prepared from human plasma by a suitable fractionation technique, and contains factor IX, together with variable amounts of factors II, VII, and X.
Available from CSL Behring (Beriplex® P/N), Octapharma (Octaplex®),

**MEDICINAL FORMS** No licensed medicines listed.

**Factor VIIIa (recombinant)**
(Eptacog alfa (activated))

**INDICATIONS AND DOSE**
Treatment and prophylaxis of haemorrhage in patients with haemophilia A or B with inhibitors to factors VIII or IX, acquired haemophilia, factor VII deficiency, or Glanzmann’s thrombasthenia

▶ BY INTRAVENOUS INJECTION
▶ Adult: (consult haematologist)

**CAUTIONS** Disseminated intravascular coagulation - risk of thrombosis

**SIDE-EFFECTS**
Uncommon: Embolism and thrombosis - fever - hepatic disorders - intestinal ischaemia - skin reactions

▶ Rare or very rare: Angina pectoris - cerebrovascular insufficiency - coagulation disorders - headache - myocardial infarction - nausea - peripheral ischaemia

**Frequency not known**: Angioedema - flushing

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- NoveSeven (Novo Nordisk Ltd)
  - Eptacog alfa activated 50000 unit: NoveSeven 1mg (50,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection £525.20 (Hospital only)
  - NovoSeven 1mg (50,000units) powder and solvent for solution for injection vials | 1 vial £525.20 (Hospital only)
  - Eptacog alfa activated 100000 unit: NovoSeven 2mg (100,000units) powder and solvent for solution for injection vials | 1 vial £1,050.60 (Hospital only)
  - NovoSeven 2mg (100,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection £525.20 (Hospital only)
- Eptacog alfa activated 250000 unit: NovoSeven 5mg (250,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection £2,662.00 (Hospital only)
  - NovoSeven 5mg (250,000units) powder and solvent for solution for injection vials | 1 vial £2,662.00 (Hospital only)
  - Eptacog alfa activated 400000 unit: NovoSeven 8mg (400,000units) powder and solvent for solution for injection vials | 1 vial £4,201.00 (Hospital only)
  - NovoSeven 8mg (400,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection £4,201.00 (Hospital only)

**Factor VIII fraction, dried**
(Human coagulation factor VIII, dried)

**INDICATIONS AND DOSE**
Treatment and prophylaxis of haemorrhage in congenital factor VIII deficiency (haemophilia A), acquired factor VIII deficiency (Von Willebrand's disease)

▶ BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY CONTINUOUS INTRAVENOUS INFUSION
▶ Adult: (consult haematologist)

**CAUTIONS** Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB—less likely with high potency concentrates

**SIDE-EFFECTS**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- Factor VIII fraction, dried (Non-proprietary)
  - Factor VIII 500 unit: Dried Factor VIII Fraction type BY 500unit powder and solvent for solution for injection vials | 1 vial £210.00
  - Advate (Baxalta UK Ltd)
    - Octocog alfa 250 unit: Advate 250unit powder and solvent for solution for injection vials | 1 vial £177.50
    - Octocog alfa 500 unit: Advate 500unit powder and solvent for solution for injection vials | 1 vial £355.00
    - Octocog alfa 1000 unit: Advate 1000unit powder and solvent for solution for injection vials | 1 vial £710.00
  - Octocog alfa 2000 unit: Advate 2000unit powder and solvent for solution for injection vials | 1 vial £1,420.00
- Alphanate (Grifols UK Ltd)
  - Factor VIII high purity 1000 unit, von Willebrand factor 1200 unit: Alphanate 100unit powder and solvent for solution for injection vials | 1 vial £330.00
  - Factor VIII high purity 1500 unit, von Willebrand factor 1800 unit: Alphanate 150unit powder and solvent for solution for injection vials | 1 vial £495.00
  - Elocta (Swedish Orphan Biovitrum Ltd)
    - Efmoroctocog alfa 250 unit: Elocta 250unit powder and solvent for solution for injection vials | 1 vial £600.00 (Hospital only)
    - Efmoroctocog alfa 500 unit: Elocta 500unit powder and solvent for solution for injection vials | 1 vial £1,050.60 (Hospital only)
    - Efmoroctocog alfa 1000 unit: Elocta 1000unit powder and solvent for solution for injection vials | 1 vial £1,500.00 (Hospital only)
    - Efmoroctocog alfa 1500 unit: Elocta 1500unit powder and solvent for solution for injection vials | 1 vial £1,775.00 (Hospital only)
    - Efmoroctocog alfa 2000 unit: Elocta 2000unit powder and solvent for solution for injection vials | 1 vial £2,310.00 (Hospital only)
    - Efmoroctocog alfa 3000 unit: Elocta 3000unit powder and solvent for solution for injection vials | 1 vial £3,150.00 (Hospital only)
- Fanhdi (Grifols UK Ltd)
  - Factor VIII high purity 500 unit: Fanhdi 500unit powder and solvent for solution for injection vials | 1 vial £1,650.00 (Hospital only)
  - Factor VIII high purity 1000 unit: Fanhdi 1000unit powder and solvent for solution for injection vials | 1 vial £3,300.00 (Hospital only)
  - Factor VIII high purity 1500 unit: Fanhdi 1500unit powder and solvent for solution for injection vials | 1 vial £4,950.00
- Haemocin (Biotest (UK) Ltd)
  - Factor VIII high purity 250 unit: Haemocin 250unit powder and solvent for solution for injection vials | 1 vial £150.00 (Hospital only)
  - Factor VIII high purity 500 unit: Haemocin 500unit powder and solvent for solution for injection vials | 1 vial £300.00 (Hospital only)
  - Factor VIII high purity 1000 unit: Haemocin 1000unit powder and solvent for solution for injection vials | 1 vial £600.00 (Hospital only)
- Kogenate (Bayer Plc)
  - Octocog alfa 2000 unit: Kogenate Bayer 200unit powder and solvent for solution for injection vials | 1 vial £1,260.00
  - Kogenate Bayer (Bayer Plc)
    - Octocog alfa 250 unit: Kogenate Bayer 250unit powder and solvent for solution for injection vials | 1 vial £1,750.00
    - Octocog alfa 500 unit: Kogenate Bayer 500unit powder and solvent for solution for injection vials | 1 vial £3,150.00
    - Octocog alfa 1000 unit: Kogenate Bayer 1000unit powder and solvent for solution for injection vials | 1 vial £6,300.00

**MONITORING REQUIREMENTS**
Monitor for development of factor VIII inhibitors.

**PRESCRIBING AND DISPENSING INFORMATION**
Dried factor VIII fraction is prepared from human plasma by a suitable fractionation technique; it may also contain varying amounts of von Willebrand factor. Optivate®, Fanhdi®, and Octanate® are not indicated for use in von Willebrand’s disease.

Recombinant human coagulation factor VIII including octocog alfa, moroctocog alfa, and simoctocog alfa are not indicated for use in von Willebrand’s disease.
Coagulation factor deficiencies

**CONTRA-INDICATIONS** Disseminated intravascular coagulation

**CAUTIONS** Risk of thrombosis—principally with former low purity products

**SIDE-EFFECTS**
- Common or very common Anxiety, back pain, dyspnoea, hypersensitivity, nausea, skin reactions - vasodilation
- Rare or very rare Angioedema, cardiac discomfort, disseminated intravascular coagulation, embolism and thrombosis, headache, hypotension, lehargy, myocardial infarction, tachycardia, vomiting, wheezing
- Frequency not known Nephrotic syndrome

**PRESCRIBING AND DISPENSING INFORMATION** Dried factor IX fraction is prepared from human plasma by a suitable fractionation technique; it may also contain clotting factors II, VII, and X.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - Alphanine (Grifols UK Ltd)
  - Factor IX high purity 1000 unit (Hospital only)
  - Haemonine (Biotest (UK) Ltd)
  - ReFacto AF (Bio Products Laboratory Ltd)
  - ReFacto high purity 1000 unit (Hospital only)

- **Powder and solvent for solution for infusion**
  - Benefix (Pfizer Ltd)
  - Nonacog alfa 250 unit (Hospital only)
  - Replene-F (Bio Products Laboratory Ltd)
  - Replene-VF (Bio Products Laboratory Ltd)

**Factor XII fraction, dried**

(Human fibrin-stabilising factor, dried)

**INDICATIONS AND DOSE**
- BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
- Adult: (consult haematologist)

**SIDE-EFFECTS**
- Rare or very rare Anaphylactoid reaction - dyspnoea - skin reactions

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - Fibrogammin P (CSL Behring UK Ltd)
  - Factor XIII 250 unit (Hospital only)

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**BNF 78**

**Medicines for the Cardiovascular System**

**Factor IX fraction, dried**

Treatment and prophylaxis of haemorrhage in congenital factor IX deficiency (haemophilia B)

- BY INTRAVENOUS INJECTION, OR BY CONTINUOUS INTRAVENOUS INFUSION
- Adults: (consult haematologist)
Fibrinogen, dried
(Human fibrinogen)

- **INDICATIONS AND DOSE**
  Treatment of haemorrhage in congenital hypofibrinogenaemia or afibrinogenaemia
  - By Intravenous injection, or by Intravenous infusion
  - Adult: (consult haematologist)

- **CAUTIONS** Risk of thrombosis
- **SIDE-EFFECTS**
  - Common or very common: Fever, thromboembolism
  - Frequency not known: Chest pain, chills, cough, dyspnoea, nausea, skin reactions, tachycardia, vomiting
- **PREGNANCY** Manufacturer advises not known to be harmful—no information available.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Fibrinogen is prepared from human plasma.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - Powder for solution for infusion
    - Ristap (CSL Behring UK Ltd)
      - Fibrinogen 1 gram: Ristap 1g powder for solution for infusion vials | 1 vial PDP £400.00

Protein C concentrate

- **INDICATIONS AND DOSE**
  Congenital protein C deficiency
  - By Intravenous Injection
  - Adult: (consult haematologist)

- **CAUTIONS** Hypersensitivity to heparins
- **SIDE-EFFECTS**
  - Rare or very rare: Dizziness, fever, skin reactions
  - Frequency not known: Haemorrhaxia, hyperhidrosis, restlessness

- **PRESCRIBING AND DISPENSING INFORMATION**
  Protein C is prepared from human plasma.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - Powder and solvent for solution for injection
    - Ceprotin (Baxalta UK Ltd)
      - Protein C 500 unit: Ceprotin 500 unit powder and solvent for solution for injection vials | 1 vial PDP £2,000.00
      - Protein C 1000 unit: Ceprotin 1000 unit powder and solvent for solution for injection vials | 1 vial PDP £1,000.00

Factor VIII inhibitor bypassing fraction

- **INDICATIONS AND DOSE**
  Treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors
  - Treatment of haemorrhage in non-haemophilic patients with acquired factor VIII inhibitors
  - By Intravenous infusion, or by Intravenous injection
  - Adult: (consult haematologist)

- **CONTRA-INDICATIONS**
  Disseminated intravascular coagulation

- **SIDE-EFFECTS**
  - Common or very common: Dizziness, headache, hypersensitivity, hypotension, skin reactions
  - Frequency not known: Abdominal discomfort, anamnestic reaction, angioedema, chest discomfort, chills, cough, diarrhoea, disseminated intravascular coagulation, drowsiness, dyspnoea, embolism and thrombosis, fever, flushing, hypertension, ischaemic stroke, malaise, myocardial infarction, nausea, paraesthesia, respiratory disorders, restlessness, tachycardia, taste altered, vomiting

- **PRESCRIBING AND DISPENSING INFORMATION**
  Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - Powder and solvent for solution for injection
    - FEIBA Imuno (Baxalta UK Ltd)
      - Factor VIII inhibitor bypassing fraction 500 unit: FEIBA 500 unit powder and solvent for solution for injection vials | 1 vial PDP £390.00
      - Factor VIII inhibitor bypassing fraction 1000 unit: FEIBA 1,000 unit powder and solvent for solution for infusion vials | 1 vial PDP £780.00

Fresh frozen plasma

- **INDICATIONS AND DOSE**
  Replacement of coagulation factors or other plasma proteins where their concentration or functional activity is critically reduced
  - By Intravenous infusion
  - Adult: (consult haematologist)

  Major bleeding in patients on warfarin following phytomenadione (if dried prothrombin complex is unavailable)
  - Adult: 15 mL/kilogram

- **CONTRA-INDICATIONS**
  Avoid use as a volume expander - IgA deficiency with confirmed antibodies to IgA

- **CAUTIONS**
  Cardiac decompensation - need for compatibility - pulmonary oedema - severe protein S deficiency (avoid products with low protein S activity e.g. OctaplasLG)

- **SIDE-EFFECTS**
  - Common or very common: Skin reactions
  - Uncommon: Fever, hypersensitivity, hypoxia, nausea, sensation abnormal, vomiting
  - Rare or very rare: Abdominal pain, anxiety, arrhythmias, back pain, cardiac arrest, chest discomfort, chills, circulatory collapse, citrate toxicity, dizziness, dyspnoea, flushing, haemolytic anaemia, haemorrhage, hyperhidrosis, hypertension, hypotension, localised oedema, malaise, procedural complications, pulmonary oedema, respiratory disorders, thromboembolism

- **PRESCRIBING AND DISPENSING INFORMATION**
  Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood.
  A preparation of solvent/detergent treated human plasma (frozen) from pooled donors is available from Octapharma (OctaplasLG).
2.2 Subarachnoid haemorrhage

CALCIUM-CHANNEL BLOCKERS

Nimodipine

07-Feb-2018

● DRUG ACTION Nimodipine is a dihydropyridine calcium-channel blocker.

● INDICATIONS AND DOSE

Prevention of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage

BY MOUTH

Adult: 60 mg every 4 hours, to be started within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days.

Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage

BY INTRAVENOUS INFUSION

Adult (body-weight up to 70 kg): Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

Adult (body-weight 70 kg and above): Initially 1 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage in patients with unstable blood pressure

BY INTRAVENOUS INFUSION

Adult: Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter.

IMPORTANT SAFETY INFORMATION

SAFE PRACTICE

Nimodipine has been confused with amlodipine; care must be taken to ensure the correct drug is prescribed and dispensed.

● CONTRA-INDICATIONS Unstable angina - within 1 month of myocardial infarction

● CAUTIONS Cerebral oedema - hypotension - severely raised intracranial pressure

● INTERACTIONS Appendix 1: calcium channel blockers

● SIDE-EFFECTS

Uncommon

Thrombocytopenia - vasodilatation

Rare or very rare

Bradycardia - ileus

● PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

● BREAST FEEDING Manufacturer advises avoidance—present in milk.

● RENAL IMPAIRMENT Monitoring - With intravenous use Manufacturer advises monitor renal function closely in renal impairment.

● DIRECTIONS FOR ADMINISTRATION Avoid concomitant administration of nimodipine infusion and tablets.

- With oral use For administration by mouth, tablets may be crushed or halved but are light sensitive—administer immediately.

- With intravenous use For intravenous infusion, give via drip tubing in Glucose 5% or Sodium chloride 0.9%. Not to be added to infusion container; administer via an infusion pump through a Y-piece into a central catheter; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light.

- With intravenous use Polyethylene, polypropylene, or glass apparatus should be used.

2.3 Antithrombotic drugs

3 Blood clots

3.1 Blocked catheters and lines

Other drugs used for Blocked catheters and lines

Heparin (unfractionated), p. 133 · Urokinase, p. 138

ANTITHROMBOTIC DRUGS

Epoprostenol

(Prostacyclin)

● DRUG ACTION Epoprostenol is a prostaglandin and a potent vasodilator. It is also a powerful inhibitor of platelet aggregation.

● INDICATIONS AND DOSE

Inhibition of platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated

Treatment of primary pulmonary hypertension resistant to other treatments, usually with oral anti-coagulation (initiated by a specialist)

BY CONTINUOUS INTRAVENOUS INFUSION

Adult: (consult product literature)

- Initial dose - 0.5 μg/kg/min, increased after 30 minutes to 1 μg/kg/min

- Maximum dose - 20 μg/kg/min

- Bolus - 15 μg/kg

PHARMACOKINETICS

- Short half-life of approximately 3 minutes, therefore it must be administered by continuous intravenous infusion.

- Contra-indications

Severe left ventricular dysfunction

Avoid abrupt withdrawal when used for primary pulmonary hypertension (risk of rebound pulmonary hypertension) - extreme caution in coronary artery disease - haemorrhagic diathesis - pulmonary veno-occlusive disease - reconstituted solution highly alkaline—avoid extravasation (irritant to tissues) - risk of pulmonary

www.getintopharma.com
Venous thromboembolism prophylaxis

Overview
Venous thromboembolism includes deep-vein thrombosis and pulmonary embolism and occurs as a result of thrombus formation in a vein.

Venous thromboembolism prophylaxis

All patients should undergo a risk assessment to identify their risk of venous thromboembolism and bleeding on admission to hospital. Commonly used risk assessment tools can be found at www.nice.org.uk/guidance/ng89/resources. Patients considered to be at high risk of venous thromboembolism include those who are anticipated to have a substantial reduction in mobility, those with obesity, malignant disease, history of venous thromboembolism, thrombophilic disorder, and patients over 60 years of age. Pregnancy and the postpartum period are also risk factors for venous thromboembolism.

There are two methods of thromboprophylaxis: mechanical and pharmacological. Options for mechanical prophylaxis are anti-embolism stockings that provide graduated compression and produce a calf pressure of 14–15 mmHg, and intermittent pneumatic compression.

Anti-embolism stockings should be worn day and night until the patient is sufficiently mobile; they should not be offered to patients admitted with acute stroke or those with conditions such as peripheral arterial disease, peripheral neuropathy, severe leg oedema, or local conditions (e.g. gangrene, dermatitis).

When using pharmacological prophylaxis, in most cases, it should start as soon as possible or within 14 hours of admission. Patients with risk factors for bleeding (e.g. acute stroke, thrombocytopenia, acquired or untreated inherited bleeding disorders) should only receive pharmacological prophylaxis when their risk of venous thromboembolism outweighs their risk of bleeding. Patients receiving anticoagulant therapy who are at high risk of venous thromboembolism should be considered for prophylaxis if their anticoagulant therapy is interrupted, for example during the peri-operative period.

For full guidance on prophylaxis of venous thromboembolism, see NICE guideline 89 (www.nice.org.uk/guidance/ng89).

Surgical patients
To reduce the risk of venous thromboembolism in surgical patients, regional anaesthesia over general anaesthesia should be used if possible.

Mechanical prophylaxis (e.g. anti-embolism stockings or intermittent pneumatic compression) should be offered to patients with major trauma, or undergoing cranial, abdominal, bariatric, thoracic, maxillofacial, ear, nose, and throat, cardiac or elective spinal surgery. Prophylaxis should continue until the patient is sufficiently mobile or discharged from hospital (or for 30 days in spinal injury, elective spinal surgery or cranial surgery). Choice of mechanical prophylaxis depends on factors such as the type of surgery, suitability for the patient, and their condition.

Pharmacological prophylaxis should be considered in patients undergoing general or orthopaedic surgery when the risk of venous thromboembolism outweighs the risk of bleeding. The choice of prophylaxis will depend on the type of surgery, suitability for the patient, and local policy.

A low molecular weight heparin is suitable in all types of general and orthopaedic surgery; heparin (unfractionated) p. 133 is preferred in patients with renal impairment.

Fondaparinux sodium p. 127 is an option for patients undergoing abdominal, bariatric, thoracic or cardiac surgery, or for patients with lower limb immobilisation or fragility fractures of the pelvis, hip or proximal femur.

Pharmacological prophylaxis in general surgery should usually continue for at least 7 days post-surgery, or until sufficient mobility has been re-established. Pharmacological prophylaxis should be extended to 28 days after major cancer surgery in the abdomen, and to 30 days in spinal surgery.

Mechanical prophylaxis with intermittent pneumatic compression should be considered when pharmacological prophylaxis is contra-indicated in patients undergoing lower limb amputation, or those with major trauma or fragility fractures of the pelvis, hip or proximal femur.

Patients undergoing an elective hip replacement should be given thromboprophylaxis with either a low molecular weight heparin administered for 10 days followed by low-dose aspirin p. 121 for a further 28 days, or a low molecular weight heparin administered for 28 days in combination with anti-embolism stockings until discharge, or rivaroxaban p. 128. If these options are unsuitable, apixaban p. 125 or dabigatran etexilate p. 136 can be considered as alternatives. If pharmacological prophylaxis is contra-indicated, anti-embolism stockings can be used until discharge.

Patients undergoing an elective knee replacement should be given thromboprophylaxis with either low-dose aspirin p. 121 for 14 days, or a low molecular weight heparin administered for 14 days in combination with anti-embolism stockings until discharge, or rivaroxaban. If these options are
unsuitable, apixaban or dabigatran etexilate can be considered as alternatives. If pharmacological prophylaxis is contra-indicated, intermittent pneumatic compression can be used until the patient is mobile.

**Medical patients**

The choice of prophylaxis will depend on the medical condition, suitability for the patient, and local policy. Acutely ill medical patients who are at high risk of venous thromboembolism should be offered pharmacological prophylaxis. Patients should be given either a low molecular weight heparin as a first-line option, or fondaparinux sodium as an alternative, for a minimum of 7 days. Patients with renal impairment should be given either a low molecular weight heparin or heparin (unfractionated) and the dose should be adjusted as necessary.

Mechanical prophylaxis can be considered when pharmacological prophylaxis is contra-indicated; their use should be continued until the patient is sufficiently mobile. In patients admitted with acute stroke, mechanical prophylaxis with intermittent pneumatic compression should be considered, as anti-embolism stockings are unsuitable in these patients; their use should be started within 3 days of the acute stroke and continued for 30 days, or until the patient is sufficiently mobile or discharged from hospital.

**Thromboprophylaxis in pregnancy**

All pregnant women (who are not in active labour), or women who have given birth, had a miscarriage or termination of pregnancy during the past 6 weeks, with a risk of venous thromboembolism that outweighs the risk of bleeding should be considered for pharmacological prophylaxis with a low molecular weight heparin during hospital admission. In pregnant women, prophylaxis should be continued until there is no longer a risk of venous thromboembolism, or until discharge from hospital. Women who have given birth, had a miscarriage or termination of pregnancy during the past 6 weeks, should start thromboprophylaxis with a low molecular weight heparin 4–8 hours after the event, unless contra-indicated, and continue for a minimum of 7 days.

Additional mechanical prophylaxis should be considered for women who are likely to be immobilised or have significantly reduced mobility and continued until the woman is sufficiently mobile or discharged from hospital. Intermittent pneumatic compression should be used as the first-line option and anti-embolism stockings as an alternative.

**Edoxaban**

Edoxaban p. 126, an inhibitor of factor Xa, can be given orally for the treatment and prophylaxis of venous thromboembolism, although, it should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy. Duration of therapy should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e. recent surgery, trauma, immobilisation, and longer durations should be based on permanent risk factors or idiopathic deep-vein thrombosis or pulmonary embolism.

**Treatment of venous thromboembolism**

For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used; alternatively, heparin (unfractionated) p. 133 is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or (for deep-vein thrombosis only) by intermittent subcutaneous injection. Intermittent intravenous injection of heparin (unfractionated) is no longer recommended. An oral anticoagulant (usually warfarin sodium p. 140 is started at the same time as unfractionated or low molecular weight heparin (the heparin needs to be continued for at least 5 days and until the INR is ≥2 for at least 24 hours). Laboratory monitoring for heparin (unfractionated), preferably on a daily basis, is essential; determination of the activated partial thromboplastin time (APTT) is the most widely used measure (for heparin (unfractionated). A low molecular weight heparin or, in some circumstances, heparin (unfractionated) is also used in regimens for the management of myocardial infarction and unstable angina.

**Treatment of venous thromboembolism in pregnancy**

Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin sodium p. 131, enoxaparin sodium p. 132, and tinzaparin sodium p. 134. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

**Extracorporeal circuits**

Heparin (unfractionated) is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

**Haemorrhage**

If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate p. 1368 is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

**Advanced Pharmacy Services**

Patients with, or at risk of venous thromboembolism may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

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**Stroke**

**Overview**

Stroke is associated with a significant risk of morbidity and mortality. Patients presenting with acute symptoms should be immediately transferred to hospital for accurate diagnosis of stroke type, and urgent initiation of appropriate treatment; patients should be managed by a specialist multidisciplinary stroke team.

The following notes give an overview of the initial and long-term management of transient ischaemic attack, ischaemic stroke, and intra-cerebral haemorrhage.

**Transient ischaemic attack**

Patients suspected of having a transient ischaemic attack should immediately receive aspirin p. 121 (patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel p. 123 [unlicensed use] as an alternative). Following a confirmed diagnosis, patients should receive treatment for secondary prevention (see Long-term Management, under Ischaemic Stroke).

**Ischaemic stroke**

**Initial management**

Alteplase p. 216 is recommended in the treatment of acute ischaemic stroke if it can be administered within 4.5 hours of symptom onset; it should be given by medical staff...
Cardiovascular system

already receiving anticoagulation for a prosthetic heart valve

be considered for anticoagulant treatment. Patients

fibrillation following a disabling ischaemic stroke should receive aspirin before

in the acute phase of ischaemic stroke.

Anticoagulants should be considered after cardio-embolic

be initiated 24 hours after thrombolysis (or as soon as possible within

patients who are in sinus rhythm. However, parenteral anticoagulants may

are symptomomatic of, or at high

risk of developing, deep vein thrombosis or pulmonary embolism; warfarin sodium p. 140 should not be commenced

in the acute phase of ischaemic stroke.

Anticoagulants are not recommended as an alternative to

antiplatelet drugs in acute ischaemic stroke in patients who

which include both antiplatelets and anticoagulants: dipyridamole and

ischaemic stroke in patients with atrial

in the acute phase of ischaemic stroke. Statins should be avoided following

intracerebral haemorrhage, however they can be used with caution when the risk of a vascular event outweighs the risk

of further haemorrhage.

Advanced Pharmacy Services

Patients at risk of, or patients with a history of stroke or

transient ischaemic attack, may be eligible for the New

Medicines Service / Medicines Use Review service provided by

a community pharmacist. For further information, see

Advanced Pharmacy Services in Guidance on prescribing p. 1.

Oral anticoagulants

Overview

The main use of anticoagulants is to prevent thrombus

formation or extension of an existing thrombus in the

slower-moving venous side of the circulation, where the

thrombus consists of a fibrin web enmeshed with platelets and

red cells.

Anticoagulants are of less use in preventing thrombus

formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

Coumarins and phenindione

The oral anticoagulants warfarin sodium p. 140,

acenocoumarol p. 139 and phenindione p. 140, antagonise

the effects of vitamin K, and take at least 48 to 72 hours for

the anticoagulant effect to develop fully; warfarin sodium is the
drug of choice. If an immediate effect is required, unfraccionated or low molecular weight heparin must be
given concomitantly.

These oral anticoagulants should not be used in cerebral

artery thrombosis or peripheral artery occlusion as first-line

treatment; aspirin p. 121 is more appropriate for reduction of

risk in transient ischaemic attacks. Unfraccionated or a low

molecular weight heparin (see under Parenteral anticoagulants p. 120) is usually preferred for the

prophylaxis of venous thromboembolism in patients

undergoing surgery; alternatively, warfarin sodium can be

continued in selected patients currently taking long-term

warfarin sodium and who are at high risk of

thromboembolism (seek expert advice).

Dose

The base-line prothrombin time should be determined but

the initial dose should not be delayed whilst awaiting the

result.

Target INR

The following indications and target INRs for adults for

warfarin take into account recommendations of the British

Society for Haematology guidelines on oral anticoagulation with warfarin—fourth edition. Br J Haematol 2011; 154:

311–324:

An INR which is within 0.5 units of the target value is
generally satisfactory; larger deviations require dosage
adjustment. Target values (rather than ranges) are now recommended.
INR 2.5 for:

- treatment of deep-vein thrombosis or pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin sodium)
- atrial fibrillation
- cardioversion—target INR should be achieved at least 3 weeks before cardioversion and anticoagulation should continue for at least 4 weeks after the procedure (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR)
- dilated cardiomyopathy
- mitral stenosis or regurgitation in patients with either atrial fibrillation, a history of systemic embolism, a left atrial thrombus, or an enlarged left atrium
- bioprosthetic heart valves in the mitral position (treat for 3 months), or in patients with a history of systemic embolism (treat for at least 3 months), or with a left atrial thrombus at surgery (treat until clot resolves), or with other risk factors (e.g. atrial fibrillation or a low ventricular ejection fraction)
- acute arterial embolism requiring embolectomy (consider long-term treatment)
- myocardial infarction INR 3.5 for:
- recurrent deep-vein thrombosis or pulmonary embolism in patients currently receiving anticoagulation and with an INR above 2;
- Mechanical prosthetic heart valves:
  - the recommended target INR depends on the type and location of the valve, and patient-related risk factors
  - consider increasing the INR target or adding an antplatelet drug, if an embolic event occurs whilst anticoagulated at the target INR.

**Duration**
The risks of thromboembolism recurrence and anticoagulant-related bleeding should be considered when deciding the duration of anticoagulation.


- 6 weeks for isolated calf-vein deep-vein thrombosis
- 3 months for venous thromboembolism provoked by surgery or other transient risk factor (e.g. combined oral contraceptive use, pregnancy, plaster cast)
- at least 3 months for unprovoked proximal deep-vein thrombosis or pulmonary embolism; long-term anticoagulation may be required.

**Haemorrhage**
The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The cause of an elevated INR should be investigated. The following recommendations (which take into account the recommendations of the British Society for Haematology Guidelines on Oral Anticoagulation with Warfarin—fourth edition. Br J Haematol 2011; 154: 311–324) are based on the result of the INR and whether there is major or minor bleeding; the recommendations apply to adults taking warfarin:

- Major bleeding—stop warfarin sodium; give phytonadionide p. 1089 (vitamin K) by slow intravenous injection; give dried prothrombin complex p. 111 (factors II, VII, IX, and X); if dried prothrombin complex unavailable, fresh frozen plasma can be given but is less effective; recombinant factor VIIa is not recommended for emergency anticoagulation reversal
- INR >8.0, minor bleeding—stop warfarin sodium; give phytonadionide (vitamin K) by slow intravenous injection; repeat dose of phytonadionide if INR still too high after 24 hours; restart warfarin sodium when INR <5.0
- INR >8.0, no bleeding—stop warfarin sodium; give phytonadionide (vitamin K) by mouth using the intravenous preparation orally [unlicensed use]; repeat dose of phytonadionide if INR still too high after 24 hours; restart warfarin when INR <5.0
- INR 5.0–8.0, minor bleeding—stop warfarin sodium; give phytonadionide (vitamin K) by slow intravenous injection; restart warfarin sodium when INR <5.0
- INR 5.0–8.0, no bleeding— withholding 1 or 2 doses of warfarin sodium and reduce subsequent maintenance dose
- Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

**Peri-operative anticoagulation**
Warfarin sodium should usually be stopped 5 days before elective surgery; phytonadionide (vitamin K) by mouth (using the intravenous preparation orally [unlicensed use]) should be given the day before surgery if the INR is >1.5. If haemostasis is adequate, warfarin sodium can be resumed at the normal maintenance dose on the evening of surgery or the next day.

Patients stopping warfarin sodium prior to surgery who are considered to be at high risk of thromboembolism (e.g. those with a venous thromboembolic event within the last 3 months, atrial fibrillation with previous stroke or transient ischaemic attack, or mitral mechanical heart valve) may require interim therapy (“bridging”) with a low molecular weight heparin (using treatment dose). The low molecular weight heparin should be stopped at least 24 hours before surgery; if the surgery carries a high risk of bleeding, the low molecular weight heparin should not be restarted until at least 48 hours after surgery.

Patients on warfarin sodium p. 140 who require emergency surgery that can be delayed for 6–12 hours can be given intravenous phytonadionide p. 1089 (vitamin K) to reverse the anticoagulant effect. If surgery cannot be delayed, dried prothrombin complex p. 111 can be given in addition to intravenous phytonadionide (vitamin K) and the INR checked before surgery.

**Combined anticoagulant and antiplatelet therapy**
Existing antiplatelet therapy following an acute coronary syndrome or percutaneous coronary intervention should be continued for the necessary duration according to the indication being treated. The addition of warfarin sodium, when indicated (e.g. for venous thromboembolism or atrial fibrillation) should be considered following an assessment of the patient’s risk of bleeding and discussion with a cardiologist. The duration of treatment with dual therapy (e.g. aspirin and warfarin sodium) or triple therapy (e.g. aspirin with clopidogrel and warfarin sodium) should be kept to a minimum where possible. The risk of bleeding with aspirin and warfarin sodium dual therapy is lower than with clopidogrel and warfarin sodium. Depending on the indications being treated and the patient’s risk of thromboembolism, it may be possible to withhold antiplatelet therapy until warfarin sodium therapy is complete, or vice versa (on specialist advice) in order to reduce the length of time on dual or triple therapy.

**Advanced Pharmacy Services**
Patient taking oral anticoagulants may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further
Parenteral anticoagulants

Overview
The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

Heparin
Heparin initiates anticoagulation rapidly but has a short duration of action. It is often referred to as ‘standard’ or heparin (unfractionated) p. 133 to distinguish it from the low molecular weight heparins, which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, heparin (unfractionated) can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.

Low molecular weight heparins
Low molecular weight heparins (dalteparin sodium p. 131, enoxaparin sodium p. 132, and tinzaparin sodium p. 134) are usually preferred over heparin (unfractionated) in the prevention of venous thromboembolism because they are as effective and they have a lower risk of heparin-induced thrombocytopenia. The standard prophylactic regimen does not require anticoagulant monitoring. The duration of action of low molecular weight heparins is longer than that of heparin (unfractionated) and once-daily subcutaneous administration is possible for some indications, making them convenient to use.

Low molecular weight heparins are generally preferred over heparin (unfractionated) in the treatment of deep vein thrombosis and pulmonary embolism, and are also used in the treatment of myocardial infarction, unstable coronary artery disease (see under Acute coronary syndromes p. 213) and for the prevention of clotting in extracorporeal circuits.

Dalteparin sodium and tinzaparin sodium (only 20 000 unit/mL syringe) are also licensed for the extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours; treatment is recommended for a duration of 6 months. Treatment should be initiated by healthcare professionals experienced in the treatment of venous thromboembolism.

Heparinoids
Danaparoid sodium p. 130 is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery. Providing there is no evidence of cross-reactivity, it also has a role in patients who develop heparin-induced thrombocytopenia.

Argatroban
An oral anticoagulant can be given with argatroban monohydrate p. 135, but it should only be started once thrombocytopenia has substantially resolved.

Hirudins
Bivalirudin, a hirudin analogue, is a thrombin inhibitor which is licensed for unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention, and as an anticoagulant for patients undergoing percutaneous coronary intervention (including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention—see also Management of ST-segment elevation myocardial infarction (STEMI) in Acute coronary syndromes p. 213).

Heparin flushes
The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride injection 0.9% is as effective as heparin flushes. The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Epoprostenol
Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatment, usually with oral anticoagulation; it should be initiated by specialists in pulmonary hypertension.

Epoprostenol is a potent vasodilator. It has a short half-life of approximately 3 minutes and therefore it must be administered by continuous intravenous infusion.

Fondaparinux
Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

ANTIDOTES AND CHELATORS

Idarucizumab

- **DRUG ACTION** Idarucizumab is a humanised monoclonal antibody fragment that binds specifically to dabigatran and its metabolites, thereby reversing the anticoagulant effect.

- **INDICATIONS AND DOSE** Rapid reversal of dabigatran for emergency procedures, or in life-threatening or uncontrolled bleeding (specialist supervision in hospital)
  - By intravenous injection, or by intravenous infusion
  - Adult: 5 g, followed by 5 g if required

- **CAUTIONS** Risk of thrombosis
  - **FURTHER INFORMATION** Manufacturer advises to consider re-starting anticoagulant therapy as soon as medically appropriate to reduce the risk of thrombosis.
  - Dabigatran can be re-started 24 hours after administration of idarucizumab; other anticoagulant therapy can be started at any time.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises that one dose of Praxbind is administered as either two consecutive intravenous infusions, each given over 5–10 minutes, or as a bolus injection.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator at 2–8°C.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
    - SMC No. 1178/16
    - The Scottish Medicines Consortium has advised (September 2016) that idarucizumab (Praxbind) is accepted for use within NHS Scotland for adults treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.

Other drugs used for Thromboembolism Streptokinase, p. 217
Antiplatelet drugs

Overview

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.

Use of aspirin below in primary prevention of cardiovascular disease, in patients with or without diabetes, or hypertension, is not recommended. Long-term use of low-dose aspirin is recommended in patients with established cardiovascular disease (secondary prevention); a unduly high blood pressure must be controlled before aspirin is given. If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor can be added. For full guidance on the assessment and prevention of cardiovascular disease risk, see Cardiovascular disease risk assessment and prevention p. 189.

Aspirin is given following coronary bypass surgery. It is also used in atrial fibrillation, for intermittent claudication, for stable angina and acute coronary syndromes, for use following placement of coronary stents and for use in stroke.

Clopidogrel p. 123 is used for the prevention of atherothrombotic events in patients with a history of symptomatic ischaemic disease (e.g. ischaemic stroke).

In patients with non-ST elevation acute coronary syndromes, clopidogrel, should be given for three months in addition to long-term low-dose aspirin. a

Clopidogrel is also used, in combination with low-dose aspirin, for the prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation (and at least one risk factor for a vascular event), and for whom warfarin sodium p. 140 is unsuitable.

Use of clopidogrel with aspirin increases the risk of bleeding. Clopidogrel monotherapy may be an alternative when aspirin is contra-indicated, for example in patients with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor.

Dipyridamole p. 124 is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.

Prasugrel p. 214, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention; the combination is usually given for up to 12 months.

Ticagrelor p. 215, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome; the combination is usually given for up to 12 months.

Cangrelor p. 209, in combination with aspirin, is licensed for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received treatment with oral clopidogrel, prasugrel or ticagrelor prior to the procedure and in whom oral therapy with these drugs is not suitable. Cangrelor is to be used under expert supervision only.

Antiplatelet drugs and coronary stents

Patients selected for percutaneous coronary intervention, with the placement of a coronary stent, will require dual antiplatelet therapy with aspirin and either cangrelor, clopidogrel, prasugrel, or ticagrelor [unlicensed]. Aspirin therapy should continue indefinitely. a Following percutaneous coronary intervention in patients with stable angina, clopidogrel is recommended in addition to aspirin for at least 1 month after placement of a bare-metal stent, and for at least 6 months if a drug-eluting stent is used. a

Clopidogrel should not be discontinued prematurely in patients with a drug-eluting stent—there is an increased risk of stent thrombosis as a result of the eluted drug slowing the re-endothelialisation process. Patients considered to be at high-risk of developing late stent thrombosis with a drug-eluting stent may require a longer duration of treatment with clopidogrel combined with aspirin. Prasugrel or ticagrelor are alternatives to clopidogrel in certain patients undergoing percutaneous coronary intervention.

Glycoprotein Ilb/IIa inhibitors

Glycoprotein Ilb/IIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. Abciximab is a monoclonal antibody which binds to glycoprotein Ilb/IIa receptors and to other related sites; it is licensed as an adjunct to heparin (unfractionated) p. 133 and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only (to avoid additional risk of thrombocytopenia). Epifibatide p. 210 (in combination with heparin (unfractionated) and aspirin) and tirofiban p. 210 (in combination with heparin (unfractionated), aspirin, and clopidogrel) also inhibit glycoprotein Ilb/IIa receptors; they are licensed for use to prevent early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction. Tirofiban is also licensed for use in combination with heparin (unfractionated), aspirin, and clopidogrel, for the reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention. Abciximab, epifibatide and tirofiban should be used by specialists only.

Epoprostenol p. 115 is also used to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated.

Advanced Pharmacy Services

Patients taking antiplatelet drugs may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Aspirin

(Acetylsalicylic Acid)

INDICATIONS AND DOSE

Cardiovascular disease (secondary prevention)

BY MOUTH

Adult: 75 mg daily

Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) / Management of ST-segment elevation myocardial infarction (STEMI)

BY MOUTH

Adult: 300 mg, chewed or dispersed in water continued
Cardiovascular system

Rare or very rare

With oral use

Uncommon

Common or very common

Rare or very rare

SIDE-EFFECTS

CAUTIONS

CONTRA-INDICATIONS

Active peptic ulceration - bleeding disorders (antiplatelet dose) - children under 16 years (risk of Reye’s syndrome) - haemophilia - previous peptic ulceration (analgesic dose) - severe cardiac failure (analgesic dose)

CONTRA-INDICATIONS, FURTHER INFORMATION

Reye’s syndrome Owing to an association with Reye’s syndrome, aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g. for Kawasaki disease.

CAUTIONS

Allergic disease - anaemia - asthma - dehydraton - elderly - G6PD deficiency - preferably avoid during fever or viral infection in children (risk of Reye’s syndrome) - previous peptic ulceration (but manufacturers may advise avoidance of low-dose aspirin in history of peptic ulceration) - thyrotoxicosis - uncontrolled hypertension

INTERACTIONS

Appendix 1: aspirin

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Rare or very rare

Asthmatic attack - bronchospasm

SPECIFIC SIDE-EFFECTS

Common or very common

With oral use

Dyspepsia - haemorrhage

Uncommon

With oral use

Dyspnoea - rhinitis - severe cutaneous adverse reactions (SCARs) - skin reactions

Rare or very rare

With oral use

Aplastic anaemia - erythema nodosum - gastrointestinal haemorrhage (severe) - granulocytosis - haemorrhagic vasculitis - intracranial haemorrhage - menorrhagia - nausea - thrombocytopenia - vomiting

Frequency not known

With oral use

Fluid retention - gastrointestinal disorders - headache - hearing loss - hepatic failure - hyperuricaemia - iron deficiency anaemia - renal impairment - sodium retention - tinnitus - vertigo

Overdose

The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning.

For specific details on the management of poisoning, see Aspirin, under Emergency treatment of poisoning p. 1359.

ALLERGY AND CROSS-SENSITIVITY

Aspirin is contra-indicated in history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

PREGNANCY

Use antiplatelet doses with caution during third trimester; impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); high doses may be related to intra-uterine growth restriction, teratogenic effects, closure of fetal ductus arteriosus in uterus and possibly persistent pulmonary hypertension of newborn; kernicterus may occur in jaundiced neonates.

BREAST FEEDING

Avoid—possible risk of Reye’s syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low.

HEPATIC IMPAIRMENT

Manufacturer advises use with caution in mild-to-moderate impairment; avoid in severe impairment.

RENAL IMPAIRMENT

Use with caution; avoid in severe impairment; sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding.

PRESCRIBING AND DISPENSING INFORMATION

BP directs that when no strength is stated the 300 mg strength should be dispensed, and that when soluble aspirin tablets are prescribed, dispersible aspirin tablets shall be dispensed.

PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary

Aspirin Dispersible Tablets 300 mg may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY

Can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 5, 25, 32

Aspirin (Non-proprietary)

Aspirin 75 mg

Aspirin 75mg gastro-resistant tablets | 28 tablet | £0.71 DT + £0.71 | 56 tablet | £1.42–£1.66

Aspirin 300 mg

Aspirin 300mg gastro-resistant tablets | 100 tablet | £25.28 DT + £25.21

Miconprin (Dexel-Pharma Ltd)

Aspirin 75 mg

Miconprin 75mg gastro-resistant tablets | 28 tablet | £1.45 DT + £0.71 | 56 tablet | £2.87

Nu-Seals (Alliance Pharmaceuticals Ltd)

Aspirin 75 mg

Nu-Seals 75 gastro-resistant tablets | 56 tablet | £3.12

www.getintopharma.com
Clopidogrel  

**INDICATIONS AND DOSE**

Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin) in patients not already on clopidogrel

- **BY MOUTH**
  - Adult: Loading dose 300 mg, to be taken prior to the procedure, alternatively loading dose 600 mg, higher dose may produce a greater and more rapid inhibition of platelet aggregation

Transient ischaemic attack for patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor: Acute ischaemic stroke for patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor

- **BY MOUTH**
  - Adult: 75 mg once daily

Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke

- **BY MOUTH**
  - Adult: 75 mg once daily

**Unlicensed use**

- 600 mg loading dose prior to percutaneous coronary intervention is an unlicensed dose. Use in transient ischaemic attack or acute ischaemic stroke, in patients with aspirin hypersensitivity or intolerant of aspirin, is unlicensed.

**CONTRA-INDICATIONS**

- Active bleeding

**CAUTIONS**

- Discontinue 7 days before elective surgery if antiplatelet effect not desirable - patients at risk of increased bleeding from trauma, surgery, or other pathological conditions

**INTERACTIONS**

- Appendix 1: clopidogrel

**SIDE-EFFECTS**

- Common or very common: Diarrhoea, gastrointestinal discomfort, haemorrhage, skin reactions

- Uncommon: Constipation, dizziness, eosinophilia, gastrointestinal disorders, headache, intracranial haemorrhage, leucopenia, nausea, paraesthesia, thrombocytopenia, vomiting

- Rare or very rare: Acquired haemophilia, agranulocytosis, anaemia, angioedema, arthralgia, arthritis, bone marrow disorders, confusion, fever, glomerulonephritis, gynaecomastia, hallucination, hepatic disorders, hypersensitivity, hypotension, myalgia, neutropenia, pancreatitis, respiratory disorders, severe cutaneous adverse reactions (SCARs), stomatitis, taste altered, ulcerative colitis, vasculitis, vertigo, wound haemorrhage

- Frequency not known: Kounis syndrome

**ALLERGY AND CROSS-SENSITIVITY**

- Caution with history of hypersensitivity reactions to thienopyridines (e.g. prasugrel).

**PREGNANCY**

- Manufacturer advises avoid — no information available.

**BREAST FEEDING**

- Manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in moderate impairment in patients with an increased risk of bleeding—limited information available; avoid in severe impairment.

**RENAL IMPAIRMENT**

- Manufacturer advises caution.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (December 2010)

**SMC No. 88/04**

The Scottish Medicines Consortium has advised (March 2004) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients only.

**SMC No. 390/07**

The Scottish Medicines Consortium has advised (August 2007) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.

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**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- Aspirin (Non-proprietary)
  - Aspirin 75 mg: 28 tablet [POM] £3.50 DT = £1.12
  - Aspirin 300 mg: 100 tablet [POM] £1.12–£10.69

**Suppository**

**CAUTIONARY AND ADVISORY LABELS**

- Aspirin (Non-proprietary)
  - Aspirin 150 mg: 10 suppository [P] £18.67 DT = £18.67
  - Aspirin 300 mg: 10 suppository [P] £35.89 DT = £35.89

**Dispersible tablet**

**CAUTIONARY AND ADVISORY LABELS**

- Aspirin (Non-proprietary)
  - Aspirin 75 mg: 1000 tablet [POM] £18.57–£20.00
  - Aspirin 300 mg: 100 tablet [POM] £5.59 DT = £6.34
  - Danamep (Ecogen Europe Ltd)
  - Aspirin 75 mg: 28 tablet [POM] £0.50 DT = £0.56

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**NATIONAL FUNDING/ACCESS DECISIONS**

**SMC No. 88/04**

The Scottish Medicines Consortium has advised (March 2004) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients only.

**SMC No. 390/07**

The Scottish Medicines Consortium has advised (August 2007) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.

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**Frequency not known**

- Kounis syndrome

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**SIDE-EFFECTS**

- Common or very common: Diarrhoea, gastrointestinal discomfort, haemorrhage, skin reactions

- Uncommon: Constipation, dizziness, eosinophilia, gastrointestinal disorders, headache, intracranial haemorrhage, leucopenia, nausea, paraesthesia, thrombocytopenia, vomiting

- Rare or very rare: Acquired haemophilia, agranulocytosis, anaemia, angioedema, arthralgia, arthritis, bone marrow disorders, confusion, fever, glomerulonephritis, gynaecomastia, hallucination, hepatic disorders, hypersensitivity, hypotension, myalgia, neutropenia, pancreatitis, respiratory disorders, severe cutaneous adverse reactions (SCARs), stomatitis, taste altered, ulcerative colitis, vasculitis, vertigo, wound haemorrhage

- Frequency not known: Kounis syndrome

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**ALLERGY AND CROSS-SENSITIVITY**

- Caution with history of hypersensitivity reactions to thienopyridines (e.g. prasugrel).

---

**PREGNANCY**

- Manufacturer advises avoid — no information available.

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**BREAST FEEDING**

- Manufacturer advises avoid.

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**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in moderate impairment in patients with an increased risk of bleeding—limited information available; avoid in severe impairment.

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**RENAL IMPAIRMENT**

- Manufacturer advises caution.

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**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (December 2010)

**SMC No. 88/04**

The Scottish Medicines Consortium has advised (March 2004) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients only.

**SMC No. 390/07**

The Scottish Medicines Consortium has advised (August 2007) that clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.
**Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (December 2010)**

## MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

- **Clopidogrel (Non-proprietary)**
  - Clopidogrel 75 mg: Clopidogrel 75mg tablets | 28 tablet | £33.94 DT = £1.40
  - 30 tablet | £1.40-£36.95
- **Plavix (Sanofi)**
  - Clopidogrel 75 mg: Plavix 75mg tablets | 30 tablet | £35.64
  - 300mg tablets | 30 tablet | £142.54 DT = £142.54

## INDICATIONS AND DOSE

**Secondary prevention of ischaemic stroke (not associated with atrial fibrillation) and transient ischaemic attacks (used alone or with aspirin)**

- **Adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves**
  - By mouth using modified-release medicines
  - Adult: 200 mg twice daily, to be taken preferably with food

- **Adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves**
  - By mouth using immediate-release medicines
  - Adult: 300–600 mg daily in 3–4 divided doses

- **Myocardial imaging—diagnostic use only**
  - By intravenous injection
  - Adult: (consult product literature)

## CAUTIONS

- Aortic stenosis, coagulation disorders, heart failure, hypotension, left ventricular outflow obstruction, may exacerbate migraine, myasthenia gravis (risk of exacerbation), rapidly worsening angina, recent myocardial infarction

## INTERACTIONS

- Appendix 1: dipyridamole

## SIDE-EFFECTS

- Common or very common: Angina pectoris, diarrhoea, dizziness, headache, myalgia, nausea, skin reactions, vomiting
- Frequency not known: Angioedema, bronchospasm, haemorrhage, hot flush, hypotension, tachycardia, thrombocytopenia

## PREGNANCY

- Not known to be harmful.

## BREAST FEEDING

- Manufacturers advise use only if essential—small amount present in milk.

## PRESCRIBING AND DISPENSING INFORMATION

- Modified-release capsules should be dispensed in original container (pack contains a desiccant) and any capsules remaining should be discarded 6 weeks after opening.

## NATIONAL FUNDING/ACCESS DECISIONS

### NICE decisions

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (December 2010)

  The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does not apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures.

  Modified-release dipyridamole, in combination with aspirin, is recommended as an option to prevent occlusive vascular events in patients who have had:
  - a transient ischaemic attack, or
  - an ischaemic stroke, only if clopidogrel is contra-indicated or not tolerated.

  Modified-release dipyridamole monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:
  - an ischaemic stroke, only if aspirin and clopidogrel are contra-indicated or not tolerated, or
  - a transient ischaemic attack, only if aspirin is contra-indicated or not tolerated.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/ta210

## Dipyridamole

### 14-Feb-2019

#### Dipyridamole with aspirin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dipyridamole above, aspirin p. 121.

#### INDICATIONS AND DOSE

- **Secondary prevention of ischaemic stroke and transient ischaemic attacks**

  - By mouth using modified-release medicines
  - Adult: 25/200 mg twice daily

#### INTERACTIONS

- Appendix 1: aspirin · dipyridamole

#### PRESCRIBING AND DISPENSING INFORMATION

- Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Dipyridamole (Non-proprietary)**
  - Dipyridamole 10 mg per 1 ml: Dipyridamole 50mg/5ml oral suspension sugar free sugar-free | 150 ml | £39.40 DT = £39.40
  - Dipyridamole 40 mg per 1 ml: Dipyridamole 200mg/5ml oral suspension sugar free sugar-free | 150 ml | £133.53 DT = £133.53

- **Modified-release capsule**

  - CAUTIONARY AND ADVISORY LABELS 21, 25
  - **Attila (Dr Reddy's Laboratories (UK) Ltd)**
    - Dipyridamole 200 mg: Attila 200mg modified-release capsules | 60 capsule | £9.56 DT = £9.56
  - **Ofcram PR (Advanz Pharma)**
    - Dipyridamole 200 mg: Ofcram PR 200mg capsules | 60 capsule | £10.06 DT = £9.56
  - **Dipyridamole 100 mg**
    - Dipyridamole 25mg tablets | 84 tablet | £0.39 DT = £9.40
    - Dipyridamole 100mg tablets | 84 tablet | £12.50 DT = £4.66
Apixaban

**DRUG ACTION** Apixaban is a direct inhibitor of activated factor X (factor Xa).

**INDICATIONS AND DOSE**
- **Prophylaxis of venous thromboembolism following knee replacement surgery**
  - **BY MOUTH**
  - Adult: 2.5 mg twice daily for 10–14 days, to be started 12–24 hours after surgery
- **Prophylaxis of venous thromboembolism following hip replacement surgery**
  - **BY MOUTH**
  - Adult: 2.5 mg twice daily for 32–38 days, to be started 12–24 hours after surgery
- **Treatment of deep-vein thrombosis**
  - **BY MOUTH**
  - Adult: Initially 10 mg twice daily for 7 days, then maintenance 5 mg twice daily
- **Prophylaxis of recurrent deep-vein thrombosis**
- **Prophylaxis of recurrent pulmonary embolism**
- **Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and at least one risk factor (such as previous stroke or transient ischaemic attack, symptomatic heart failure, diabetes mellitus, hypertension, or age 75 years and over)**
  - **BY MOUTH**
  - Adult: 5 mg twice daily, reduce dose to 2.5 mg twice daily in patients with at least two of the following characteristics: age 80 years and over, body-weight less than 61 kg, or serum creatinine 133 micromol/litre and over

**DOSE EQUIVALENCE AND CONVERSION**
- For information on changing from, or to, other anticoagulants, consult product literature.

**CONTRA-INDICATIONS**
- Active, clinically significant bleeding
- Risk factors for major bleeding

**SIDE-EFFECTS**
- Common or very common: Anaemia, haemorrhage, nausea, skin reactions
- Uncommon: CNS haemorrhage, hypotension, post-procedural haematoma, thrombocytopenia, wound complications

**PREGNANCY**
- Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in mild to moderate impairment (or if hepatic transaminases greater than 2 times the upper limit of normal, or if bilirubin is equal or greater than 1.5 times the upper limit of normal); avoid in severe impairment or impairment associated with coaguropathy and clinically relevant bleeding risk.

**RENAL IMPAIRMENT**
- Manufacturer advises avoid if creatinine clearance less than 15 mL/minute—no information available. When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery, prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism, and treatment of deep-vein thrombosis or pulmonary embolism, use with caution if creatinine clearance 15–29 mL/minute.

**Dose adjustments**
- When used for prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation, reduce dose to 2.5 mg twice daily if serum-creatinine 133 micromol/litre and over is associated with age 80 years and over or body-weight less than 61 kg; reduce dose to 2.5 mg twice daily if creatinine clearance 15–29 mL/minute.

**MONITORING REQUIREMENTS**
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).

**PRESCRIBING AND DISPENSING INFORMATION**
- Duration of treatment should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e recent surgery, trauma, immobilisation.
- Apixaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy.

**PATIENT AND CARER ADVICE**
- Patients should be provided with an alert card and advised to keep it with them at all times.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (January 2012) NICE TA245
- Apixaban (Eliquis ®) is an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [www.nice.org.uk/guidance/ta245](http://www.nice.org.uk/guidance/ta245)
- Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (February 2013) NICE TA275
- Apixaban (Eliquis ®) is an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation in accordance with its licensed indication; with one or more of the following risk factors:
  - previous stroke or transient ischaemic attack
  - symptomatic heart failure
  - age >75 years
  - diabetes mellitus
  - hypertension.
- The risks and benefits of apixaban compared to warfarin, dabigatran etexilate, and rivaroxaban should be discussed with the patient. [www.nice.org.uk/guidance/ta275](http://www.nice.org.uk/guidance/ta275)
Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (June 2015) NICE TA341

Apixaban (Eliquis®) is an option for the treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults.

www.nice.org.uk/guidance/ta341

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **10**
      - **Eliquis (Bristol-Myers Squibb Pharmaceuticals Ltd)**
        - Apixaban 2.5 mg: Eliquis 2.5mg tablets | 10 tablet (Pm) £9.50 | 20 tablet (Pm) £19.00 | 60 tablet (Pm) £51.00 DT + £5.00
        - Apixaban 5 mg: Eliquis 5mg tablets | 28 tablet (Pm) £26.60 | 56 tablet (Pm) £53.20 DT + £53.20

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**Edoxaban**

**DRUG ACTION** Edoxaban is a direct and reversible inhibitor of activated factor X (factor Xa), which prevents conversion of prothrombin to thrombin and prolongs clotting time, thereby reducing the risk of thrombus formation.

**INDICATIONS AND DOSE**

- **Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation, in patients with at least one risk factor (such as congestive heart failure, hypertension, aged 75 years and over, diabetes mellitus, previous stroke or transient ischaemic attack)**
  - **BY MOUTH**
    - Adult (body-weight up to 61 kg): 30 mg once daily
    - Adult (body-weight 61 kg and above): 60 mg once daily

- **Treatment of deep vein thrombosis | Prophylaxis of recurrent deep vein thrombosis | Treatment of pulmonary embolism | Prophylaxis of recurrent pulmonary embolism**
  - **BY MOUTH**
    - Adult (body-weight up to 61 kg): 30 mg once daily, duration of treatment adjusted according to risk factors—consult product literature, treatment should follow initial use of parenteral anticoagulant for at least 5 days
    - Adult (body-weight 61 kg and above): 60 mg once daily, duration of treatment adjusted according to risk factors—consult product literature, treatment should follow initial use of parenteral anticoagulant for at least 5 days

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises max. dose of 30 mg once daily with concurrent ciclosporin, dronedarone, erythromycin, or ketoconazole.

**DOSE EQUIVALENCE AND CONVERSION**

- For information on changing from, or to, other anticoagulants, consult product literature.

**CONTRA-INDICATIONS** Active bleeding · arteriovenous malformations · current or recent gastro-intestinal ulceration · hepatic disease (associated with coagulopathy and clinically relevant bleeding risk) · known or suspected oesophageal varices · major intrasplinal or intracerebral vascular abnormalities · presence of malignant neoplasms at high risk of bleeding · recent brain or spinal injury · recent brain, spinal or ophthalmic surgery · recent intraocular haemorrhage · uncontrolled severe hypertension · vascular aneurysms

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- Risk for major bleeding Edoxaban treatment is contra-indicated in patients with significant risk factors for major bleeding, these include those listed above.

**CAUTIONS**

- Moderate to severe mitral stenosis (safety and efficacy not established) · prosthetic heart valve (safety and efficacy not established) · risk of bleeding · surgery

**CAUTIONS, FURTHER INFORMATION**

- Surgery 
  - Manufacturer recommends to discontinue treatment at least 24 hours before a surgical procedure; the risk of bleeding should be weighed against the urgency of the intervention—consult product literature.

**INTERACTIONS**

- Appendix 1: edoxaban

**SIDE-EFFECTS**

- Common or very common 
  - Anaemia · haemorrhage · nausea · skin reactions

- Uncommon 
  - CNS haemorrhage

**SIDE-EFFECTS, FURTHER INFORMATION**

- Should a bleeding complication arise in a patient receiving edoxaban, the manufacturer recommends to delay the next dose or treatment should be discontinued as appropriate.

**PREGNANCY**

- Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**

- Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in mild to moderate impairment, or if liver transaminases greater than 2 times the upper limit of normal, or total bilirubin 1.5 times the upper limit of normal or greater; avoid in severe impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

**RENAL IMPAIRMENT**

- Manufacturer advises avoid if creatinine clearance less than 15 mL/minute.

**Monitoring requirements**

- Manufacturer advises monitor renal function before treatment and when clinically indicated during treatment; monitor hepatic function before treatment and repeat periodically if treatment duration longer than 1 year.

- Manufacturer advises monitor for signs of mucosal bleeding and anaemia in patients at increased risk; treatment should be stopped if severe bleeding occurs.

- No routine anticoagulant monitoring required (INR tests are unreliable).

**PATIENT AND CARER ADVICE**

- Patients should be provided with an alert card and advised to keep it with them at all times.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Edoxaban for treating and preventing deep vein thrombosis and pulmonary embolism (August 2015) NICE TA354
  - Edoxaban (Lixiana®) is recommended as an option for treating and preventing recurrent deep vein thrombosis and pulmonary embolism.
  - www.nice.org.uk/guidance/ta354

- Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (September 2015) NICE TA355
  - Edoxaban (Lixiana®) is an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, with one or more of the following risk factors:
    - previous stroke or transient ischaemic attack
    - congestive heart failure
    - age ≥ 75 years
    - diabetes mellitus
    - hypertension

The risks and benefits of edoxaban treatment compared to warfarin, apixaban, dabigatran etexilate, and rivaroxaban should be discussed with the patient.

www.nice.org.uk/guidance/ta355
**Fondaparinux sodium**

**DRUG ACTION** Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

**INDICATIONS AND DOSE**

Prophylaxis of venous thromboembolism in patients after undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 2.5 mg, dose to be given 6 hours after surgery, then 2.5 mg once daily.

Prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 2.5 mg once daily.

**TREATMENT OF SUPERFICIAL-VEIN THROMBOSIS**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 2.5 mg once daily for at least 30 days (max. 45 days if high risk of thromboembolic complications), treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively.

**TREATMENT OF UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION**

- **INITIALLY BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 2.5 mg daily for the first day, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

**TREATMENT OF DEEP-VEIN THROMBOSIS AND PULMONARY EMBOLISM**

- **BY SUBCUTANEOUS INJECTION**
  - Adult (body-weight up to 50 kg): 5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).
  - Adult (body-weight 50-100 kg): 7.5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).
  - Adult (body-weight 101 kg and above): 10 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).

**CONTRA-INDICATIONS** Active bleeding • bacterial endocarditis

**CAUTIONS** Active gastro-intestinal ulcer disease • bleeding disorders • brain surgery • elderly patients • low body-weight • ophthalmic surgery • recent intracranial haemorrhage • risk of catheter thrombus during percutaneous coronary intervention • spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses) • spinal surgery

**INTERACTIONS** → Appendix 1: fondaparinux

**SIDE-EFFECTS**

- Common or very common Anaemia • haemorrhage
- Uncommon Chest pain • coagulation disorder • dyspnoea • fever • hepatic function abnormal • nausea • oedema • platelet abnormalities • skin reactions • thrombocytopenia • vomiting • wound secretion

**RARE OR VERY RARE** Anxiety • confusion • constipation • cough • diarrhoea • dizziness • drowsiness • fatigue • gastritis • gastrointestinal discomfort • genitai oedema • headache • hyperbilirubinaemia • hypersensitivity • hypokalaemia • hypotension • leg pain • post procedural infection • syncope • vasodilation • vertigo

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs possible risk—no information available.

**BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

- When used for Venous thromboembolism, unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction Manufacturer advises caution in severe impairment (increased risk of bleeding complications).
- When used for Superficial-vein thrombosis Manufacturer advises avoid in severe impairment (no information available).

**RENAL IMPAIRMENT** Increased risk of bleeding in renal impairment.

- When used for treatment of acute coronary syndromes or prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis Avoid if eGFR less than 20 mL/minute/1.73 m².
- When used for treatment of venous thromboembolism Use with caution if eGFR 30–50 mL/minute/1.73 m², avoid if eGFR less than 30 mL/minute/1.73 m².

**DOSAGE ADJUSTMENTS** When used for prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis Reduce dose to 1.5 mg daily if eGFR 20–50 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Arixtra®), give intermittently in Sodium chloride 0.9%. For ST-segment elevation myocardial infarction, add requisite dose to 25-50 mL infusion fluid and give over 1-2 minutes.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Fondaparinux sodium (Non-proprietary)**
  - Fondaparinux sodium 5 mg per 1 ml Fondaparinux sodium 2.5mg/0.5ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £82.79 DT = £82.79
  - Fondaparinux sodium 12.5 mg per 1 ml Fondaparinux sodium 5mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £110.70 DT = £116.53
  - Fondaparinux sodium 10mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £110.70 DT = £116.53
  - Fondaparinux sodium 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £110.70 DT = £116.53
  - Arixtra (Aspen Pharma Trading Ltd)
  - Fondaparinux sodium 5 mg per 1 ml Arixtra 2.5mg/0.5ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £82.79 DT = £82.79
Cardiovascular system

CONTRA-INDICATIONS

DRUG ACTION

Rivaroxaban is a direct inhibitor of activated factor X (factor Xa).

INDICATIONS AND DOSE

Prophylaxis of venous thromboembolism following knee replacement surgery
- BY MOUTH
  - Adult: 10 mg once daily for 2 weeks, to be started 6–10 hours after surgery.

Prophylaxis of venous thromboembolism following hip replacement surgery
- BY MOUTH
  - Adult: 10 mg once daily for 5 weeks, to be started 6–10 hours after surgery.

Treatment of deep-vein thrombosis | Treatment of pulmonary embolism
- BY MOUTH
  - Adult: Initially 15 mg twice daily for 21 days, then maintenance 20 mg once daily, to be taken with food, for duration of treatment, consult product literature.

Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism
- BY MOUTH
  - Adult: 10 mg once daily, following completion of at least 6 months of anticoagulant treatment, to be taken with food, consider 20 mg once daily in those at high risk of recurrence (such as complicated comorbidities, or previous recurrence with rivaroxaban 10 mg once daily).

Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age > 75 years, or diabetes mellitus
- BY MOUTH
  - Adult: 20 mg once daily, to be taken with food.

Prophylaxis of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel)
- BY MOUTH
  - Adult: 2.5 mg twice daily usual duration 12 months.

Prophylaxis of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events (in combination with aspirin)
- BY MOUTH
  - Adult: 2.5 mg twice daily.

DOSE EQUIVALENCE AND CONVERSION
- For information on changing from, or to, or other anticoagulants—consult product literature.

CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS
Active bleeding - malignant neoplasms - oesophageal varices - recent brain surgery - recent gastro-intestinal ulcer - recent intracranial haemorrhage - recent ophthalmic surgery - recent spine surgery - significant risk of major bleeding - vascular aneurysm

SPECIFIC CONTRA-INDICATIONS
- When used for prophylaxis of atherothrombotic events following an acute coronary syndrome Previous stroke - transient ischaemic attack.
- When used for prophylaxis of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease previous stroke (no information available).

CAUTIONS

GENERAL CAUTIONS
Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal) - bronchiectasis - elderly - prostatic heart valve (efficacy not established) - risk of bleeding - rivaroxaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy - severe hypertension - vascular retinopathy.

SPECIFIC CAUTIONS
- When used for prophylaxis of atherothrombotic events following an acute coronary syndrome
  - Body-weight less than 60 kg.
- When used for prophylaxis of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease
  - Body-weight less than 60 kg.

INTERACTIONS
- Appendix 1: rivaroxaban.

SIDE-EFFECTS
- Common or very common
- Uncommon
- Rare or very rare
  - Vascular pseudoanoeurn.

PREGNANCY
- Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING
- Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
- Manufacturer advises avoid in hepatic disease with coagulopathy and clinically-relevant bleeding risk including patients with moderate to severe cirrhosis.

RENAL IMPAIRMENT
- Manufacturer advises caution if creatinine clearance 15–29 mL/minute; avoid if creatinine clearance less than 15 mL/minute. Use with caution if concomitant use of drugs that increase plasma-rivaroxaban concentration (consult product literature).

Dose adjustments
- When used for Treatment of deep-vein thrombosis or pulmonary embolism Following the first 21 days of treatment for deep-vein thrombosis or pulmonary embolism, the usual dose of 20 mg once daily can be given, but manufacturer advises consider reducing to 15 mg once daily if creatinine clearance 15–49 mL/minute and the risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism.
- When used for Prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism When the recommended dose is 20 mg once daily, manufacturer advises consider reducing to 15 mg once daily if creatinine clearance 15–49 mL/minute and the risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism.
- When used for Prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism When the recommended dose is 20 mg once daily, manufacturer advises consider reducing to 15 mg once daily if creatinine clearance 15–49 mL/minute.

Arixtra 1.5mg/0.3ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (Plast) £62.79 £62.79 (Hospital only).
Fondaparinux sodium 12.5 mg per 1 ml Arixtra 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (Plast) £116.53 £116.53.
Arixtra 5mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (Plast) £116.53 £116.53.
Arixtra 1mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (Plast) £116.53 £116.53.

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Thromboembolism 129

Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs. No routine anticoagulant monitoring required (INR tests are unreliable).

Directions for Administration Tablets may be crushed and mixed with water or apple puree just before administration.

Prescribing and Dispensing Information Low-dose rivaroxaban, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers. Treatment should be started as soon as possible after the patient has been stabilised following the acute coronary event, at the earliest 24 hours after admission to hospital, and at the time when parenteral anticoagulation therapy would normally be discontinued; the usual duration of treatment is 12 months.

Patient and Carer Advice Patients should be provided with an alert card and advised to keep it with them at all times.

National Funding/Access Decisions

NICE decisions

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009) NICE TA170 Rivaroxaban (Xarelto (Bayer Plc)) is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. www.nice.org.uk/guidance/ta170

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (May 2012) NICE TA256 Rivaroxaban (Xarelto (Bayer Plc)) is an option for the prevention of stroke and systemic embolism (in accordance with its licensed indication) in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: previous stroke or transient ischaemic attack, congestive heart failure, age ≥75 years, diabetes mellitus, hypertension. The risks and benefits of rivaroxaban compared with warfarin should be discussed with the patient. www.nice.org.uk/guidance/ta256


Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (June 2013) NICE TA287 Rivaroxaban (Xarelto (Bayer Plc)) is an option for treating pulmonary embolism and preventing recurrent deep-vein thrombosis and pulmonary embolism in adults. www.nice.org.uk/guidance/ta287

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (March 2015) NICE TA335 Rivaroxaban (Xarelto (Bayer Plc)) is an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in patients who have had an acute coronary syndrome with elevated cardiac biomarkers.

The patient’s risk of bleeding should be carefully assessed before treatment is initiated and the risks and benefits of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone should be discussed with the patient. A decision on continuation of treatment should be taken no later than 12 months after starting treatment. www.nice.org.uk/guidance/ta335

Scottish Medicines Consortium (SMC) decisions

SMC No. 519/08 The Scottish Medicines Consortium has advised (December 2008) that rivaroxaban (Xarelto (Bayer Plc)) is accepted for use within NHS Scotland for the prevention of venous thromboembolism in adults undergoing elective hip or knee replacement surgery. www.nice.org.uk/guidance/ta287

SMC No. 756/12 The Scottish Medicines Consortium has advised (February 2012) that rivaroxaban (Xarelto (Bayer Plc)) is accepted for restricted use within NHS Scotland for the treatment of stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Its use is restricted to patients with poor INR control despite compliance with coumarin anticoagulant therapy, or to patients who are allergic to, or unable to tolerate, a coumarin anticoagulant. www.nice.org.uk/guidance/ta287

SMC No. 755/12 The Scottish Medicines Consortium has advised (February 2012) that rivaroxaban (Xarelto (Bayer Plc)) is accepted for use within NHS Scotland for the treatment of deep-vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults. SMC No. 852/13 The Scottish Medicines Consortium has advised (March 2013) that rivaroxaban (Xarelto (Bayer Plc)) is accepted for use within NHS Scotland for the treatment of pulmonary embolism (PE), and prevention of recurrent deep-vein thrombosis and PE in adults. SMC No. SMC2128 The Scottish Medicines Consortium has advised (February 2019) that rivaroxaban (Xarelto (Bayer Plc)) is accepted for restricted use within NHS Scotland in combination with acetylsalicylic acid for the prevention of atherothrombotic events in adults with stable coronary artery disease that does not require dual antiplatelet therapy.

Medicinal Forms There can be variation in the licensing of different medicines containing the same drug.

Tablet

| Rivaroxaban 2.5 mg | Xarelto 2.5mg tablets | 56 tablet pack | £50.40 DT = £50.40 |
| Rivaroxaban 10 mg | Xarelto 10mg tablets | 10 tablet pack | £18.00 |
| Rivaroxaban 15 mg | Xarelto 15mg tablets | 14 tablet pack | £25.20 |
| Rivaroxaban 20 mg | Xarelto 20mg tablets | 28 tablet pack | £38.00 |

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### Danaparoid sodium

**24-Jul-2018**

#### INDICATIONS AND DOSE
- **Prevention of deep-vein thrombosis in general or orthopaedic surgery**
  - Adult: 750 units twice daily for 7–10 days, initiate treatment before operation, with last pre-operative dose 1–4 hours before surgery
- **Thromboembolic disease in patients with history of heparin-induced thrombocytopenia**
  - **INITIALLY BY INTRAVENOUS INJECTION**
    - Adult (body-weight up to 55 kg): Initially 1250 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
    - Adult (body-weight 55–89 kg): Initially 2500 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
    - Adult (body-weight 90 kg and above): Initially 3750 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days

#### CONTRA-INDICATIONS
- Active peptic ulcer (unless this is the reason for operation), acute bacterial endocarditis, diabetic retinopathy, epidermal anaesthesia (with treatment doses), haemophilia and other haemorrhagic disorders, recent cerebral haemorrhage, severe hypertension, spinal anaesthesia (with treatment doses), thrombocytopenia (unless patient has heparin-induced thrombocytopenia).

#### CAUTIONS
- Antibodies to heparins (risk of antibody-induced thrombocytopenia), body-weight over 90 kg, recent bleeding, risk of bleeding.

#### SIDE-EFFECTS
- Common or very common: Haemorrhage, heparin-induced thrombocytopenia, skin reactions, thrombocytopenia.
- Uncommon: Procedural haematomata.
- Rare or very rare: Anaphylactic reaction, heparin-induced thrombocytopenia.

#### INTERACTIONS
- Appendix 1: danaparoid.

#### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection
- **Danaparoid sodium (Non-proprietary)**
  - Danaparoid sodium 1250 unit per 1 ml
  - 750 units/0.7 ml solution for injection ampoules: 10 ampoules
  - £59.99

### Heparins

#### CONTRA-INDICATIONS
- Acute bacterial endocarditis, major trauma, epidural anaesthesia with treatment doses, haemophilia and other haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage, recent surgery to eye, recent surgery to nervous system, severe hypertension, spinal anaesthesia with treatment doses, thrombocytopenia (including history of heparin-induced thrombocytopenia).

#### CAUTIONS
- Elderly.

#### SIDE-EFFECTS
- Common or very common: Haemorrhage, heparin-induced thrombocytopenia, skin reactions, thrombocytopenia, thrombosis.
- Uncommon: CNS haemorrhage.
- Rare or very rare: Alopecia, hyperkalaemia, osteoporosis, priapism.
- Frequency not known: Hypoaldosteronism.

#### SIDE-EFFECTS, FURTHER INFORMATION
- **Haemorrhage**
  - If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

- **Heparin-induced thrombocytopenia**
  - Clinically important heparin-induced thrombocytopenia is immune-mediated and can be complicated by thrombosis. Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be stopped and an alternative anticoagulant, such as danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

- **Hyperkalaemia**
  - Inhibition of aldosterone secretion by unfractionated or low molecular weight heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy.

#### ALLERGY AND CROSS-SENSITIVITY
- Hypersensitivity to unfractionated or low molecular weight heparin.

#### MONITORING REQUIREMENTS
- **Heparin-induced thrombocytopenia**
  - Platelet counts should be measured just before treatment with unfractionated or low molecular weight heparin, and regular monitoring of platelet counts may be required if given for longer than 4 days. See the British Society for Haematology’s Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. *Br J Haematol* 2012; 159: 528–540.

- **Hyperkalaemia**
  - Plasma-potassium concentration should be measured in patients at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days.
Dalteparin sodium

**INDICATIONS AND DOSE**

**FRAGMIN®**

**Treatment of deep-vein thrombosis** | **Treatment of pulmonary embolism**

- BY SUBCUTANEOUS INJECTION
  - Adult: 200 units/kg daily (max. per dose 18 000 units) until adequate oral anticoagulation with vitamin K antagonist established (at least 5 days of combined treatment is usually required)

**Treatment of deep-vein thrombosis** (in patients at increased risk of haemorrhage) | **Treatment of pulmonary embolism** (in patients at increased risk of haemorrhage)

- BY SUBCUTANEOUS INJECTION
  - Adult: 100 units/kg twice daily until adequate oral anticoagulation with vitamin K antagonist established (at least 5 days of combined treatment is usually required)

**Unstable coronary artery disease**

- BY SUBCUTANEOUS INJECTION
  - Adult: 120 units/kg every 12 hours (max. per dose 10 000 units twice daily) for 5–8 days

**Prevention of clotting in extracorporeal circuits**

- TO THE DEVICE AS A FLUSH
  - Adult: (consult product literature)

**FRAGMIN® GRADUATED SYRINGES**

**Unstable coronary artery disease** (including non-ST-segment-elevation myocardial infarction)

- BY SUBCUTANEOUS INJECTION
  - Adult: 120 units/kg every 12 hours (max. per dose 10 000 units twice daily) for up to 8 days

**Patients with unstable coronary artery disease** (including non-ST-segment-elevation myocardial infarction) awaiting angiography or revascularisation and having already had 8 days treatment with dalteparin

- BY SUBCUTANEOUS INJECTION
  - Adult (body-weight up to 70 kg and male): 5000 units every 12 hours until the day of the procedure (max. 45 days).
  - Adult (body-weight up to 80 kg and female): 5000 units every 12 hours until the day of the procedure (max. 45 days).
  - Adult (body-weight 70 kg and above and male): 7500 units every 12 hours until the day of the procedure (max. 45 days).
  - Adult (body-weight 80 kg and above and female): 7500 units every 12 hours until the day of the procedure (max. 45 days).

**FRAGMIN® SINGLE-DOSE SYRINGES**

**Prophylaxis of deep-vein thrombosis** in surgical patients—moderate risk

- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 2500 units for 1 dose, dose to be given 1–2 hours before surgery, then 2500 units every 24 hours

**Prophylaxis of deep-vein thrombosis** in surgical patients—high risk

- BY SUBCUTANEOUS INJECTION
  - Adult: Initially 2500 units for 1 dose, dose to be administered 1–2 hours before surgery, followed by 2500 units after 8–12 hours, then 5000 units every 24 hours, alternatively initially 5000 units for 1 dose, dose to be given on the evening before surgery, followed by 5000 units after 24 hours, then 5000 units every 24 hours
UNLICENSÉ USE  Not licensed for treatment of venous thromboembolism in pregnancy.

INTERACTIONS  → Appendix 1: low molecular-weight heparins

SIDE-EFFECTS  Epidural haematoma - prothrombotic cardiac valve thrombosis

PREGNANCY  Not known to be harmful, low molecular weight heparins do not cross the placenta. Multidose vial contains benzyl alcohol—manufacturer advises avoid.

RENAL IMPAIRMENT  Due to the relatively high molecular weight and inactivation in the gastro-intestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible, however manufacturers advise avoid.

HEPATIC IMPAIRMENT  Manufacturer advises caution in severe impairment (increased risk of bleeding complications).

DOSE adjustments  Manufacturer advises consider dose reduction in severe impairment.

RENAL IMPAIRMENT  Use of unfractionated heparin may be preferable.

DOSE adjustments  Risk of bleeding may be increased—dose reduction may be required.

MONITORING REQUIREMENTS

▶ For monitoring during treatment of deep-vein thrombosis and of pulmonary embolism, blood should be taken 3–4 hours after a dose (recommended plasma concentration of anti–Factor Xa 0.5–1 unit/mL); monitoring not required for once–daily treatment regimen and not generally necessary for twice–daily regimen.

▶ Routine monitoring of anti–Factor Xa activity is not usually required during treatment with dalteparin, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SMC No. 683/11 The Scottish Medicines Consortium has advised (March 2011) that dalteparin (Fragmin®) is accepted for restricted use within NHS Scotland as extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence in patients with solid tumours, if initiated by healthcare professionals experienced in the treatment of VTE.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

▶ Fragmin (Pfizer Ltd)

Dalteparin sodium 2500 unit per 1 ml  Fragmin 10,000 units/4ml solution for injection ampoules | 10 ampoule (PS) £51.22

Dalteparin sodium 10000 unit per 1 ml  Fragmin 10,000 units/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PS) £28.23 DT = £28.23

Dalteparin sodium 5000 unit per 1 ml  Fragmin 10,000 units/1ml solution for injection pre-filled syringes | 10 ampoule (PS) £51.22

Dalteparin sodium 12500 unit per 1 ml  Fragmin 2,500 units/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PS) £18.58 DT = £18.58

Dalteparin sodium 25000 unit per 1 ml  Fragmin 18,000 units/0.2ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PS) £50.62 DT = £50.82

Fragmin 15,000 units/0.6ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PS) £62.34 DT = £62.34

Fragmin 5,000 units/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PS) £28.23 DT = £28.23

Fragmin 12,500 units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PS) £35.29 DT = £35.29

Fragmin 7,500 units/0.3ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PS) £42.34 DT = £42.34

Fragmin 100,000 units/4ml solution for injection vials | 1 vial (PS) £48.66

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**INDICATIONS AND DOSE**

**Treatment of venous thromboembolism in pregnancy**

▶ BY SUBCUTANEOUS INJECTION

Adult (body-weight up to 50 kg): 40 mg twice daily, dose based on early pregnancy body-weight

Adult (body-weight 50–69 kg): 60 mg twice daily, dose based on early pregnancy body-weight

Adult (body-weight 70–89 kg): 80 mg twice daily, dose based on early pregnancy body-weight

Adult (body-weight 90 kg and above): 100 mg twice daily, dose based on early pregnancy body-weight

**Prophylaxis of deep-vein thrombosis, especially in surgical patients—moderate risk**

▶ BY SUBCUTANEOUS INJECTION

Adult: 20 mg for 1 dose, dose to be given approximately 2 hours before surgery, then 20 mg every 24 hours

**Prophylaxis of deep-vein thrombosis, especially surgical patients—high risk (e.g. orthopaedic surgery)**

▶ BY SUBCUTANEOUS INJECTION

Adult: 40 mg for 1 dose, dose to be given 12 hours before surgery, then 40 mg every 24 hours

**Prophylaxis of deep-vein thrombosis in medical patients**

▶ BY SUBCUTANEOUS INJECTION

Adult: 40 mg every 24 hours

**Treatment of deep-vein thrombosis in uncomplicated patients with low risk of recurrence**

Treatment of pulmonary embolism in uncomplicated patients with low risk of recurrence

▶ BY SUBCUTANEOUS INJECTION

Adult: 1.5 mg/kg every 24 hours until adequate oral anticoagulation established

**Treatment of deep-vein thrombosis in patients with risk factors such as obesity, cancer, recurrent VTE, or proximal thrombosis**

Treatment of pulmonary embolism in patients with risk factors such as obesity, symptomatic pulmonary embolism, cancer, or recurrent VTE

▶ BY SUBCUTANEOUS INJECTION

Adult: 1 mg/kg every 12 hours until adequate oral anticoagulation established

**Treatment of acute ST-segment elevation myocardial infarction (patients not undergoing percutaneous coronary intervention)**

▶ INITIALLY BY INTRAVENOUS INJECTION

Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only

▶ BY SUBCUTANEOUS INJECTION

Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only

**Treatment of acute ST-segment elevation myocardial infarction (patients undergoing percutaneous coronary intervention)**

▶ INITIALLY BY INTRAVENOUS INJECTION

Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the

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**BFN 78**

Fragmin 10,000 units/0.4ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PS) £28.23 DT = £28.23

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last subcutaneous dose was given more than 8 hours previously

- INITIALLY BY SUBCUTANEOUS INJECTION
- Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the last subcutaneous dose was given more than 8 hours previously

**Unstable angina | Non-ST-segment-elevation myocardial infarction**

- BY SUBCUTANEOUS INJECTION
- Adults: 1 mg/kg every 12 hours usually for 2–8 days (minimum 2 days)

**Prevention of clotting in extracorporeal circuits**

- TO THE DEVICE AS A FLUSH
- Adults: (consult product literature)

**DOSE EQUIVALENCE AND CONVERSION**

- 1 mg equivalent to 100 units.

■ **UNLICENSED USE** Not licensed for treatment of venous thromboembolism in pregnancy.

■ **CAUTIONS** Low body-weight (increased risk of bleeding)

■ **INTERACTIONS** → Appendix 1: low molecular-weight heparins

■ **SIDE-EFFECTS**

- Common or very common: Hypersensitivity
- Frequency not known: Cutaneous vasculitis • eosinophilia • haemorrhagic anaemia • headache • hepatic disorders

■ **PREGNANCY** Not known to be harmful, low molecular weight heparins do not cross the placenta. Multidose vials contain benzyl alcohol—avoid.

■ **BREAST FEEDING** Due to the relatively high molecular weight of enoxaparin and inactivation in the gastrointestinal tract, passage into breast milk and absorption by the nursing infant are likely to be negligible; however manufacturers advise avoid.

■ **HEPATIC IMPAIRMENT** Manufacturer advises caution—no further information available.

■ **RENAL IMPAIRMENT** Risk of bleeding increased; use of unfractionated heparin may be preferable. Manufacturer advises avoid if creatinine clearance less than 15 mL/minute.

**Dose adjustments** Manufacturer advises reduce dose if creatinine clearance 15–30 mL/minute—consult product literature for details.

■ **MONITORING REQUIREMENTS** Routine monitoring of anti-Xa activity is not usually required during treatment with enoxaparin, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

■ **DIRECTIONS FOR ADMINISTRATION** When administered in conjunction with a thrombolytic, enoxaparin should be given between 15 minutes before and 30 minutes after the start of thrombolytic therapy.

■ **PRESCRIBING AND DISPENSING INFORMATION** Enoxaparin sodium is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

■ **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **EXCIPIENTS:** May contain Benzyl alcohol
- **Arovi** (ROVI Biotech Ltd)

  Enoxaparin sodium 100 mg per 1 ml
  - Arovi 20mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £15.65 DT + £20.86
  - Arovi 60mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £29.45 DT + £39.26

  Arovi 40mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £22.70 DT + £30.27
  - Arovi 80mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £41.35 DT + £51.79
  - Arovi 100mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £54.23 DT + £67.30
  - Enoxaparin sodium 150 mg per 1 ml
  - Arovi 150mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £74.93 DT + £99.91
  - Arovi 120mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £65.95 DT + £87.93
- **Clexane** (Sanofi)

  Enoxaparin sodium 100 mg per 1 ml
  - Clexane 60mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £39.26 DT + £49.26
  - Clexane 300mg/3ml solution for injection multidose vials
  - 1 vial
  - £21.33 DT + £21.33
  - Clexane 80mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £55.13 DT + £55.13
  - Clexane 40mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £30.27 DT + £20.86
  - Clexane 100mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £72.30 DT + £72.30
  - Clexane 20mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £20.86 DT + £20.86
  - Enoxaparin sodium 150 mg per 1 ml
  - Clexane Forte 120mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £65.95 DT + £99.91
  - Clexane Forte 100mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £87.93 DT + £87.93
  - Clexane Forte 150mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £74.93 DT + £87.93

■ **Inhixa** (Techdow Pharma England Ltd)

  Enoxaparin sodium 100 mg per 1 ml
  - Inhixa 40mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £24.22 DT + £30.27
  - Inhixa 80mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £44.10 DT + £55.13
  - Inhixa 60mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £31.14 DT + £39.26
  - Inhixa 100mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £31.14 DT + £41.10
  - Inhixa 120mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £57.84 DT + £72.30
  - Inhixa 20mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £16.69 DT + £20.86
  - Enoxaparin sodium 150 mg per 1 ml
  - Inhixa 120mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £87.93 DT + £87.93
  - Inhixa 150mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection
  - £89.92 DT + £99.91

**Thromboembolism**

**Heparin (unfractionated)**

05-May-2017

■ **INDICATIONS AND DOSE**

  Treatment of mild to moderate pulmonary embolism | Treatment of unstable angina | Treatment of acute peripheral arterial occlusion

  -> INITIALLY BY INTRAVENOUS INJECTION

  - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

  Treatment of severe pulmonary embolism

  -> INITIALLY BY INTRAVENOUS INJECTION

  - Adult: Loading dose 10 000 units, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

  Treatment of deep vein thrombosis

  -> INITIALLY BY INTRAVENOUS INJECTION

  - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous intravenous infusion) 18 units/kg/hour, alternatively (by subcutaneous injection) 15 000 units every 12 hours, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

continued →
Thromboprophylaxis in medical patients
- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units every 8–12 hours

Thromboprophylaxis in surgical patients
- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units for 1 dose, to be taken 2 hours before surgery, then 5000 units every 8–12 hours

Thromboprophylaxis during pregnancy
- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000–10 000 units every 12 hours, to be administered with monitoring. **Important**: prevention of prosthetic heart-valve thrombosis in pregnancy calls for specialist management

Haemodialysis
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 1000–5000 units, followed by (by continuous intravenous infusion) 250–1000 units/hour

Prevention of clotting in extracorporeal circuits
- **TO THE DEVICE AS A FLUSH**
  - Adult: (consult product literature)
  - To maintain patency of catheters, cannulas, other indwelling intravenous infusion devices
  - **TO THE DEVICE AS A FLUSH**
  - Adult: 10–200 units, to be flushed through every 4–8 hours, not for therapeutic use

- **INTERACTIONS** → Appendix 1: heparin (unfractionated)
- **SIDE-EFFECTS** Adrenal insufficiency, hypokalaemia, rebound hyperlipidaemia
- **PREGNANCY** Does not cross the placenta; maternal osteoporosis reported after prolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid.
- **BREAST FEEDING** Not excreted into milk due to high molecular weight.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution; consider avoiding in severe impairment (increased risk of bleeding complications).
  - **Dose adjustments** Manufacturer advises consider dose reduction if used in severe impairment.
- **RENAL IMPAIRMENT**
  - **Dose adjustments** Risk of bleeding increased in severe impairment—dose may need to be reduced.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%; administration with a motorised pump is advisable.

- **PRESCRIBING AND DISPENSING INFORMATION** Doses listed take into account the guidelines of the British Society for Haematology.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

**Solution for injection**
- **EXCIPIENTS**: May contain Benzyl alcohol
  - **Heparin (unfractionated) (Non-proprietary)**
    - Heparin sodium 1000 unit per 1 ml Heparin sodium 1000 units/1ml solution for injection ampoules | 10 ampoule (£9.05) £4.85 DT = £14.85
    - Heparin sodium 5000 units/5ml solution for injection vials | 10 vial (£6.15) £16.50–£37.41 DT = £16.50
    - Heparin sodium 20,000 units/20ml solution for injection ampoules | 10 ampoule (£30.50) £70.88 DT = £70.88
    - Heparin sodium 5000 units/5ml solution for injection ampoules | 10 ampoule (£43.05) £37.47 DT = £37.47
    - Heparin sodium 10,000 units/10ml solution for injection ampoules | 10 ampoule (£64.59) £64.59
    - Heparin sodium 5000 unit per 1 ml Heparin sodium 5000 units/1ml solution for injection ampoules | 10 ampoule (£29.04) £29.04

Heparin sodium 25,000units/5ml solution for injection vials | 10 vial (£5.00) £45.00
Heparin sodium 25,000units/5ml solution for injection ampoules | 10 ampoule (£75.78) £75.78
Heparin calcium 25000 unit per 1 ml Heparin calcium 5,000units/0.2ml solution for injection ampoules | 10 ampoule (£64.70 DT = £44.70
Heparin sodium 25000 unit per 1 ml Heparin sodium 25,000units/1ml solution for injection ampoules | 10 ampoule (£76.95 DT = £76.95
Heparin sodium 5,000units/0.2ml solution for injection ampoules | 10 ampoule (£37.35 DT = £37.35

**Intravenous flush**
- **EXCIPIENTS**: May contain Benzyl alcohol
  - **Heparin (unfractionated) (Non-proprietary)**
    - Heparin sodium 10 unit per 1 ml Heparin sodium 50units/5ml patency solution ampoules | 10 ampoule (£14.96 DT = £14.96
    - Heparin sodium 50units/5ml LV flush solution ampoules | 10 ampoule (£14.96 DT = £14.96
    - Heparin sodium 100 unit per 1 ml Heparin sodium 200units/2ml LV flush solution ampoules | 10 ampoule (£15.68 DT = £15.68
    - Heparin sodium 200units/2ml patency solution ampoules | 10 ampoule (£15.68 DT = £15.68

**Infusion**
- **Heparin (unfractionated) (Non-proprietary)**
  - Heparin sodium 2 unit per 1 ml Heparin sodium 1,000units/500ml infusion Viaflex bags 1 bar (£52.00) £52.00
  - Heparin sodium 2,000units/1 litre infusion Viaflex bags 1 bar (£68.00) £68.00
  - Heparin sodium 5 unit per 1 ml Heparin sodium 5,000units/1 litre infusion Viaflex bags 1 bar (£96.00) £96.00

**Tinzaparin sodium**

- **INDICATIONS AND DOSE**
  - **INNOHEP® 10,000 UNITS/ML**
    - **Prophylaxis of deep-vein thrombosis (general surgery)**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 3500 units for 1 dose, dose to be given 2 hours before surgery, then 3500 units every 24 hours
    - **Prophylaxis of deep-vein thrombosis (orthopaedic surgery)**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: Initially 50 units/kg for 1 dose, dose to be given 2 hours before surgery, then 50 units/kg every 24 hours, alternatively initially 4500 units for 1 dose, dose to be given 12 hours before surgery, then 4500 units every 24 hours
    - **Prevention of clotting in extracorporeal circuits**
      - **TO THE DEVICE AS A FLUSH**
      - Adult: (consult product literature)
    - **INNOHEP® 20,000 UNITS/ML**
      - **Extended treatment of venous thromboembolism and prevention of recurrence in patients with active cancer**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult: 175 units/kg once daily for 6 months; the benefit of continued treatment beyond 6 months should be evaluated
      - **Treatment of deep-vein thrombosis | Treatment of pulmonary embolism**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult: 175 units/kg once daily until adequate oral anticoagulation established, treatment regimens do not require anticoagulation monitoring
      - **Treatment of venous thromboembolism in pregnancy**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult: 175 units/kg once daily, dose based on early pregnancy body-weight, treatment regimens do not require anticoagulation monitoring

- **UNLICENSED USE** Not licensed for the treatment of venous thromboembolism in pregnancy.
Thromboembolism 135

Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (when initiating concomitant warfarin treatment)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Reduced to 2 micrograms/kg/minute, dose should be temporarily reduced and INR measured after 4–6 hours; warfarin should be initiated at intended maintenance dose (do not give loading dose of warfarin); consult product literature for further details

- **CAUTIOUS** Bleeding disorders - diabetic retinopathy - gastro-intestinal ulceration - immediately after lumbar puncture - major surgery (especially of brain, spinal cord, or eye) - risk of bleeding - severe hypertension - spinal anaesthesia

- **INTERACTIONS** → Appendix 1: argatroban

- **SIDE-EFFECTS**
  - Common or very common: Anaemia - haemorrhage - nausea - skin reactions

- **PREGNANCY** Manufacturer advises avoid unless essential—limited information available.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment—monitor aPTT; avoid in severe impairment or in patients with impairment undergoing percutaneous coronary intervention.

- **Dose adjustments** Manufacturer advises reduce initial dose to 0.5 micrograms/kg/minute in moderate impairment; adjust dose according to aPTT and as clinically indicated—consult product literature.

- **MONITORING REQUIREMENTS** Determine activated partial thromboplastin time 2 hours after start of treatment, then 2 or 4 hours after infusion rate altered (consult product literature), and at least once daily thereafter.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Exembol - Ready to use®), manufacturer advises administer 1 mg/mL solution via a syringe driver. For intravenous infusion (Exembol - Multidose®), manufacturer advises continuously in Glucose 5%, Sodium chloride 0.9% or Sodium lactate intravenous infusion compound; dilute to a concentration of 1 mg/mL prior to use.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**EXCIPIENTS:** May contain Benzyl alcohol, sulfites

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**Thromboembolism 135**

**Antithrombotic Drugs > Thrombin inhibitors, direct**

**Argatroban monohydrate**

- **INDICATIONS AND DOSE**
  - **Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment**
    - **INITIALLY BY CONTINUOUS INTRAVENOUS INFUSION**
    - Adult: Initially 2 micrograms/kg/minute, dose to be adjusted according to activated partial thromboplastin time, (by intravenous infusion) increased to up to 10 micrograms/kg/minute maximum duration of treatment 14 days
  - **Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (for dose in cardiac surgery, percutaneous coronary intervention, or critically ill patients)**
    - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - Adult: (consult product literature)

**Solution for infusion**

**EXCIPIENTS:** May contain Ethanol

- **Argatroban monohydrate (Non-proprietary)**
  - Argatroban monohydrate 1 mg per 1 mL Argatroban 50mg/50ml solution for infusion vials | 1 vial (PMD) £94.69
  - Exembol (Mitsubishi Tanabe Pharma Europe Ltd)
    - Argatroban monohydrate 1 mg per 1 mL Exembol 50mg/50ml solution for infusion vials | 4 vial (PMD) £198.80 (Hospital only)
  - Argatroban monohydrate 100 mg per 1 mL Exembol Multidose 250mg/2.5ml concentrate for solution for infusion vials | 1 vial (PMD) £5.09

www.getintopharma.com
Bivalirudin

**Drug Action**
Bivalirudin, a hirudin analogue, is a thrombin inhibitor.

**Indications and Dose**

Unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention (in addition to aspirin and clopidogrel)
- **Initially by intravenous injection**
  - Adult: Initially 100 micrograms/kg, then (by intravenous infusion) 250 micrograms/kg/hour for up to 72 hours in medically managed patients

Unstable angina or non-ST-segment elevation myocardial infarction (in addition to aspirin and clopidogrel) in patients proceeding to percutaneous coronary intervention or coronary artery bypass surgery without cardiopulmonary bypass
- **Initially by intravenous injection**
  - Adult: Initially 100 micrograms/kg, then (by intravenous infusion) 1.75 mg/kg/hour for duration of procedure; (by intravenous infusion) reduced to 250 micrograms/kg/hour for 4–12 hours as necessary following percutaneous coronary intervention, for patients proceeding to coronary artery bypass surgery with cardiopulmonary bypass, discontinue intravenous infusion 1 hour before procedure and treat with unfractionated heparin

Anticoagulation in patients undergoing percutaneous coronary intervention including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (in addition to aspirin and clopidogrel)
- **Initially by intravenous injection**
  - Adult: Initially 750 micrograms/kg, followed immediately by (by intravenous infusion) 1.75 mg/kg/hour during procedure and for up to 4 hours after procedure, then (by intravenous infusion) reduced to 250 micrograms/kg/hour for a further 4–12 hours if necessary

**Contra-Indications**
Active bleeding, bleeding disorders, severe hypertension, subacute bacterial endocarditis

**Cautions**
Brachytherapy procedures, previous exposure to lepirudin (theoretical risk from lepirudin antibodies)

**Interactions**
Appendix 3: bivalirudin

**Side-effects**

Common or very common
- Procedural complications, skin reactions
Uncommon
- Anaemia, headache, hypersensitivity, hypotension, nausea, shock, thrombocytopenia
Rare or very rare
- Arrhythmias, cardiac tamponade, chest pain, compartment syndrome, dyspnoea, embolism and thrombosis, intracranial haemorrhage, pain, vascular disorders, vomiting

**Pregnancy**
Manufacturer advises avoid unless potential benefit outweighs risk

**Breast Feeding**
Manufacturer advises caution

**Renal Impairment**
Avoid if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments
- When used for percutaneous coronary intervention: Reduce rate of infusion to 1.4 mg/kg/hour if eGFR 30–60 mL/minute/1.73 m² and monitor blood clotting parameters.

**Directions for Administration**
- For intravenous infusion (Angiox®), give continuously in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 250-mg vial with 5 mL water for injections then withdraw 5 mL and dilute to 50 mL with infusion fluid.

**National Funding/Access Decisions**

**NICE decisions**
- Bivalirudin for the treatment of ST-segment elevation myocardial infarction (July 2011) NICE TA230
  - Bivalirudin (Angiox®) in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. www.nice.org.uk/guidance/ta230

**Scottish Medicines Consortium (SMC) decisions**
SMC No. 516/08
The Scottish Medicines Consortium has advised (December 2008) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland for adults with acute coronary syndromes planned for urgent or early intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

SMC No. 638/10
The Scottish Medicines Consortium has advised (September 2010) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland as an anticoagulant in adults undergoing percutaneous coronary intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
- **Bivalirudin (Non-proprietary)**
  - Bivalirudin 250 mg

Prophylaxis of venous thromboembolism following total knee replacement surgery

**By Mouth**
- Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 10 days, to be taken on the first day after surgery
- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 10 days, to be taken on the first day after surgery

Prophylaxis of venous thromboembolism following total knee replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil
- **By Mouth**
  - Adult 18–74 years: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 10 days, to be taken on the first day after surgery
  - Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 10 days, to be taken on the first day after surgery

Prophylaxis of venous thromboembolism following total hip replacement surgery

**By Mouth**
- Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 28–35 days, to be taken on the first day after surgery
Prophylaxis of venous thromboembolism following total hip replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil

**BY MOUTH**

- Adult 75–110 years: 150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
- Adult 75 years and over: 110 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant


**BY MOUTH**

- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 28–35 days, to be taken on the first day after surgery
- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 28–35 days, to be taken on the first day after surgery
- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 28–35 days, to be taken on the first day after surgery

**SIDE-EFFECTS**

- **Common** or **very common**
  - Hepatic function abnormal
- **Uncommon**
  - Anaemia
  - Diarrhoea
  - Gastrointestinal haemorrhage
  - Hyperbilirubinaemia
  - Nausea
  - Post procedural complications
  - Vomiting
  - Wound complications
- **Rare or very rare**
  - Angioedema
  - Dysphagia
  - Gastrointestinal discomfort
  - Gastrointestinal disorders
  - Intracranial haemorrhage
  - Post procedural drainage
  - Skin reactions
  - Thrombocytopenia
  - Wound drainage
- **Frequency not known**
  - Bronchospasm

**CONTRA-INDICATIONS**

- Active bleeding
- Do not use as anticoagulant for prophylactic heart valve or valve repair
- Recent intracranial haemorrhage
- Recent intracranial haemorrhage
- Recent ophthalmic surgery
- Recent spine surgery
- Recent ophthalmic surgery
- Significant risk of major bleeding
- Vascular aneurysm

**CAUTIONS**

- Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs)
- Bacterial endocarditis
- Bleeding disorders
- Body weight less than 50 kg
- Elderly
- Gastritis
- Gastro-oesophageal reflux
- Oesophagitis
- Recent biopsy
- Recent major trauma
- Thrombocytopenia

**INTERACTIONS**

- Appendix 1: dabigatran

**DOSE EQUIVALENCE AND CONVERSION**

- For information on changing from, or to, other anticoagulants, consult product literature.

**PROPHYLAXIS OF STROKE AND SYSTEMIC EMBOLISM IN NON-VALVULAR ATRIAL FIBRILLATION**

- By mouth
- Adult: 110–150 mg twice daily

**CONTRA-INDICATIONS**

- Active bleeding
- Do not use as anticoagulant for prophylactic heart valve or valve repair
- Recent intracranial haemorrhage
- Recent ophthalmic surgery
- Recent spine surgery
- Significant risk of major bleeding
- Vascular aneurysm

**CAUTIONS**

- Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs)
- Bacterial endocarditis
- Bleeding disorders
- Body weight less than 50 kg
- Elderly
- Gastritis
- Gastro-oesophageal reflux
- Oesophagitis
- Recent biopsy
- Recent major trauma
- Thrombocytopenia

**INTERACTIONS**

- Appendix 1: dabigatran

**DOSE EQUIVALENCE AND CONVERSION**

- For information on changing from, or to, other anticoagulants, consult product literature.
Cardiovascular system

Dabigatran etexilate for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Patients should be provided with an alert card and advised to keep it with them at all times.

NATIONAL FUNDING/ACCESS DECISIONS

Dabigatran etexilate (as Dabigatran etexilate mesilate)

110 mg Pradaxa 110mg capsules | 10 capsule £8.50 | 60 capsule £51.00 DT + £51.00

Dabigatran etexilate (as Dabigatran etexilate mesilate)

150 mg Pradaxa 150mg capsules | 60 capsule £51.00 DT + £51.00

ANTITHROMBOTIC DRUGS >TISSUE PLASMINOGEN ACTIVATORS

Urokinase

INDICATIONS AND DOSE

Deep-vein thrombosis (thromboembolic occlusive vascular disease)

- Initial 4400 units/kg, to be given over 10–20 minutes, followed by 100 000 units/hour for 2–3 days

Pulmonary embolism (thromboembolic occlusive vascular disease)

- Initial 4400 units/kg, to be given over 10–20 minutes, followed by 4400 units/kg/hour for 12 hours

Occlusive peripheral arterial disease (thromboembolic occlusive vascular disease)

- By intra-arterial infusion

Occluded central venous catheters (blocked by fibrin clots)

- By intravenous infusion, or by intra-arterial infusion

- Adult: (consult product literature)

Occluded arteriovenous haemodialysis shunts (blocked by fibrin clots)

- By intravenous infusion, or by intra-arterial infusion

Syner-Kinase®

Deep-vein thrombosis (thromboembolic occlusive vascular disease)

- By intravenous infusion

Pulmonary embolism (thromboembolic occlusive vascular disease)

- Initially by intravenous infusion

- Adult: Initially 4400 units/kg, to be given over 10 minutes, dose to be made up in 15 mL sodium chloride 0.9%, followed by 4400 units/kg/hour for 12–24 hours

Occlusive peripheral arterial disease

- By intra-arterial infusion

Occluded intravenous catheters and cannulas (blocked by fibrin clots)

- By intra-arterial injection, or by intravenous injection

- Adult: 5000–25 000 units, to be injected directly into catheter or cannula, dose dissolved in suitable volume

MEDICINAL FORMS

Capsule

CAUTIONARY AND ADVISORY LABELS

- Pradaxa (Boehringer Ingelheim Ltd)

Dabigatran etexilate (as Dabigatran etexilate mesilate)

75 mg Pradaxa 75mg capsules | 10 capsule £8.50 | 60 capsule £51.00 DT + £51.00
of sodium chloride 0.9% to fill the catheter or cannula lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

- **INTERACTIONS** → Appendix 1: urokinase
- **SIDE-EFFECTS**
  - Common or very common Artery dissection - embolism and thrombosis - stroke
  - Rare or very rare Renal failure
  - Rare or very rare Vascular pseudoaneurysm
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment.
- **Dose adjustments** Manufacturer advises consider dose reduction in mild to moderate impairment.
- **RENAL IMPAIRMENT** Dose reduction may be required.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Syner-KINASE™), give continuously or intermittently in Sodium chloride 0.9%.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Syner-KINASE (Syner-Med Pharmaceutical Products) Ltd
  - Urokinase 10000 unit Syner-KINASE 10,000 unit powder for solution for injection vials | 1 vial £35.95 (Hospital only)
  - Urokinase 25000 unit Syner-KINASE 25,000 unit powder for solution for injection vials | 1 vial £45.95 (Hospital only)
  - Urokinase 100000 unit Syner-KINASE 100,000 unit powder for solution for injection vials | 1 vial £112.95 (Hospital only)
  - Urokinase 250000 unit Syner-KINASE 250,000 unit powder for solution for injection vials | 1 vial £95 (Hospital only)
  - Urokinase 500000 unit Syner-KINASE 500,000 unit powder for solution for injection vials | 1 vial £112 (Hospital only)

**Antithrombotic Drugs** → **Vitamin K Antagonists**

**Vitamin K antagonists**

**Gastrointestinal**
- **CONTRA-INDICATIONS** Avoid use within 48 hours postpartum - haemorrhagic stroke - significant bleeding
- **CAUTIONS** Bacterial endocarditis (use only if warfarin otherwise indicated) - conditions in which risk of bleeding is increased - history of gastrointestinal bleeding - hyperthyroidism - hypothyroidism - peptic ulcer - postpartum (delay warfarin until risk of haemorrhage is low—usually 5–7 days after delivery) - recent ischaemic stroke - recent surgery - uncontrolled hypertension
- **SIDE-EFFECTS**
  - Common or very common Haemorrhage
  - Rare or very rare Alopecia - nausea - vomiting
  - Frequency not known Blue toe syndrome - CNS haemorrhage - diarrhoea - fever - haemorrhaxa - jaundice - pancreatitis - skin necrosis (increased risk in patients with protein C or protein S deficiency) - skin reactions
- **CONCEPTION AND CONTRACEPTION** Women of child-bearing age should be warned of the danger of teratogenicity.

**Pregnancy**
- **INDICATIONS AND DOSE** Prophylaxis of embolism in rheumatic heart disease and atrial fibrillation | Prophylaxis and treatment of venous thrombosis and pulmonary embolism: Transient ischaemic attacks
  - **BY MOUTH**
    - Adult: Initially 2–4 mg once daily for 2 days, alternatively initially 6 mg on day 1, then 4 mg on day 2; maintenance 1–8 mg daily, adjusted according to response, dose to be taken at the same time each day, lower doses may be required in patients over 65 years, severe heart failure with hepatic congestion, and malnutrition
- **CAUTIONS** Patients over 65 years
- **INTERACTIONS** → Appendix 1: coumarins

**Acenocoumarol**

(Nicoumalone)

**Electroni...**
SIDE-EFFECTS

- Rare or very rare Appetite decreased · liver injury · skin necrosis haemorrhagic (increased risk in patients with protein C or protein S deficiency) · vasculitis

- BREAST FEEDING Risk of haemorrhage; increased by vitamin K deficiency—manufacturer recommends prophylactic vitamin K for the infant (consult product literature).

- HEPATIC IMPAIRMENT
  Dose adjustments Manufacturer advises consider dose reduction in mild to moderate impairment.

- RENAL IMPAIRMENT Caution in mild to moderate impairment. Avoid in severe impairment.

- PATIENT AND CARER ADVICE Anticoagulant card to be provided.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 10
  - Acenocoumarol 1 mg
  - Warfarin sodium 1 mg
  - Warfarin sodium 3 mg
  - Warfarin sodium 5 mg

**Phenindione**

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism

- BY MOUTH
  - Adult: Initially 200 mg on day 1, then 100 mg on day 2, then, adjusted according to response; maintenance 50–150 mg daily

**INTERACTIONS** → Appendix 1: phenindione

**SIDE-EFFECTS** Agranulocytosis · albuminuria · eosinophilia · hepatitis · increased leucocytes · kidney injury · leucopenia · lymphadenopathy · pancytopenia · renal tubular necrosis · taste altered

- BREAST FEEDING Avoid. Risk of haemorrhage; increased by vitamin K deficiency.

- RENAL IMPAIRMENT Caution in mild to moderate impairment. Avoid in severe impairment.

- PATIENT AND CARER ADVICE Patient counselling is advised for phenindione tablets (may turn urine pink or orange). Anticoagulant card to be provided.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 10, 14
  - Phenindione (Non-proprietary)
    - 10 mg
    - 25 mg

**Warfarin sodium**

10-Oct-2016

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

- BY MOUTH
  - Adult: Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time

**INTERACTIONS** → Appendix 1: coumarins

**SIDE-EFFECTS** Calciphipasis · hepatic function abnormal

**PREGNANCY** Babies of mothers taking warfarin at the time of delivery need to be offered immediate prophylaxis with intramuscular phynomenadone (vitamin K).

- BREAST FEEDING Not present in milk in significant amounts and appears safe. Risk of haemorrhage which is increased by vitamin K deficiency.

- RENAL IMPAIRMENT Use with caution in mild to moderate impairment.

- PATIENT AND CARER ADVICE Anticoagulant card to be provided.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral suspension**

- CAUTIONARY AND ADVISORY LABELS 10
  - Warfarin sodium (Non-proprietary)
    - 1 mg per ml

**Tablet**

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

- BY MOUTH
  - Adult: Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time

4 Blood pressure conditions

4.1 Hypertension

**Overview**

Lowering raised blood pressure decreases the risk of stroke, coronary events, heart failure, and renal impairment. Advice on antihypertensive therapy in this section takes into account the recommendations of NICE clinical guidance 127
Hypertension thresholds and targets for treatment

Patients presenting with a blood pressure of 140/90 mmHg or higher when measured in a clinic setting, should be offered ambulatory blood pressure monitoring (or home blood pressure monitoring if ambulatory blood pressure monitoring is unsuitable) to confirm the diagnosis and stage of hypertension.

Stage 1 hypertension:
- Clinic blood pressure 140/90 mmHg or higher, and ambulatory daytime average or home blood pressure average 135/85 mmHg or higher
- Treat patients under 80 years who have stage 1 hypertension and target-organ damage (e.g. left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy), cardiovascular disease, renal disease, diabetes, or a 10 year cardiovascular risk ≥20%; in the absence of these conditions, advise lifestyle changes and review annually. For patients under 40 years with stage 1 hypertension but no overt target-organ damage, cardiovascular disease, renal disease, or diabetes, consider seeking specialist advice for evaluation of secondary causes of hypertension.

Stage 2 hypertension:
- Clinic blood pressure 160/100 mmHg or higher, and ambulatory daytime average or home blood pressure average 150/95 mmHg or higher
- Treat all patients who have stage 2 hypertension, regardless of age

Severe hypertension:
- Clinic systolic blood pressure ≥180 mmHg or clinic diastolic blood pressure ≥110 mmHg; treat promptly—see Hypertensive Crises, below.

A target clinic blood pressure below 140/90 mmHg is suggested for patients under 80 years; a target ambulatory or home blood pressure average (during the patient’s waking hours) of below 135/85 mmHg is suggested for patients under 80 years; see also Hypertension in the Elderly, below. A target clinic blood pressure below 130/80 mmHg should be considered for those with established atherosclerotic cardiovascular disease, or diabetes in the presence of kidney, eye, or cerebrovascular disease. In some individuals it may not be possible to reduce blood pressure below the suggested targets despite the use of appropriate therapy.

Drugs for hypertension

A single antihypertensive drug is often inadequate in the management of hypertension, and additional antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently (see Hypertensive Crises), an interval of at least 4 weeks should be allowed to determine response; clinicians should ensure antihypertensive drugs are titrated to the optimum or maximum tolerated dose at each step of treatment. Response to drug treatment may be affected by age and ethnicity.

Patients under 55 years:

Step 1
- **ACE inhibitor:** if not tolerated, offer an angiotensin-II receptor antagonist. If both ACE inhibitors and angiotensin-II receptor antagonists are contra-indicated or not tolerated, consider a **beta-blocker**; beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or at high risk of developing diabetes.

Step 2
- ACE inhibitor or angiotensin-II receptor antagonist in combination with a **calcium-channel blocker**. If a calcium-channel blocker is not tolerated or if there is evidence of, or a high risk of, heart failure, give a **thiazide-related diuretic** (e.g. chlortalidone or indapamide). If a beta-blocker was given at Step 1, add a calcium channel blocker in preference to a thiazide-related diuretic (see Step 1).

Step 3
- ACE inhibitor or angiotensin-II receptor antagonist in combination with a calcium-channel blocker and a **thiazide-related diuretic**.

Step 4 (resistant hypertension)
- Consider seeking specialist advice.
- Add low-dose **spirolactone** [unlicensed indication], or use high-dose thiazide related diuretic if plasma-potassium concentration above 4.5 mmol/litre
- Monitor renal function and electrolytes
- If additional diuretic therapy is contra-indicated, ineffectivel, or not tolerated, consider an **alpha-blocker** or a beta-blocker.

Patients over 55 years, and patients of any age who are of African or Caribbean family origin:

Step 1
- Calcium-channel blocker; if not tolerated or if there is evidence of, or a high risk of, heart failure, give a thiazide-related diuretic (e.g. chlortalidone or indapamide).

Step 2
- Calcium-channel blocker or thiazide-related diuretic in combination with an ACE inhibitor or angiotensin-II receptor antagonist (an angiotensin-II receptor antagonist in combination with a calcium-channel blocker is preferred in patients of African or Caribbean family origin).

Steps 3 and 4
- Treat as for patients under 55 years

Cardiovascular risk reduction

Aspirin p. 121 reduces the risk of cardiovascular events and myocardial infarction. Unduly high blood pressure must be controlled before aspirin is given. Unless contra-indicated, aspirin is recommended for all patients with established cardiovascular disease. Use of aspirin in primary prevention, in those with or without diabetes, is of unproven benefit. For the role of aspirin in the prevention of stroke in patients with atrial fibrillation, see Arrhythmias p. 99. Statins are also of benefit in cardiovascular disease or in those who are at high risk of developing cardiovascular disease.

For full guidance on the risk assessment and prevention of cardiovascular disease, see Cardiovascular disease risk assessment and prevention p. 189.

Hypertension in the elderly

Benefit from antihypertensive therapy is evident up to at least 80 years of age, but it is probably inappropriate to apply a strict age limit when deciding on drug therapy. Patients who reach 80 years of age while taking antihypertensive drugs should continue treatment, provided that it continues to be of benefit and does not cause significant side-effects. If
Cardiovascular system

Blood pressure conditions

BNF 78

patients are aged over 80 years when diagnosed with stage 1 hypertension, the decision to treat should be based on the presence of other comorbidities; patients with stage 2 hypertension should be treated as for patients over 55 years. A target clinic blood pressure below 150/90 mmHg is suggested for patients over 80 years; the suggested target ambulatory or home blood pressure average (during the patient’s waking hours) is below 145/85 mmHg.

Isolated systolic hypertension

Isolated systolic hypertension (systolic pressure >160 mmHg, diastolic pressure <90 mmHg) is common in patients over 60 years, and is associated with an increased cardiovascular disease risk; it should be treated as for patients with both a raised systolic and diastolic blood pressure. Patients with severe postural hypotension should be referred to a specialist.

Hypertension in diabetes

Hypertension in diabetic patients should be treated aggressively with lifestyle modification and drug treatment.

For patients with diabetes, a target clinic blood pressure below 140/80 mmHg is suggested (below 130/80 mmHg is advised if kidney, eye, or cerebrovascular disease are also present). However, in some individuals, it may not be possible to achieve this level of control despite appropriate therapy. Most patients require a combination of antihypertensive drugs.

Hypertension is common in type 2 diabetes, and antihypertensive treatment prevents macrovascular and microvascular complications. In type 1 diabetes, hypertension usually indicates the presence of diabetic nephropathy. An ACE inhibitor (or an angiotensin-II receptor antagonist) may have a specific role in the management of diabetic nephropathy; in patients with type 2 diabetes, an ACE inhibitor (or an angiotensin-II receptor antagonist) can delay progression of microalbuminuria to nephropathy.

Hypertension in renal disease

A target clinic blood pressure below 140/90 mmHg is suggested (below 130/80 mmHg is advised in patients with chronic kidney disease and diabetes, or if proteinuria exceeds 1 g in 24 hours). An ACE inhibitor (or an angiotensin-II receptor antagonist) should be considered for patients with proteinuria; however, ACE inhibitors should be used with caution in renal impairment. Thiazide diuretics may be ineffective and high doses of loop diuretics may be required.

Hypertension in pregnancy

Hypertensive complications in pregnancy can be hazardous for both the mother and the fetus, and are associated with a significant risk of morbidity and mortality; complications can occur in pregnant women with pre-existing chronic hypertension, or in those who develop hypertension in the latter half of pregnancy.

Labetalol hydrochloride p. 148 is widely used for treating hypertension in pregnancy. Methyldopa p. 145 is considered safe for use in pregnancy. Modified-release preparations of nifedipine p. 162 [unlicensed] are also used. The following advice takes into account the recommendations of NICE Clinical Guideline 107 (August 2010), Hypertension in Pregnancy.

Pregnant women with chronic hypertension who are already receiving antihypertensive treatment should have their drug therapy reviewed. In uncomplicated chronic hypertension, a target blood pressure of <150/100 mmHg is recommended; women with target-organ damage as a result of chronic hypertension, and in women with chronic hypertension who have given birth, a target blood pressure of <140/90 mmHg is advised. Long-term antihypertensive treatment should be reviewed 2 weeks following the birth. Women managed with methyldopa during pregnancy should discontinue treatment and restart their original antihypertensive medication within 2 days of the birth.

Pregnant women are at high risk of developing pre-eclampsia if they have chronic kidney disease, diabetes mellitus, autoimmune disease, chronic hypertension, or if they have had hypertension during a previous pregnancy; these women are advised to take aspirin p. 121 once daily [unlicensed indication] from week 12 of pregnancy until the baby is born. Women with more than one moderate risk factor (first pregnancy, aged >40 years, pregnancy interval >10 years, BMI ≥35 kg/m² at first visit, multiple pregnancy, or family history of pre-eclampsia) for developing pre-eclampsia are also advised to take aspirin once daily [unlicensed indication] from week 12 of pregnancy until the baby is born.

Women with pre-eclampsia or gestational hypertension who present with a blood pressure over 150/100 mmHg, should receive initial treatment with oral labetalol hydrochloride to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. If labetalol hydrochloride is unsuitable, methyldopa or modified-release nifedipine may be considered. Women with gestational hypertension or pre-eclampsia who have been managed with methyldopa during pregnancy should discontinue treatment within 2 days of the birth. Women with a blood pressure of ≥160/110 mmHg who require critical care during pregnancy or after birth should receive immediate treatment with either oral or intravenous labetalol hydrochloride, intravenous hydralazine hydrochloride p. 180, or oral modified-release nifedipine to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg.

Also see use of magnesium sulfate p. 1051 in pre-eclampsia and eclampsia. Women with pre-eclampsia where birth is considered likely within 7 days, intramuscular betamethasone p. 674 [unlicensed indication] is recommended for fetal lung maturation.

Hypertensive crises

If blood pressure is reduced too quickly in the management of hypertensive crises, there is a risk of reduced organ perfusion leading to cerebral infarction, blindness, deterioration in renal function, and myocardial ischaemia.

A hypertensive emergency is defined as severe hypertension with acute damage to the target organs (e.g. severe papilloedema or retinal haemorrhage, or the presence of clinical conditions such as acute coronary syndromes, acute aortic dissection, acute pulmonary oedema, hypertensive encephalopathy, acute cerebral infarction, intracerebral or subarachnoid haemorrhage, eclampsia, or rapidly progressing renal failure); prompt treatment with intravenous antihypertensive therapy is generally required. Over the first few minutes or within 2 hours, blood pressure should be reduced by 20–25%. When intravenous therapy is indicated, treatment options include sodium nitroprusside p. 182 [unlicensed], nicardipine hydrochloride p. 161, labetalol hydrochloride, glyceryl trinitrate p. 218, phentolamine mesilate p. 181, hydralazine hydrochloride, or esmolol hydrochloride p. 154; choice of drug is dependent on concomitant conditions and clinical status of the patient.

Severe hypertension (blood pressure ≥180/110 mmHg) without acute target-organ damage is defined as a hypertensive urgency; blood pressure should be reduced gradually over 24–48 hours with oral antihypertensive therapy, such as labetalol hydrochloride, or the calcium-channel blockers amlodipine p. 156 or felodipine p. 160. Use of sublingual nifedipine is not recommended.

Also see advice on short-term management of hypertensive episodes in pheochromocytoma.
Phaeochromocytoma
Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha- and beta-adrenoceptors; the optimal choice of drug therapy remains unclear. Alpha-blockers are used in the short-term management of hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker; a cardiacselective beta-blocker is preferred.

Phenoxybenzamine hydrochloride p. 181, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects. Phentolamine mesilate is a short-acting alpha-blocker used mainly during surgery of phaeochromocytoma; its use for the diagnosis of phaeochromocytoma has been superseded by measurement of catecholamines in blood and urine.

Metirosine (available from ‘special-order’ manufacturers or specialist importing companies) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of phaeochromocytoma, and long term in patients unsuitable for surgery; an alpha-adrenoceptor blocking drug may also be required. Metirosine should not be used to treat essential hypertension.

Advanced Pharmacy Services
Patients with hypertension may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Antihypertensive drugs
Vasodilator antihypertensive drugs
Vasodilators have a potent hypertensive effect, especially when used in combination with a beta-blocker and a thiazide. Important: see Hypertension (hypertensive crises) for a warning on the hazards of a very rapid fall in blood pressure.

Hydralazine hydrochloride p. 180 is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention.

Sodium nitroprusside p. 182 [unlicensed] is given by intravenous infusion to control severe hypertensive emergencies when parenteral treatment is necessary.

Minoxidil p. 181 should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide p. 227, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for females.

Prazosin p. 784, doxazosin p. 783, and terazosin p. 786 have alpha-blocking and vasodilator properties.

Ambrisentan p. 184, bosentan p. 185, iloprost p. 184, macitentan p. 185, sildenafil p. 813, and tadalafil p. 814 are licensed for the treatment of pulmonary arterial hypertension and should be used under specialist supervision. Epoprostenol p. 115 can be used in patients with primary pulmonary hypertension resistant to other treatments. Bosentan is also licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Riociguat p. 186 is licensed for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension; it should be used under specialist supervision.

Sitaxentan has been withdrawn from the market because the benefit of treatment does not outweigh the risk of severe hepatotoxicity.

Centrally acting antihypertensive drugs
Methyldopa p. 145 is a centrally acting antihypertensive; it may be used for the management of hypertension in pregnancy.

Clonidine hydrochloride p. 145 has the disadvantage that sudden withdrawal of treatment may cause severe rebound hypertension.

Moxonidine p. 146, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

Adrenergic neurone blocking drugs
Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use, but may be necessary with other therapy in resistant hypertension.

Guanethidine monosulfate p. 182, which also depletes the nerve endings of noradrenaline, is licensed for rapid control of blood pressure, however alternative treatments are preferred.

Alpha-adrenoceptor blocking drugs
Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may, however, reduce blood pressure rapidly after the first dose and should be introduced with caution. Doxazosin, indoramin p. 784, and terazosin have properties similar to those of prazosin.

Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension.

Prostatic hyperplasia
Alfuzosin hydrochloride p. 782, doxazosin, indoramin, prazosin, tamsulosin hydrochloride p. 785, and terazosin are indicated for benign prostatic hyperplasia.

Drugs affecting the renin-angiotensin system
Angiotensin-converting enzyme inhibitors
Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. They have many uses and are generally well tolerated. The main indications of ACE inhibitors are shown below.

Heart failure
ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker. Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. However, a low dose of spironolactone p. 193 may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Prolonged first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (e.g. furosemide 80 mg daily or more). Temporary withdrawal of the loop diuretic reduces the risk, but may cause severe rebound pulmonary oedema. Therefore, for patients on high doses of loop diuretics, the ACE inhibitor may need to be initiated under specialist supervision. An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of
serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially.

**Hypertension**

An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well. ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetes with nephropathy. They may reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy.

**Diabetic nephropathy**

ACE inhibitors have a role in the management of diabetic nephropathy.

**Prophylaxis of cardiovascular events**

ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction. ACE inhibitors may also have a role in preventing cardiovascular events.

**Initiation under specialist supervision**

ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:

- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- receiving concomitant angiotensin-II receptor antagonist or aliskiren;
- with hypovolaemia;
- with hyponatraemia (plasma-sodium concentration below 130 mmol/litre);
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

**Renal effects**

Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below present); hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced. Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease, they also occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly). A specialist should be involved if renal function is significantly reduced as a result of treatment with an ACE inhibitor.

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.

ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

**ACE inhibitors in combination with other drugs**

See also, Concomitant use of drugs affecting the renin-angiotensin system, below.

**Concomitant diuretics**

ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

**Combination products**

Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.

**Angiotensin-II receptor antagonists**

Azilsartan medoxomil p. 174, candesartan cilexetil p. 175, eprosartan p. 175, irbesartan p. 175, losartan potassium p. 176, olmesartan medoxomil p. 177, telmisartan p. 178, and valsartan p. 179 are angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are less likely to cause the persistent dry cough which can complicate ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure or diabetic nephropathy. Candesartan cilexetil and valsartan are also licensed as adjuncts to ACE inhibitors under specialist supervision, in the management of heart failure when other treatments are unsuitable.

**Renal effects**

Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal effects under Angiotensin-converting enzyme inhibitors, above).

**Renin inhibitor**

Aliskiren is a renin inhibitor that is licensed for the treatment of hypertension.

**Concomitant use of drugs affecting the renin-angiotensin system**

Combination therapy with two drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin-II receptor antagonists, and aliskiren p. 179) is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment, compared to use of a single drug. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor with an angiotensin-II receptor antagonist. There is some evidence that the benefits of combination use of an
ACE inhibitor with candesartan or valsartan may outweigh the risks in selected patients with heart failure for whom other treatments are unsuitable, however, the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended.

For patients currently taking combination therapy, the need for continued combined therapy should be reviewed. If combination therapy is considered essential, it should be carried out under specialist supervision, with close monitoring of blood pressure, renal function, and electrolytes (particularly potassium); monitoring should be considered at the start of treatment, then monthly, and also after any change in dose or during intercurrent illness.

Other drugs used for Hypertension


Clonidine hydrochloride 25 microgram tablets | 112 tablets [PO] £3.15 DT £3.77
Clonidine hydrochloride 50 microgram tablets | 100 tablet [PO] £8.04 DT £8.04

ANTIHYPERTENSIVES, CENTRALLY ACTING

Clonidine hydrochloride

INDICATIONS AND DOSE

Hypertension

Adult: Initially 50–100 micrograms 3 times a day, increase dose every second or third day, usual maximum dose 1.2 mg daily

Prevention of recurrent migraine | Prevention of vascular headache | Menopausal symptoms, particularly flushing and vasomotor conditions

BY MOUTH

Adult: Initially 50 micrograms twice daily for 2 weeks, then increased if necessary to 75 micrograms twice daily

Unlicensed use

Clonidine may also be used for Tourette syndrome and sedation—unlicensed indications.

Contra-indications

Severe bradycardia secondary to second- or third-degree AV block or sick sinus syndrome

Caution

Cerebrovascular disease - constipation - depression - dizziness - dry mouth - fatigue - headache - nausea - postural hypotension - salivary gland pain - sedation - sexual dysfunction - sleep disorders - vomiting

Uncommon

Delusions - hallucination - malaise - paraesthesia - Raynaud’s phenomenon - skin reactions

Rare or very rare

Alopecia - atrophic ventricular block - dry eye - dryness - eye pain - gastrointestinal disorders - integumental pseudo-obstruction - nasal dryness

Frequency not known

Accommodation disorder - arrhythmias - confusion

Pregnancy

May lower fetal heart rate. Avoid oral use unless potential benefit outweighs risk. Avoid using injection.

Breast feeding

Avoid—present in milk.

Renal impairment

Dose adjustments

Use with caution in severe impairment—reduce initial dose and increase gradually.

Treatment cessation

In hypertension, must be withdrawn gradually to avoid severe rebound hypertension.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

Less suitable for prescribing

Clonidine is less suitable for prescribing.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

Clonidine hydrochloride (Non-proprietary)

Clonidine hydrochloride 25 microgram tablets | 112 tablet [PO] £3.15 DT £3.77
Clonidine hydrochloride 50 microgram tablets | 100 tablet [PO] £8.04 DT £8.04

Clonidine hydrochloride 10 microgram per 1 ml Clonidine 50micrograms/5ml oral solution sugar free sugar-free | 100 ml [PO] £66.80 DT £66.80

Methyldopa

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: Initially 250 mg 2–3 times a day, dose should be increased gradually at intervals of at least 2 days; maximum 3 g per day

Elderly: Initially 125 mg twice daily, dose should be increased gradually; maximum 2 g per day

Contra-indications

Acute porphyrias p. 1058 - depression - phaeochromocytoma

Caution

History of depression - history of hepatic impairment

Interactions

Appendix 1: methyldopa

Side-effects


Side-effects, further information

Side-effects are minimised if the daily dose is kept below 1g.

Pregnancy

Not known to be harmful.

Breast feeding

Amount too small to be harmful.

Hepatic impairment

Manufacturer advises avoid in active disease.

Renal impairment

Increased sensitivity to hypotensive and sedative effect.

Dose adjustments

Start with small dose.

Monitoring requirements

Monitor blood counts and liver-function before treatment and at intervals during first 6–12 weeks or if unexplained fever occurs.

www.getintopharma.com
Moxonidine

**INDICATIONS AND DOSE**

**Mild to moderate essential hypertension**

- **By mouth**
  - Adult: 200 micrograms once daily for 3 weeks, dose to be taken in the morning, then increased if necessary to 400 micrograms daily in 1–2 divided doses (max. per dose 400 micrograms), maximum daily dose to be given in 2 divided doses; maximum 600 micrograms per day

- **Contra-indications**
  - Bradycardia, conduction disorders, second- or third-degree AV block, severe heart failure, sick sinus syndrome, sino-atrial block

- **Cautions**
  - First-degree AV block, moderate heart failure, severe coronary artery disease, unstable angina

- **Interactions**
  - Appendix 1: moxonidine

- **Side-effects**
  - Common or very common: Asthenia, diarrhoea, dizziness, drowsiness, dry mouth, dyspepsia, headache, insomnia, nausea, pain, skin reactions, vertigo, vomiting

- **Uncommon**
  - Angioedema, bradycardia, nervousness, oedema, syncope, tinnitus

- **Pregnancy**
  - Manufacturer advises avoid—no information available

- **Breast Feeding**
  - Present in milk—manufacturer advises avoid

- **Renal Impairment**
  - Avoid if eGFR less than 30 mL/minute/1.73 m²

  - Dose Adjustments
    - Max. single dose 200 micrograms and max. daily dose 400 micrograms if eGFR 30–60 mL/minute/1.73 m²

- **Treatment Cessation**
  - Avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>Cautionary and Advisory Labels 3</th>
<th>Moxonidine 200 microgram</th>
<th>Moxonidine 200 microgram tablets</th>
<th>28 tablet (PDT) £5.80 DT + £1.09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxonidine (Non-proprietary)</td>
<td>Moxonidine 200 microgram</td>
<td>Moxonidine 200 microgram tablets</td>
<td>28 tablet (PDT) £5.80 DT + £1.09</td>
</tr>
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**Beta-Adrenoceptor Blocking Drugs**

**Overview**

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are now available and in general they are all equally effective. There are, however, differences between them, which may affect choice in treating particular diseases or individual patients.

Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors. Celiprolol hydrochloride p. 153, pindolol p. 156, acebutolol p. 152, and oxprenolol hydrochloride have intrinsic sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities.

Some beta-blockers are lipid soluble and some are water soluble. Atenolol p. 152, celiprolol hydrochloride, nadolol p. 149, and sotalol hydrochloride p. 108 are the most watersoluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares.

Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are, however, available in modified-release formulations so that administration once daily is adequate for hypertension. For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-blockers, such as atenolol, bisoprolol fumarate p. 153, celiprolol hydrochloride, and nadolol, have an intrinsically longer duration of action and need to be given only once daily.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure.

Labetalol hydrochloride p. 148, celiprolol hydrochloride, carvedilol p. 148, and nebivolol p. 155 are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance.

There is no evidence that these drugs have important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma, or chronic obstructive pulmonary disease (without significant reversible airways obstruction), to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects. Atenolol, bisoprolol fumarate,
metoprolol tartrate p. 154, nebivolol, and (to a lesser extent) acebutolol, have less effect on the beta,(bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardioselective. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers).

Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Hypertension

The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroreceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action.

Beta-blockers are effective for reducing blood pressure but other antihypertensives are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Other antihypertensives are therefore preferred for routine initial treatment of uncomplicated hypertension.

In general, the dose of a beta-blocker does not have to be high.

Beta-blockers can be used to control the pulse rate in patients with phaeochromocytoma. However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis. For this reason phenoxybenzamine hydrochloride p. 181 should always be used together with the beta-blocker.

Angina

By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with angina (see management of stable angina and acute coronary syndromes for further details). As with hypertension there is no good evidence of the superiority of any one drug, although occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause an exacerbation of angina and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease.

Myocardial infarction

For specific comments see management of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction.

Several studies have shown that some beta-blockers can reduce the recurrence rate of myocardial infarction. However, uncontrolled heart failure, hypertension, bradyarrhythmias, and obstructive airways disease render beta-blockers unsuitable in some patients following a myocardial infarction. Atenolol and metoprolol tartrate may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while acebutolol, metoprolol tartrate, propranolol hydrochloride p. 150, and timolol maleate p. 151 have protective value when started in the early convalescent phase. The evidence relating to other beta-blockers is less convincing; some have not been tested in trials of secondary prevention.

Arrhythmias

Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular tachycardias, and are used to control those following myocardial infarction.

Sotalol hydrochloride p. 154 is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, particularly in the peri-operative period. It may also be used in other situations, such as acute myocardial infarction, when sustained beta-blockade might be hazardous.

Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Heart failure

Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. Bisoprolol fumarate p. 153 and carvedilol p. 148 reduce mortality in any grade of stable heart failure; nebivolol p. 155 is licensed for stable mild to moderate heart failure in patients over 70 years. Ideally, treatment should be initiated by those experienced in the management of heart failure.

Thyrotoxicosis

Beta-blockers are used in pre-operative preparation for thyroidectomy. Administration of propranolol hydrochloride p. 150 can reverse clinical symptoms of thyrotoxicosis within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier.

Other uses

Beta-blockers have been used to alleviate some symptoms of anxiety; probably patients with palpitation, tremor, and tachycardia respond best. Beta-blockers are also used in the prophylaxis of migraine. Betaxolol p. 1180, levobunolol hydrochloride p. 1180, and timolol maleate p. 1180 are used topically in glaucoma.

Beta-adrenoceptor blockers (systemic)

- **CONTRA-INDICATIONS**
  - Asthma - cardiogenic shock - hypotension - marked bradycardia - metabolic acidosis - phaeochromocytoma (apart from specific use with alpha-blockers) - Prinzmetal's angina - second-degree AV block - severe peripheral arterial disease - sick sinus syndrome - third-degree AV block - uncontrolled heart failure

  **CONTRA-INDICATIONS, FURTHER INFORMATION**
  - Bronchospasm Beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma, bronchospasm or a history of obstructive airways disease. However, when there is no

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alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

- **CAUTIONS** Diabetes - first-degree AV block - history of obstructive airways disease (introduce cautiously) - myasthenia gravis - portal hypertension (risk of deterioration in liver function) - psoriasis - symptoms of hypoglycaemia may be masked - symptoms of thyrotoxicosis may be masked

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal discomfort - bradycardia - confusion - depression - diarrhoea - dizziness - dry eye (reversible on discontinuation) - dyspnoea - erectile dysfunction - fatigue - headache - heart failure - nausea - paraesthesia - peripheral coldness - peripheral vascular disease - rash (reversible on discontinuation) - sleep disorders - syncope - visual impairment - vomiting
  - **Uncommon** Atrioventricular block - bronchospasm
  - **Rare or very rare** Hallucination

- **SIDE-EFFECTS, FURTHER INFORMATION** With administration by intravenous injection, excessive bradycardia can occur and may be countered with intravenous injection of atropine sulfate.

- **Overdose** Therapeutic overdoses with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. With administration by intravenous injection, excessive bradycardia can occur and may be countered with intravenous injection of atropine sulfate.

- **SIDE-EFFECTS, FURTHER INFORMATION** With administration by intravenous injection, excessive bradycardia can occur and may be countered with intravenous injection of atropine sulfate.

- **MONITORING REQUIREMENTS** Monitor lung function (in patients with a history of obstructive airway disease).

- **TREATMENT CESSATION** Avoid abrupt withdrawal especially in ischaemic heart disease. Sudden cessation of a beta-blocker can cause a rebound worsening of myocardial ischaemia and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped.

**BETA-ADRENOCEPTOR BLOCKERS**

**BETA-ADRENOCEPTOR BLOCKERS**

**Beta-Adrenoceptor Blockers**

**Carvedilol**

15-Jun-2018

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
    - Adult: Initially 12.5 mg once daily for 2 days, then increased to 25 mg once daily; increased if necessary up to 50 mg daily, dose to be increased at intervals of at least 2 weeks and can be given as a single dose or in divided doses

**Labetalol hydrochloride**

01-Aug-2018

- **INDICATIONS AND DOSE**
  - Controlled hypotension in anaesthesia
    - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
    - Adult: (consult product literature or local protocols)
Hypertension

Hypertension of pregnancy

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 20 mg/hour, then increased if necessary to 40 mg/hour after 30 minutes, then increased if necessary to 80 mg/hour after 30 minutes, then increased if necessary to 160 mg/hour after 30 minutes, adjusted according to response; Usual maximum 160 mg/hour
  - **BY MOUTH**
  - Adult: Use dose for hypertension

Hypertensive emergencies

- **BY INTRAVENOUS INJECTION**
  - Adult: 50 mg, to be given over at least 1 minute, then 50 mg every 5 minutes if required until a satisfactory response occurs; maximum 200 mg per course
  - **BY INTRAVENOUS INFUSION**
  - Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 100 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day
  - Elderly: Initially 50 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day
  - **BY INTRAVENOUS INJECTION**
  - Adult: 50 mg, dose to be given over at least 1 minute, then 50 mg after 5 minutes if required; maximum 200 mg per course
  - **BY INTRAVENOUS INFUSION**
  - Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

- **CAUTIONS**  Liver damage
- **INTERACTIONS**  – Appendix 1: beta blockers, non-selective
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Drug fever, ejaculation failure, hyper-sensitivity, urinary disorders
  - **RARE or VERY RARE**  Hepatic disorders, systemic lupus erythematosus (SLE), toxic myopathy, tremor
  - **FREQUENCY NOT KNOWN**  Alopecia, cyanosis, hyperhidrosis, hyperkalaemia, interstitial lung disease, lethargy, muscle cramps, nasal congestion, peripheral oedema, postural hypotension, psychosis, skin reactions, thrombocytopenia
  - **SPECIFIC SIDE-EFFECTS**
    - With intravenous use: Fever, hypoglycaemia masked, thyrotoxicosis masked
    - With oral use: Photosensitivity reaction
  - **PREGNANCY**  The use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester. If labetalol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta-blockade).
  - **PEDIATRICS**
  - **BREAST FEEDING**  Infants should be monitored as there is a risk of possible toxicity due to alpha-blockade (in addition to beta-blockade).

**HEPATIC IMPAIRMENT**  Manufacturer advises caution (risk of slow metabolism).

- **Dose adjustments**  Manufacturer advises consider dose reduction.

**RENAL IMPAIRMENT**

- **Dose adjustments**  Dose reduction may be required.

**MONITORING REQUIREMENTS**

- Liver damage: Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted.

**EFFECT ON LABORATORY TESTS**  Interferes with laboratory tests for catecholamines.

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion, give intermittently in glucose 5% or sodium chloride and glucose. Dilute to a concentration of 1 mg/mL; suggested volume 200 mL; adjust rate with in-line burette. Avoid upright position during and for 3 hours after intravenous administration.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Solution for injection**

- **Labetalol hydrochloride (Non-proprietary)**
  - Labetalol hydrochloride 5 mg per 1 ml Labetalol 100mg/20ml solution for injection ampoules | 5 ampoules £78.05 DT = £77.01

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**  8, 21
- **Labetalol hydrochloride (Non-proprietary)**
  - Labetalol hydrochloride 100 mg Labetalol 100mg tablets | 100 tablets £47.15 DT = £46.15
  - Labetalol hydrochloride 200 mg Labetalol 200mg tablets | 100 tablets £78.05 DT = £77.01
  - **Trandate** (RPH Pharmaceuticals AB)
    - Labetalol hydrochloride 400 mg Labetalol 400mg tablets | 100 tablets £121.12 DT = £115.41
    - Labetalol hydrochloride 50 mg Labetalol 50mg tablets | 100 tablets £13.79 DT = £13.79
    - Labetalol hydrochloride 100 mg Labetalol 100mg tablets | 100 tablets £21.12 DT = £20.41
    - Labetalol hydrochloride 200 mg Labetalol 200mg tablets | 100 tablets £37.41 DT = £36.71

- **Labetalol hydrochloride 400 mg Trandate 400mg tablets | 100 tablets £58.76 DT = £57.16
  - Labetalol hydrochloride 50 mg Trandate 50mg tablets | 100 tablets £11.05 DT = £10.41

**Labetalol hydrochloride 400 mg Trandate 400mg tablets | 100 tablets £58.76 DT = £57.16
  - Labetalol hydrochloride 50 mg Trandate 50mg tablets | 100 tablets £11.05 DT = £10.41

**Nadolol**

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 80 mg once daily, then increased in steps of up to 80 mg every week if required, doses higher than the maximum are rarely necessary; maximum 240 mg per day
  - **Angina**
    - **BY MOUTH**
      - Adult: Initially 40 mg once daily, then increased if necessary up to 160 mg daily, doses should be increased at weekly intervals, maximum dose rarely is used; maximum 240 mg per day
  - **Arrhythmias**
    - **BY MOUTH**
      - Adult: Initially 40 mg once daily, then increased if necessary up to 160 mg once daily, doses should be increased at weekly intervals; reduced to 40 mg daily if bradycardia occurs

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Migraine prophylaxis

- **BY MOUTH**
- Adult: Initially 40 mg once daily, then increased in steps of 40 mg every week, adjusted according to response; maintenance 80–160 mg once daily

Thyrotoxicosis (adjunct)

- **BY MOUTH**
- Adult: 80–160 mg once daily

- **INTERACTIONS** → Appendix 1: beta blockers, non-selective
- **SIDE-EFFECTS** Uncommon Appetite decreased · behaviour abnormal · constipation · cough · dry mouth · dyspepsia · facial swelling · flatulence · hyperhidrosis · nasal congestion · sedation · sexual dysfunction · skin reactions · speech slurred · tinnitus · vision blurred · weight increased
- **Frequency not known** Alopecia · hypoglycaemia

- **BREAST FEEDING** Water soluble beta-blockers such as nadolol are present in breast milk in greater amounts than other beta blockers.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution.

- **RENAL IMPAIRMENT** Dose adjustments: Increase dosage interval if eGFR less than 50 mL/minute/1.73 m².

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution

Tablet

| Cautionary and advisory labels | 8 |
| Corgard (Sandoz) |
| Nadolol 80 mg | Corgard 80mg tablets | 28 tablet | £6.00 | DT = £6.00 |

Pindolol

- **INDICATIONS AND DOSE**

Hypertension

- **BY MOUTH**
- Adult: Initially 5 mg 2–3 times a day, alternatively 15 mg once daily, doses to be increased as required at weekly intervals; maintenance 15–30 mg daily; maximum 45 mg per day

Angina

- **BY MOUTH**
- Adult: 2.5–5 mg up to 3 times a day

- **INTERACTIONS** → Appendix 1: beta blockers, non-selective

- **SIDE-EFFECTS** Agranulocytosis · arrhythmia · arthralgia · constipation · cutaneous lupus erythematosus · diabetes mellitus · dry mouth · dyspepsia · gastrointestinal disorders · glycosuria · hyperglycaemia · hyperhidrosis · hyperpyrexia · hypoglycaemia · hypoglycaemia masked · keratoconjunctivitis · muscle complaints · myasthenia gravis · psychosis · sexual dysfunction · skin reactions · thrombocytopenia · thyrotoxicosis masked · toxic epidermal necrolysis · tremor · vasculitis necrotising · vision blurred

- **RENAL IMPAIRMENT** May adversely affect renal function in severe impairment—manufacturer advises avoid.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Tablet

| Cautionary and advisory labels | 8 |
| Pindolol (non-proprietary) |
| Pindolol 5 mg | Pindolol 5mg tablets | 100 tablet | FSH | £15.00 | DT = £8.22 |

Propranolol hydrochloride

- **INDICATIONS AND DOSE**

Thyrotoxicosis (adjunct)

- **BY MOUTH**
- Adult: 10–40 mg 3–4 times a day

Thyrotoxic crisis

- **BY INTRAVENOUS INJECTION**
- Adult: 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum total dose is 5 mg in anaesthesia; maximum 10 mg per course

Hypertension

- **BY MOUTH**
- Adult: Initially 80 mg twice daily, dose should be increased at weekly intervals as required; maintenance 160–320 mg daily

Prophylaxis of variceal bleeding in portal hypertension

- **BY MOUTH**
- Adult: Initially 40 mg twice daily, then increased to 80 mg twice daily (max. per dose 160 mg twice daily), dose to be adjusted according to heart rate

Phaeochromocytoma (only with an alpha-blocker) in preparation for surgery

- **BY MOUTH**
- Adult: 60 mg daily for 3 days before surgery

Phaeochromocytoma (only with an alpha-blocker) in patients unsuitable for surgery

- **BY MOUTH**
- Adult: 30 mg daily

Angina

- **BY MOUTH**
- Adult: 40 mg once daily, then increased if necessary to 40 mg 3 times a day

Essential tremor

- **BY MOUTH**
- Adult: Initially 40 mg 2–3 times a day; maintenance 120–240 mg daily

Hypertrophic cardiomyopathy · Anxiety tachycardia

- **BY MOUTH**
- Adult: 10–40 mg 3–4 times a day

Anxiety with symptoms such as palpitation, sweating and tremor

- **BY MOUTH**
- Adult: 40 mg once daily, then increased if necessary to 40 mg 3 times a day

Prophylaxis after myocardial infarction

- **BY MOUTH**
- Adult: Initially 40 mg 4 times a day for 2–3 days, then 80 mg twice daily, start treatment 5 to 21 days after infarction

Essential tremor

- **BY MOUTH**
- Adult: Initially 40 mg 2–3 times a day; maintenance 80–160 mg daily

Migraine prophylaxis

- **BY MOUTH**
- Adult: 80–240 mg daily in divided doses

Arrhythmias

- **BY MOUTH**
- Adult: 10–40 mg 3–4 times a day

- **BY INTRAVENOUS INJECTION**
- Adult: 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum 10 mg per course (5 mg in anaesthesia)

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**

Propranolol has been confused with prednisolone; care must be taken to ensure the correct drug is prescribed and dispensed.

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Hypertension

Timolol maleate

- **INDICATIONS AND DOSE**
  - **Hypertension**
  - **By mouth**
  - Adult: Initially 10 mg daily in 1–2 divided doses, then increased if necessary up to 60 mg daily, doses to be increased gradually. Doses above 30 mg daily given in divided doses, usual maintenance 10–30 mg daily; maximum 60 mg per day

- **SIDE-EFFECTS**
  - Rare or very rare: Alopecia, memory loss, mood altered; neuromuscular dysfunction, postural hypotension, psychosis, skin reactions, thrombocytopenia
  - Frequency not known: Hypoglycaemia

- **HEPATIC IMPAIRMENT**
  - Dose adjustments: Reduce oral dose. Manufacturer advises caution; dose reduction may be required.

- **RENAL IMPAIRMENT**
  - Dose adjustments: Manufacturer advises caution; dose reduction may be required.

- **PRESCRIBING AND DISPENSING INFORMATION** Modified-release preparations can be used for once daily administration.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- **Oral solution**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Propranolol hydrochloride (Non-proprietary)**
    - Propranolol hydrochloride 1 mg per 1 ml
    - Propranolol hydrochloride 2 mg per 1 ml
    - Propranolol hydrochloride 4 mg per 1 ml
    - Propranolol hydrochloride 8 mg per 1 ml
    - Propranolol hydrochloride 16 mg per 1 ml
  - **Modified-release capsule**
    - **CAUTIONARY AND ADVISORY LABELS**
      - Bedranol SR
      - Propranolol hydrochloride 80 mg
      - Propranolol hydrochloride 40 mg
      - Propranolol hydrochloride 20 mg
      - Propranolol hydrochloride 10 mg
    - **Tablet**
      - Propranolol hydrochloride 80 mg
      - Propranolol hydrochloride 40 mg
      - Propranolol hydrochloride 20 mg
      - Propranolol hydrochloride 10 mg

Timolol with amiloride and hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate above, amiloride hydrochloride p. 229, hydrochlorothiazide p. 166.

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **By mouth**
    - Adult: 1–2 tablets daily

- **INTERACTIONS**
  - Appendix 1: beta blockers, non-selective; potassium-sparing diuretics, thiazide diuretics

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Timolol maleate

- **INDICATIONS AND DOSE**
  - **Hypertension**
  - **By mouth**
  - Adult: Initially 5 mg twice daily, then increased in steps of 10 mg daily (max. per dose 30 mg twice daily), to be increased every 3–4 days

- **Prophylaxis after myocardial infarction**
  - **By mouth**
  - Adult: Initially 5 mg twice daily for 2 days, then increased if tolerated to 10 mg twice daily

- **Migraine prophylaxis**
  - **By mouth**
  - Adult: 10–20 mg daily in 1–2 divided doses
### Timolol with bendroflumethiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate p. 151, bendroflumethiazide p. 166.

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: 1–2 tablets daily; maximum 4 tablets per day

**INTERACTIONS** → Appendix 1: beta blockers, non-selective - thiazide diuretics

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 8
  - Timolol with bendroflumethiazide (Non-proprietary)
    - Bendroflumethiazide 2.5 mg, Timolol maleate 10 mg
    - Timolol 10mg / Bendroflumethiazide 2.5mg tablets | 30 tablet
  - **Price** £23.75–£63.05

**SIDE-EFFECTS**

- **INTERACTIONS**
- **MEDICATIONS**
- **MEDICALLY IMPORTANT INTERACTIONS**
- **UNLICENSED USE**

### Acebutolol

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 400 mg daily for 2 weeks, alternatively initially 200 mg twice daily for 2 weeks, then increased if necessary to 400 mg twice daily; maximum 1.2 g per day

**Angina**
- **BY MOUTH**
  - Adult: Initially 400 mg daily, alternatively initially 200 mg twice daily; maximum 1.2 g per day

**Arrhythmias**
- **BY MOUTH**
  - Adult: 0.4–1.2 g daily in 2–3 divided doses

**Severe angina**
- **BY MOUTH**
  - Adult: Initially 300 mg 3 times a day; maximum 1.2 g per day

**INTERACTIONS** → Appendix 1: beta blockers, selective

**SIDE-EFFECTS**

- **Common or very common** Gastrointestinal disorder
- **Frequency not known** Cyanosis - hepatic disorders - lupus-like syndrome - nervous system disorder - psychosis - respiratory disorders - sexual dysfunction

**BREAST FEEDING**

Acebutolol and water soluble beta-blockers are present in breast milk in greater amounts than other beta-blockers.

**RENAL IMPAIRMENT**

**Dose adjustments**
- **Halve dose if eGFR 25–50 mL/minute/1.73 m²**; use quarter dose if eGFR less than 25 mL/minute/1.73 m²; do not administer more than once daily.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 8
  - **Sectral** (Sanofi)
    - Acebutolol (as Acebutolol hydrochloride) 400 mg | Sectral 400mg tablets | 28 tablet
  - **Price** £18.62

### Atenolol

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: 25–50 mg daily, higher doses are rarely necessary

**Angina**
- **BY MOUTH**
  - Adult: 100 mg daily in 1–2 divided doses

**Arrhythmias**
- **BY MOUTH**
  - Adult: 50–100 mg daily

**Migraine prophylaxis**
- **BY MOUTH**
  - Adult: 150 micrograms/kg every 12 hours if required, to be given over 20 minutes

**Early intervention within 12 hours of myocardial infarction**
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, to be given at a rate of 1 mg/minute, followed by (by mouth) 50 mg after 15 minutes, then (by mouth) 50 mg after 12 hours, then (by mouth) 100 mg after 12 hours, then (by mouth) 100 mg once daily

**INTERACTIONS** → Appendix 1: beta blockers, selective

**SIDE-EFFECTS**

- **Common or very common** Gastrointestinal disorder
- **Rare or very rare** Alopecia - dry mouth - hepatic disorders - mood altered - postural hypotension - psychosis - skin reactions - thrombocytopenia

**BREAST FEEDING**

Water soluble beta-blockers such as atenolol are present in breast milk in greater amounts than other beta-blockers.

**RENAL IMPAIRMENT**

**Dose adjustments**
- **With oral use**
  - Max. 50 mg daily if eGFR 15–35 mL/minute/1.73 m²; max. 25 mg daily or 50 mg on alternate days if eGFR less than 15 mL/minute/1.73 m².
  - With intravenous use
    - Max. 10 mg on alternate days if eGFR 15–35 mL/minute/1.73 m²; max. 10 mg every 4 days if eGFR less than 15 mL/minute/1.73 m².

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**

Atenolol has been confused with amiodipine; care must be taken to ensure the correct drug is prescribed and dispensed.
DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Tenormin®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Suggested infusion time 20 minutes.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Solution for injection
Tenormin (AstraZeneca UK Ltd)
Atenolol 500 microgram per 1 ml Tenormin 5mg/10ml solution for injection ampoules 10 ampoule £34.45 (Hospital only)

Oral solution
Atenolol (Non-proprietary)
Atenolol 5 mg per 1 ml Atenolol 25mg/5ml oral solution sugar free sugar-free | 300 ml £6.72 DT + £5.59

Tablet
CAUTIONARY AND ADVISORY LABELS B
Atenolol (Non-proprietary)
Atenolol 25 mg Atenolol 25mg tablets | 28 tablet £1.39 DT = £0.57
Atenolol 50 mg Atenolol 50mg tablets | 28 tablet £4.09 DT = £0.63
Atenolol 100 mg Atenolol 100mg tablets | 28 tablet £5.19 DT = £0.62

Interactions with nifedipine
The properties listed below are those particular to the combination only. For the properties of the components please consider, atenolol p. 152, nifedipine p. 162.

INDICATIONS AND DOSE
Hypertension
BY MOUTH
Adult: 1 capsule daily, increased if necessary to 1 capsule twice daily
Elderly: 1 capsule daily

Angina
BY MOUTH
Adult: 1 capsule twice daily

INTERACTIONS → Appendix 1: beta blockers, selective calcium channel blockers

PRESCRIBING AND DISPENSING INFORMATION Only indicated when calcium-channel blocker or beta-blocker alone proves inadequate.

INDICATIONS AND DOSE
Hypertension
BY MOUTH
Adult: 5–10 mg once daily; maximum 20 mg per day

Adjunct in heart failure
BY MOUTH
Adult: Initially 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 1 week, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily; maximum 10 mg per day

CONTRA-INDICATIONS Acute or decompensated heart failure requiring intravenous inotropes · sino-atrial block

CAUTIONS Ensure heart failure not worsening before increasing dose

INTERACTIONS → Appendix 1: beta blockers, selective

SIDE-EFFECTS
– Common or very common Constipation
– Uncommon Muscle cramps · muscle weakness · postural hypotension
– Rare or very rare Allergic rhinitis · alopecia · auditory disorder · conjunctivitis · flushing · hepatitis · hypersensitivity · pruritus

HEPATIC IMPAIRMENT
Dose adjustments Max. 10 mg daily in severe impairment.

RENAL IMPAIRMENT
Dose adjustments Reduce dose if eGFR less than 20 mL/minute/1.73 m² (max. 10 mg daily).

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS B
Bisoprolol fumarate (Non-proprietary)
Bisoprolol fumarate 1.25 mg Bisoprolol 1.25mg tablets | 28 tablet £7.43 DT = £0.76
Bisoprolol fumarate 2.5 mg Bisoprolol 2.5mg tablets | 28 tablet £4.39 DT = £0.69
Bisoprolol fumarate 3.75 mg Bisoprolol 3.75mg tablets | 28 tablet £6.50 DT = £0.93
Bisoprolol fumarate 5 mg Bisoprolol 5mg tablets | 28 tablet £5.89 DT = £0.68
Bisoprolol fumarate 7.5 mg Bisoprolol 7.5mg tablets | 28 tablet £5.89 DT = £0.97
Bisoprolol fumarate 10 mg Bisoprolol 10mg tablets | 28 tablet £6.86 DT = £0.75
Cardicor (Merck Serono Ltd)
Bisoprolol fumarate 1.25 mg Cardicor 1.25mg tablets | 28 tablet £2.35 DT = £0.76
Bisoprolol fumarate 2.5 mg Cardicor 2.5mg tablets | 28 tablet £2.35 DT = £0.63
Bisoprolol fumarate 3.75 mg Cardicor 3.75mg tablets | 28 tablet £4.90 DT = £0.93
Bisoprolol fumarate 5 mg Cardicor 5mg tablets | 28 tablet £5.90 DT = £0.68
Bisoprolol fumarate 7.5 mg Cardicor 7.5mg tablets | 28 tablet £5.90 DT = £0.97
Bisoprolol fumarate 10 mg Cardicor 10mg tablets | 28 tablet £5.90 DT = £0.75

INDICATIONS AND DOSE
Mild to moderate hypertension
BY MOUTH
Adult: 200 mg once daily, dose to be taken in the morning, then increased if necessary to 400 mg once daily

INTERACTIONS → Appendix 1: beta blockers, selective

SIDE-EFFECTS
Alveolitis allergic · dermatitis psoriasiform · drowsiness · hypoglycaemia masked · palpitations · thyrotoxicosis masked · tremor

BREAST FEEDING Manufacturers advise avoidance.

HEPATIC IMPAIRMENT
Dose adjustments Consider dose reduction.

RENAL IMPAIRMENT Avoid if eGFR less than 15 mL/minute/1.73 m².
Dose adjustments Reduce dose by half if eGFR 15–40 mL/minute/1.73 m².

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Co-tenidone

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: 50/12.5 mg daily, alternatively increased if necessary to 100/25 mg daily, doses higher than 50 mg atenolol rarely necessary

**DOSE EQUIVALENCE AND CONVERSION**

- A mixture of atenolol and chlortalidone in mass proportions corresponding to 4 parts of atenolol and 1 part chlortalidone.

**INTERACTIONS**

- Appendix 1: beta blockers, selective - thiazide diuretics

**SIDE-EFFECTS**

- Common or very common - Gastrointestinal disorder - glucose tolerance impaired
- Rare or very rare - Alopecia - dry mouth - hepatic disorders - mood altered - neutropenia - psychosis - skin reactions
- Frequency not known - Lupus-like syndrome
- **PREGNANCY** Avoid. Diuretics not used to treat hypertension in pregnancy.
- **BREAST FEEDING** Atenolol present in milk in greater amounts than some other beta-blockers. Possible toxicity due to beta-blockade—monitor infant. Large doses of chlortalidone may suppress lactation.
- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m²—consider alternative treatment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**SPECIAL OR EQUIVALENTS**

- **Tablet**
  - Celiprolol hydrochloride 200 mg Celiprolol 200 mg tablets | 28 tablet (Pfizer) £4.81 DT + £6.9
  - Celiprolol hydrochloride 400 mg Celiprolol 400 mg tablets | 28 tablet (Pfizer) £10.20 DT + £10.78
  - Co-tenidone (Sanofi)
  - Celiprolol hydrochloride 200 mg Celiprolot 200 mg tablets | 28 tablet (Pfizer) £11.83 DT + £6.56
  - Celiprolol hydrochloride 400 mg Celiprolot 400 mg tablets | 28 tablet (Pfizer) £39.65 DT + £10.78

Esmolol hydrochloride

**INDICATIONS AND DOSE**

Short-term treatment of supraventricular arrhythmias (including atrial fibrillation, atrial flutter, sinus tachycardia) / Tachycardia and hypertension in peri-operative period

- **BY INTRAVENOUS INFUSION**
  - Adult: 50–200 micrograms/kg/minute, consult product literature for details of dose titration and doses during peri-operative period

**INTERACTIONS**

- Appendix 1: beta blockers, selective

**SIDE-EFFECTS**

- Common or very common - Anxiety - appetite decreased - concentration impaired - drowsiness - hyperhidrosis
- Rare or very rare - Cardiac arrest - extravasation necrosis - thrombophlebitis
- Frequency not known - Angioedema - coronary vasospasm - hyperkalaemia - metabolic acidosis
- **BREAST FEEDING** Manufacturer advises avoidance.
- **RENAL IMPAIRMENT** Manufacturer advises caution.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Esmolol hydrochloride (Non-proprietary)
  - Esmolol hydrochloride 10 mg per 1 ml Esmolol hydrochloride 100mg/10ml solution for injection vials | 5 vial (Pfizer) £38.95 (Hospital only)
  - Esmolol 100 mg/10 ml solution for injection vials | 10 vial (Pfizer) £100.00 (Hospital only)
  - Esmolol hydrochloride 100 mg per 1 ml Brevibloc Premixed 100 mg/10 ml solution for injection vials | 5 vial (Pfizer)

**Solution for infusion**

- Brevibloc (Baxter Healthcare Ltd)
  - Esmolol hydrochloride 10 mg per 1 ml Brevibloc Premixed 2.5 g/250 ml infusion bags | 1 bag (Pfizer) £89.69

**Metoprol tartrate**

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses, high doses are rarely required; maximum 400 mg per day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 200 mg once daily

**Angina**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 50–100 mg 2–3 times a day
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 200–400 mg daily

**Arrhythmias**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg daily in divided doses
- **BY INTRAVENOUS INJECTION**
  - Adult: Up to 5 mg, dose to be given at a rate of 1–2 mg/minute, then up to 5 mg after 5 minutes if required, total dose of 10–15 mg
Hypertension

Migraine prophylaxis
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 100–200 mg daily in divided doses
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200 mg daily

Hyperthyroidism (adjunct)
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 50 mg 4 times a day

Early intervention within 12 hours of infarction
- **INITIALLY BY INTRAVENOUS INJECTION**
- Adult: Initially 2–4 mg, given at induction or to control arrhythmias developing during anaesthesia, then 2 mg, repeated if necessary; maximum 10 mg per course

INTERACTIONS → Appendix 1: beta blockers, selective

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- **Common or very common** Constriction, palpitations, postural disorders
- **Uncommon** Chest pain, drowsiness, dystrophic skin lesion, hyperhidrosis, muscle cramps, oedema, skin reactions, weight increased
- **Rare or very rare** Alopecia, arrhythmia, conjunctivitis, dry mouth, eye irritation, gangrene, hepatitis, rhinitis, sexual dysfunction, thrombocytopenia

SPECIFIC SIDE-EFFECTS
- **Uncommon**
  - With intravenous use: Cardiogenic shock, concentration impaired
  - Rare or very rare
    - With intravenous use: Anxiety, arthralgia, atrioventricular block exacerbated, memory loss, photosensitivity reaction, taste altered, tinnitus
    - With oral use: Alertness decreased, arthritis, auditory disorder, personality disorder
    - **Frequency unknown**
      - With oral use: Peyronie’s disease, retroperitoneal fibrosis

HEPATIC IMPAIRMENT

Dose adjustments: Reduce dose in severe impairment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet
- **CAUTIONARY AND ADVISORY LABELS**
- Nebivolol (Non-proprietary)
  - Nebivolol (as Nebivolol hydrochloride) 2.5 mg Nebivolol 2.5 mg tablets | 28 tablet (PO) £6.84 DT + £11.70
  - Nebivolol (as Nebivolol hydrochloride) 5 mg Nebivolol 5 mg tablets | 28 tablet (PO) £9.23 DT + £4.37
  - Nebivolol (as Nebivolol hydrochloride) 10 mg Nebivolol 10 mg tablets | 28 tablet (PO) £25.88 DT + £25.88
  - Nebilet (A. Menarini Farmaceutica Internazionale SRL) Nebivolol (as Nebivolol hydrochloride) 5 mg Nebilet 5 mg tablets | 28 tablet (PO) £9.23 DT + £4.37

CALCIUM-CHANNEL BLOCKERS

Calcium-channel blockers

Overview

Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important differences between verapamil hydrochloride p. 164, diltiazem hydrochloride p. 157, and the dihydropyridine calcium-channel blockers (amlodipine p. 156, felodipine p. 160, lercanidipine hydrochloride p. 161, nicardipine hydrochloride p. 161, nifedipine p. 162, and nimodipine p. 115). Calcium channel blockers, with the exception of amloidipine, should be avoided in heart failure as they can further depress cardiac function and exacerbate symptoms. For further guidance on the management of heart failure, see Chronic heart failure p. 191. With the exception of amloidipine, they can also increase mortality after myocardial infarction in patients with left ventricular dysfunction and pulmonary congestion.

Verapamil hydrochloride is used for the treatment of angina, hypertension, and arrhythmias. It is a highly negatively inotropic calcium channel–blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers. Constipation is the most common side-effect.

Nebivolol

- **INDICATIONS AND DOSE**
  - **Essential hypertension**
    - **BY MOUTH**
      - Adult: 5 mg daily
      - Elderly: Initially 2.5 mg daily, then increased if necessary to 5 mg daily
  - **Hypertension in patient with renal impairment**
    - **BY MOUTH**
      - Adult: Initially 2.5 mg once daily, then increased if necessary to 5 mg once daily
  - **Adjunct in stable mild to moderate heart failure**
    - **BY MOUTH**
      - Adult 70 years and over: Initially 1.25 mg once daily for 1–2 weeks, then increased if tolerated to 2.5 mg once daily for 1–2 weeks, then increased if tolerated to 5 mg once daily for 1–2 weeks, then increased if tolerated to 10 mg once daily

- **CONTRA-INDICATIONS**
  - Acute or decompensated heart failure requiring intravenous inotropes

- **INTERACTIONS** → Appendix 1: beta blockers, selective

- **SIDE-EFFECTS**
  - **Common or very common** Constipation, palpitations, postural hypertension
  - **Uncommon** Dyspepsia, flatulence, skin reactions

- **BREAST FEEDING**
  - Manufacturers advise avoidance.

- **HEPATIC IMPAIRMENT**
  - No information available—manufacturers advise avoidance.

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid in heart failure if serum creatinine greater than 250 micromol/litre.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Nebivolol</th>
<th>Metoprolol</th>
<th>Betaxolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol (as Nebivolol hydrochloride) 2.5 mg Nebivolol 2.5 mg tablets</td>
<td>28 tablet (PO) £6.23 DT + £1.02</td>
<td>56 tablet (PO) £1.56–£1.46</td>
</tr>
<tr>
<td>Nebivolol (as Nebivolol hydrochloride) 5 mg Nebivolol 5 mg tablets</td>
<td>28 tablet (PO) £9.23 DT + £4.37</td>
<td></td>
</tr>
<tr>
<td>Nebivolol (as Nebivolol hydrochloride) 10 mg Nebivolol 10 mg tablets</td>
<td>28 tablet (PO) £25.88 DT + £25.88</td>
<td></td>
</tr>
<tr>
<td>Nebilet (A. Menarini Farmaceutica Internazionale SRL) Nebivolol (as Nebivolol hydrochloride) 5 mg Nebilet 5 mg tablets</td>
<td>28 tablet (PO) £9.23 DT + £4.37</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metoprolol tartrate</th>
<th>Dose for hypertension</th>
<th>Solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol tartrate 50 mg</td>
<td>Metoprol 50 mg tablets</td>
<td>28 tablet (PO) £6.23 DT + £1.02</td>
</tr>
<tr>
<td>Metoprolol tartrate 100 mg</td>
<td>Metoprol 100 mg tablets</td>
<td>28 tablet (PO) £6.47 DT + £1.17</td>
</tr>
<tr>
<td>Betaxolol (Astrazeneca UK Ltd)</td>
<td>Metoprolol tartrate 1 mg per 1 ml</td>
<td>Betaxolol IV, 5 mg/5 ml solution for injection ampoules</td>
</tr>
</tbody>
</table>

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Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil hydrochloride, and unlike verapamil hydrochloride has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work.

Nifedipine hydrochloride has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. Amlodipine and felodipine also resemble nifedipine and nicardipine hydrochloride in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure. They have a longer duration of action and can be given once daily. Nifedipine, nicardipine hydrochloride, amlodipine, and felodipine are used for the treatment of angina or hypertension. All are valuable in forms of angina associated with vasodilatation such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

Intravenous nicardipine hydrochloride is licensed for the treatment of acute life-threatening hypertension, for example in the event of malignant arterial hypertension or hypertensive encephalopathy; aortic dissection, when a short-acting beta-blocker is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective; severe pre-eclampsia, when other intravenous anti-hypertensives are not recommended or are contra-indicated; and for treatment of postoperative hypertension.

Lacidipine and lercanidipine hydrochloride have similar effects to those of nifedipine and nicardipine hydrochloride; they are indicated for hypertension only.

Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

Diltiazem hydrochloride is effective in most forms of angina; the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil hydrochloride and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.

Unstable angina
Calcium-channel blockers do not reduce the risk of myocardial infarction in unstable angina. The use of diltiazem hydrochloride or verapamil hydrochloride should be reserved for patients resistant to treatment with beta-blockers.

Calcium-channel blockers

**DRUG ACTION**
Calcium-channel blockers (less correctly called ‘calcium-antagonists’) interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

**SIDE-EFFECTS**
- Common or very common Dizziness · flushing · headache · nausea · palpitations · peripheral oedema · rash · tachycardia · vomiting
- Uncommon Gingival hyperplasia

**INTERACTIONS**
- Appendix 1: calcium channel blockers

**CONTRA-INDICATIONS**
- Cardiogenic shock · significant aortic stenosis · unstable angina

**TREATMENT CESSATION**
- There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of myocardial ischaemia.

**INDICATIONS AND DOSE**

### Prophylaxis of angina
- **BY MOUTH**
  - Adult: Initially 5 mg once daily; maximum 10 mg per day

### Hypertension
- **BY MOUTH**
  - Adult: Initially 5 mg once daily; maximum 10 mg per day

### DOSE EQUIVALENCE AND CONVERSION
- Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable.

**IMPORTANT SAFETY INFORMATION**
**SAFE PRACTICE**
Amlodipine has been confused with nimodipine and atenolol; care must be taken to ensure the correct drug is prescribed and dispensed.

**CONTRA-INDICATIONS**
- Cardiogenic shock · significant aortic stenosis · unstable angina

**INTERACTIONS**
- Appendix 1: calcium channel blockers

**SIDE-EFFECTS**
- Common or very common Asthenia · constipation · diarrhoea · drowsiness · dyspnoea · gastrointestinal discomfort · gastrointestinal disorders · joint disorders · muscle complaints · oedema · vision disorders
- Uncommon Alopecia · anxiety · arrhythmias · chest pain · cough · depression · dry mouth · erectile dysfunction · gynaecomastia · hyperhidrosis · hypertension · insomnia · malaise · mood altered · pain · rhinitis · sensation abnormal · skin reactions · syncope · taste altered · tinnitus · tremor · urinary disorders · weight changes
- Rare or very rare Angioedema · confusion · hepatic disorders · hyperglycaemia · hypersensitivity · leucopenia · muscle tone increased · myocardial infarction · pancreatitis · peripheral neuropathy · photosensitivity reaction · Stevens-Johnson syndrome · thrombocytopenia · vasculitis
- Frequency not known Extrapyramidal symptoms · pulmonary oedema

**PREGNANCY**
- No information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension.

**CREST FEEDING**
- Manufacturer advises avoid—no information available.
**Hypertension**

- **INDICATIONS AND DOSE**
  - Hypertension in patients stabilised on the individual components in the same proportions
    - **BY MOUTH**
    - Adult: (consult product literature)
  - **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists - calcium channel blockers

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

### Diltiazem hydrochloride

- **INDICATIONS AND DOSE**
  - **Prophylaxis and treatment of angina**
    - **BY MOUTH**
    - Adult: Initially 60 mg 3 times a day, adjusted according to response; maximum 360 mg per day
    - Elderly: Initially 60 mg twice daily, adjusted according to response; maximum 360 mg per day
  - **Chronic anal fissure**
    - **BY RECTUM USING CREAM, OR BY RECTUM USING OINTMENT**
    - Adult: Apply twice daily until pain stops. Max. duration of use 8 weeks, apply to the anal canal, using 2% topical preparation
    - **BY MOUTH**
    - Adult: 60 mg twice daily until pain stops. Max. duration of use 8 weeks

### Clevidipine

- **INDICATIONS AND DOSE**
  - Hypertension in the peri-operative setting (specialist use only)
    - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 2 mg/hour, dose may be doubled every 90 seconds as necessary; usual dose 4–6 mg/hour (max. per dose 32 mg/hour); maximum 500 mg per day

### Amlodipine with valsartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, amlodipine p. 156, valsartan p. 179.

- **INDICATIONS AND DOSE**
  - Hypertension in patients stabilised on the individual components in the same proportions
    - **BY MOUTH**
    - Adult: (consult product literature)

- **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists - calcium channel blockers

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

### Diltiazem hydrochloride

- **INDICATIONS AND DOSE**
  - **Prophylaxis and treatment of angina**
    - **BY MOUTH**
    - Adult: Initially 60 mg 3 times a day, adjusted according to response; maximum 360 mg per day
    - Elderly: Initially 60 mg twice daily, adjusted according to response; maximum 360 mg per day
  - **Chronic anal fissure**
    - **BY RECTUM USING CREAM, OR BY RECTUM USING OINTMENT**
    - Adult: Apply twice daily until pain stops. Max. duration of use 8 weeks, apply to the anal canal, using 2% topical preparation
    - **BY MOUTH**
    - Adult: 60 mg twice daily until pain stops. Max. duration of use 8 weeks

### Clevidipine

- **INDICATIONS AND DOSE**
  - Hypertension in the peri-operative setting (specialist use only)
    - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 2 mg/hour, dose may be doubled every 90 seconds as necessary; usual dose 4–6 mg/hour (max. per dose 32 mg/hour); maximum 500 mg per day

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ADIZEM-XL®

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 240 mg once daily, increased if necessary to 300 mg once daily
Elderly: Initially 120 mg once daily, increased if necessary to 300 mg once daily

DILZEM® SR

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily
Elderly: Initially 60 mg twice daily; increased if necessary to 90 mg twice daily

DILZEM® XL

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 180 mg once daily; increased if necessary to 360 mg once daily
Elderly: Initially 120 mg once daily; increased if necessary to 360 mg once daily

SLOZEM®

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily
Elderly: Initially 60 mg twice daily; increased if necessary to 180 mg twice daily

TILDIELM RETARD®

Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 90–120 mg twice daily; increased if necessary to 360 mg daily in divided doses
Elderly: Initially 120 mg once daily; increased if necessary to 120 mg twice daily

Angina
▶ BY MOUTH
Adult: Initially 90–120 mg twice daily; increased if necessary to 480 mg daily in divided doses
Elderly: Up to 120 mg twice daily, dose form not appropriate for initial dose titration

TILDIELM® LA

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 200 mg once daily, to be taken with or before food, increased if necessary to 300–400 mg once daily; maximum 500 mg per day
Elderly: Initially 200 mg once daily, increased if necessary to 300 mg once daily

VIAZEM® XL

Angina | Mild to moderate hypertension
▶ BY MOUTH
Adult: Initially 180 mg once daily, adjusted according to response to 240 mg once daily; maximum 360 mg per day
Elderly: Initially 120 mg once daily, adjusted according to response

ZEMTARO®

Angina
▶ BY MOUTH
Adult: 180–300 mg once daily, increased if necessary to 480 mg once daily
Elderly: Initially 120 mg once daily, increased if necessary to 480 mg once daily

Mild to moderate hypertension
▶ BY MOUTH
Adult: 180–300 mg once daily, increased if necessary to 360 mg once daily
Elderly: Initially 120 mg once daily, increased if necessary to 360 mg once daily

UNLICENSED USE (EXC) Diltiazem is used for the treatment of chronic anal fissures, but it is not licensed for this indication.

CONTRA-INDICATIONS
With systemic use Acute porphyrias p. 1058. Left ventricular failure with pulmonary congestion - second- or third-degree AV block (unless pacemaker fitted) - severe bradycardia - sick sinus syndrome

CONTRA-INDICATIONS, FURTHER INFORMATION
Systemic absorption following rectal use is unknown, therefore consider the possibility of contra-indications listed for systemic use.

CAUTIONS
With systemic use Bradycardia (avoid if severe) - first degree AV block - heart failure - prolonged PR interval - significantly impaired left ventricular function

CAUTIONS, FURTHER INFORMATION Systemic absorption following rectal use is unknown, therefore consider the possibility of cautions listed for systemic use.

INTERACTIONS → Appendix 1: calcium channel blockers

SIDE-EFFECTS
Common or very common Cardiac conduction disorders - constipation - gastrointestinal discomfort - malaise - skin reactions

Uncommon Arrhythmias - diarrhoea - insomnia - nervousness - postural hypotension

Rare or very rare Dry mouth

Frequency not known Angioedema - cardiac arrest - congestive heart failure - depression - extrapyramidal symptoms - fever - gynaecomastia - hepatitis - hyperglycaemia - hyperhidrosis - mood altered - photosensitivity reaction - severe cutaneous adverse reactions (SCARs) - thrombocytopenia - vasculitis

SIDE-EFFECTS, FURTHER INFORMATION Systemic absorption following rectal use is unknown, therefore consider the possibility of side-effects listed for oral use.

OVERDOSE With oral use In overdose, diltiazem has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.

PREGNANCY With systemic use Avoid.

BREAST FEEDING With systemic use Significant amount present in milk—no evidence of harm but avoid unless no safer alternative.
RENAL IMPAIRMENT

Hypertension

For treatment of angina, dose form not appropriate for initial dose titration; up to 120 mg twice a day may be required. ADIZEM-XL® Dose for angina and mild to moderate hypertension—initially 120 mg once daily. DILZEM® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily. ZEMTARD® Dose for angina and mild to moderate hypertension—initially 120 mg once daily. DILCARDIA® SR Dose for angina and mild to moderate hypertension—initially 60 mg twice a day; maximum 90 mg twice a day. ANGITIL® XL Dose form not appropriate for initial dose titration. SLOZEM® Dose for angina and mild to moderate hypertension—initially 120 mg once daily. TILDIE® LA Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily. VIAZEM® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

RENAL IMPAIRMENT

Dose adjustments • With systemic use Start with smaller dose. TILDIE® RETARD® Dose for mild to moderate hypertension—initially 120 mg once a day; increased if necessary to 120 mg twice a day.

For treatment of angina, dose form not appropriate for initial titration; up to 120 mg twice a day may be required.

ADIZEM-XL® Dose for angina and mild to moderate hypertension—initially 120 mg once daily. DILZEM® XL Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily. VIAZEM® XL Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

PRESCRIBING AND DISPENSING INFORMATION

• With systemic use The standard formulations containing 60 mg dilatiazem hydrochloride are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation ‘modified-release’, their duration of action corresponds to that of tablets requiring administration more frequently. Different versions of modified-release preparations containing more than 60 mg dilatiazem hydrochloride may not have the same clinical effect. To avoid confusion between these different formulations of dilatiazem, prescribers should specify the brand to be dispensed.

PATIENT AND CARER ADVICE

TILDIE® RETARD® Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

Diltiazem hydrochloride (Non-proprietary)

Diltiazem hydrochloride 60 mg Diltiazem 60mg modified-release tablets | 84 tablet (P) £43.46 DT + £42.82 | 100 tablet (P) £50.86 + £51.74

Retailazem (Kent Pharmaceuticals Ltd)

Diltiazem hydrochloride 60 mg Retailazem 60 modified-release tablets | 84 tablet (P) £7.43 DT + £42.82

Tildiem (Sanofi)

Diltiazem hydrochloride 60 mg Tildiem 60mg modified-release tablets | 90 tablet (P) £7.96

Tildiem Retard (Sanofi)

Diltiazem hydrochloride 90 mg Tildiem Retard 90mg tablets | 56 tablet (P) £7.27 DT + £7.27

Diltiazem hydrochloride 120 mg Tildiem Retard 120mg tablets | 56 tablet (P) £7.15 DT + £7.15

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 25

Adizem-SR (Napp Pharmaceuticals Ltd)

Diltiazem hydrochloride 90 mg Adizem-SR 90mg capsules | 56 capsule (P) £8.50 DT + £8.50

Diltiazem hydrochloride 120 mg Adizem-SR 120mg capsules | 56 capsule (P) £9.45 DT + £9.45

Diltiazem hydrochloride 180 mg Adizem-SR 180mg capsules | 56 capsule (P) £14.15 DT + £14.15

Adizem-XL (Napp Pharmaceuticals Ltd)

Diltiazem hydrochloride 120 mg Adizem-XL 120mg capsules | 28 capsule (P) £9.14 DT + £9.14

Diltiazem hydrochloride 180 mg Adizem-XL 180mg capsules | 28 capsule (P) £10.37 DT + £10.37

Diltiazem hydrochloride 200 mg Adizem-XL 200mg capsules | 28 capsule (P) £6.30 DT + £6.29

Diltiazem hydrochloride 240 mg Adizem-XL 240mg capsules | 28 capsule (P) £11.52 DT + £11.52

Diltiazem hydrochloride 300 mg Adizem-XL 300mg capsules | 28 capsule (P) £9.14 DT + £9.01

ANGITIL SR (Ethypharm UK Ltd)

Diltiazem hydrochloride 90 mg Angitil SR 90 capsules | 56 capsule (P) £7.03 DT + £8.50

Diltiazem hydrochloride 120 mg Angitil SR 120 capsules | 56 capsule (P) £6.91 DT + £9.45

Diltiazem hydrochloride 180 mg Angitil SR 180 capsules | 56 capsule (P) £13.27 DT + £14.15

ANGITIL XL (Ethypharm UK Ltd)

Diltiazem hydrochloride 240 mg Angitil XL 240 capsules | 28 capsule (P) £7.94 DT + £11.52

Diltiazem hydrochloride 300 mg Angitil XL 300 capsules | 28 capsule (P) £6.98 DT + £9.01

Dilocardia SR (Mylan)

Diltiazem hydrochloride 90 mg Dilocardia SR 90mg capsules | 56 capsule (P) £3.61 DT + £8.50

Diltiazem hydrochloride 120 mg Dilocardia SR 120mg capsules | 56 capsule (P) £10.69 DT + £9.45

Dilzem XL (Teva UK Ltd)

Diltiazem hydrochloride 120 mg Dilzem XL 120 capsules | 28 capsule (P) £7.78 DT + £9.14

Diltiazem hydrochloride 180 mg Dilzem XL 180 capsules | 28 capsule (P) £11.55 DT + £10.37

Diltiazem hydrochloride 240 mg Dilzem XL 240 capsules | 28 capsule (P) £11.03 DT + £11.52

SLOZEM (Merck Serono Ltd)

Diltiazem hydrochloride 120 mg Slozem 120mg capsules | 28 capsule (P) £7.00 DT + £9.14

Diltiazem hydrochloride 180 mg Slozem 180mg capsules | 28 capsule (P) £7.80 DT + £10.37

Diltiazem hydrochloride 240 mg Slozem 240mg capsules | 28 capsule (P) £8.20 DT + £11.52

Diltiazem hydrochloride 300 mg Slozem 300mg capsules | 28 capsule (P) £8.50 DT + £9.01

www.getintopharma.com
Felodipine

**DRUG ACTION** Felodipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Prophylaxis of angina**

- **BY MOUTH**
  - Adult: Initially 5 mg once daily; increased if necessary to 10 mg once daily, to be taken in the morning
  - Elderly: Initially 2.5 mg once daily; increased if necessary to 10 mg once daily, to be taken in the morning

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 5 mg once daily; usual maintenance 5–10 mg once daily, to be taken in the morning, doses above 20 mg rarely needed
  - Elderly: Initially 2.5 mg daily; usual maintenance 5–10 mg once daily, to be taken in the morning, doses above 20 mg rarely needed

**SIDE-EFFECTS**

- **Uncommon** Abdominal pain, fatigue, paresthesia, skin reactions
- **Rare or very rare** Arthralgia, gingivitis, hypersensitivity vasculitis, myalgia, photosensitivity reaction, sexual dysfunction, syncope, urinary frequency increased

**PREGNANCY** Avoid; toxicity in animal studies; may inhibit labour.

**BREAST FEEDING** Present in milk but amount probably too small to be harmful.

**HEPATIC IMPAIRMENT** Dose adjustments Manufacturer advises consider dose reduction.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Modified-release tablet**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dosage Form</th>
<th>BNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiolan XL</td>
<td>2.5 mg</td>
<td>25</td>
</tr>
</tbody>
</table>

**FACED tokens**

- **Cardiovascular system**
- **Blood pressure conditions**
- **Lacidipine**

**Lacidipine**

**DRUG ACTION** Lacidipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 2 mg daily; increased if necessary to 4 mg daily, then increased if necessary to 6 mg daily, dose increases should occur at intervals of 3–4 weeks, to be taken preferably in the morning

**SIDE-EFFECTS**

- **Uncommon** Abdominal pain, fatigue, paresthesia, skin reactions
- **Rare** Azoospermia, arthralgia, asymptomatic asymptomatic, cyanosis, epistaxis, gingivitis, hypotension, hypothyroidism, increased urination, periorbital oedema, sexual dysfunction, syncope, urinary frequency increased

**CONTRA-INDICATIONS** Acute porphyrias p. 1058, aortic stenosis - avoid within 1 month of myocardial infarction, cardiogenic shock - unstable angina

**CAUTIONS** Cardiac conduction abnormalities - poor cardiac reserve
Hypertension 161

Nicardipine hydrochloride

**DRUG ACTION** Nicardipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

Prophylaxis of angina

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20 mg 3 times a day, then increased to 30 mg 3 times a day, dose increased after at least 3 days; usual dose 60–120 mg daily

Mild to moderate hypertension

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20 mg 3 times a day, then increased to 30 mg 3 times a day, dose increased after at least 3 days; usual dose 60–120 mg daily

Life-threatening hypertension (specialist use only) | Postoperative hypertension (specialist use only)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 3–5 mg/hour for 15 minutes, increased in steps of 0.5–1 mg every 15 minutes, adjusted according to response, maximum rate 15 mg/hour, reduce dose gradually when target blood pressure achieved; maintenance 2–4 mg/hour
  - Elderly: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, maximum rate 15 mg/hour

Life-threatening hypertension in patients with hepatic or renal impairment (specialist use only) | Postoperative hypertension in patients with hepatic or renal impairment (specialist use only)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, maximum rate 15 mg/hour

Acute life-threatening hypertension in pregnancy (specialist use only)

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Initially 1–5 mg/hour, then adjusted in steps of 500 micrograms/hour after 30 minutes, adjusted according to response, usual maximum rate 4 mg/hour in treatment of pre-eclampsia (maximum rate 15 mg/hour)

**CONTRA-INDICATIONS**

- General contra-indications
  - Acute porphyrias p. 1058
  - Cardiogenic shock
  - Significant or advanced aortic stenosis
  - Unstable or acute attacks of angina

Specific contra-indications

- With intravenous use: avoid within 8 days of myocardial infarction or compensatory hypertension
- With oral use: avoid within 1 month of myocardial infarction

**CAUTIONS**

- Congestive heart failure: elderly
- Pulmonary oedema
- Significantly impaired left ventricular function: stroke
- Withdraw if ischaemic pain occurs or existing pain worsens within 30 minutes of initiating treatment or increasing dose

**SPECIFIC CAUTIONS**

- With intravenous use: Elevated intracranial pressure

**INTERACTIONS**

- Appendix 1: calcium channel blockers
162 Blood pressure conditions

Nifedipine

**INDICATIONS AND DOSE**

**Raynaud’s syndrome**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 5 mg 3 times a day, then adjusted according to response to 20 mg 3 times a day

**Angina prophylaxis (not recommended)**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 5 mg 3 times a day, then adjusted according to response to 20 mg 3 times a day

**Postponement of premature labour**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20 mg, followed by 10–20 mg 3–4 times a day, adjusted according to uterine activity

**Hiccups in palliative care**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 10 mg 3 times a day

**Chronic anal fissure**

- **BY RECTUM USING OINTMENT**
  - Adult: Apply 2–3 times a day until pain stops. Max. duration of use 8 weeks, apply to anal canal, using 0.2%–0.5% topical preparation
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: 20 mg twice daily until pain stops. Max. duration of use 8 weeks

**ADALAT RETARD®**

**Hypertension | Angina prophylaxis**

- **BY MOUTH**
  - Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

**ADALAT® LA**

**Hypertension**

- **BY MOUTH**
  - Adult: 20–30 mg once daily, increased if necessary up to 90 mg once daily

**Angina prophylaxis**

- **BY MOUTH**
  - Adult: 30 mg once daily, increased if necessary up to 90 mg once daily

**ADIPINE® MR**

**Hypertension | Angina prophylaxis**

- **BY MOUTH**
  - Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

**ADIPINE® XL**

**Hypertension**

- **BY MOUTH**
  - Adult: 30 mg daily, increased if necessary up to 90 mg daily

**CORACTEN® SR**

**Hypertension | Angina prophylaxis**

- **BY MOUTH**
  - Adult: Initially 10 mg twice daily, increased if necessary up to 40 mg twice daily

**CORACTEN® XL**

**Hypertension | Angina prophylaxis**

- **BY MOUTH**
  - Adult: Initially 30 mg daily, increased if necessary up to 90 mg daily

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Hypotension
- Frequency not known Pulmonary oedema, thrombocytopenia

**SPECIFIC SIDE-EFFECTS**

- With intravenous use: Atrioventricular block, erythema, hepatic disorders, ischaemic heart disease, paralytic ileus
- With oral use: Abdominal distress, angina pectoris, exacerbated asthenia, depression, drowsiness, dyspnoea, erectile dysfunction, feeling hot, hepatic function abnormal, insomnia, nervous system disorder, paraesthesia, renal impairment, skin reactions, tinnitus, urinary frequency increased

**SIDE-EFFECTS, FURTHER INFORMATION**

Systemic hypotension and reflex tachycardia with rapid reduction of blood pressure may occur — during intravenous use consider stopping infusion or decreasing dose by half.

**PREGNANCY**

May inhibit labour. Not to be used in multiple pregnancy (twins or more) unless there is no other acceptable alternative. Toxicity in animal studies. Risk of severe maternal hypotension and fatal fetal hypoxia — avoid excessive decrease in blood pressure.

For treatment of acute life-threatening hypertension only.

**BREAST FEEDING**

Manufacturer advises avoid — present in breast milk.

**HEPATIC IMPAIRMENT**

Dose adjustments
- With oral use: Manufacturer advises consider using lowest initial dose and extending dosing interval according to individual response
- With intravenous use: See Indications and dose section.

**RENAL IMPAIRMENT**

Dose adjustments
- With oral use: Consider using lowest initial dose and extending dosing interval according to individual response
- With intravenous use: Use with caution — use lower initial dose

**MONITORING REQUIREMENTS**

Monitor blood pressure and heart rate at least every 5 minutes during intravenous infusion, and then until stable, and continue monitoring for at least 12 hours after end of infusion.

**DIRECTIONS FOR ADMINISTRATION**

Intravenous nifedipine should only be administered under the supervision of a specialist and in a hospital or intensive care setting in which patients can be closely monitored. For **intravenous infusion** give continuously in Glucose 5%; dilute dose in infusion fluid to a final concentration of 100–200 micrograms/mL (undiluted solution via central venous line only) and give via volumetric infusion pump or syringe driver; protect from light; to minimise peripheral venous irritation, change site of infusion every 12 hours; risk of adsorption on to plastic of infusion set in the presence of saline solutions; incompatible with bicarbonate or alkaline solutions — consult product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Solution for infusion**

- **Nifedipine hydrochloride (Non-proprietary)**
  - Nicardipine hydrochloride 1 mg per 1 ml Nicardipine 10mg/10ml solution for injection ampoules | 5 ampoule (£0.40) £2.00
  - Nicardipine hydrochloride 2.5 mg per 1 ml Cardene IV 25mg/10ml solution for infusion ampoules | 10 ampoule (£0.45) £7.50

**Capsule**

- **Nifedipine hydrochloride (Non-proprietary)**
  - Nicardipine hydrochloride 20 mg — Nicardipine 20mg capsules | 56 capsule (£0.38 DT = £6.00)

- **Nifedipine hydrochloride 30 mg — Nicardipine 30mg capsules | 56 capsule (£0.73 DT = £7.50

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**Cardene (Astellas Pharma Ltd)**

- Nicardipine hydrochloride 20 mg Cardene 20mg capsules | 56 capsule (£0.40 DT = £6.00)
- Nicardipine hydrochloride 30 mg Cardene 30mg capsules | 56 capsule (£0.73 DT = £7.50

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www.getintopharma.com
Hypertension | Angina prophylaxis

- **BY MOUTH**
  - Adult: Initially 40 mg once daily, increased if necessary to 80 mg daily in 1–2 divided doses

**NIFEDIPRESS** ® MR

Hypertension | Angina prophylaxis

- **BY MOUTH**
  - Adult: 10 mg twice daily, adjusted according to response to 40 mg twice daily

**TENSIPINE** ® MR

Hypertension | Angina prophylaxis

- **BY MOUTH**
  - Adult: Initially 10 mg twice daily, adjusted according to response to 40 mg twice daily

**VALNI** ® XL

Severe hypertension | Prophylaxis of angina

- **BY MOUTH**
  - Adult: 30 mg once daily, increased if necessary up to 90 mg once daily

- **UNLICENSED USE**
  - With systemic use Not licensed for use in postponing premature labour.
  - With oral use Not licensed for use in postponing premature labour.
  - With systemic use Nifedipine is used for the treatment of chronic anal fissure, but is not licensed for this indication.

- **CONTRA-INDICATIONS**
  - With systemic use Acute attacks of angina - cardiogenic shock - significant aortic stenosis - unstable angina - within 1 month of myocardial infarction

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Systemic absorption following rectal use is unknown, therefore consider the possibility of contra-indications listed for systemic use.

- **CAUTIONS**
  - With systemic use Diabetes mellitus - elderly - heart failure - poor cardiac reserve - severe hypotension - short-acting formulations are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia - significantly impaired left ventricular function (heart failure deterioration observed) - withdrawn if ischaemic pain occurs or existing pain worsens shortly after initiating treatment

**CAUTIONS, FURTHER INFORMATION**

Systemic absorption following rectal use is unknown, therefore consider the possibility of cautions listed for systemic use.

**ADALAT** ® LA

Crohn’s disease - decreased lumen diameter of the gastro-intestinal tract - history of gastro-intestinal obstruction - history of oesophageal obstruction - inflammatory bowel disease

**CAUTIONS, FURTHER INFORMATION**

Dose form not appropriate for use where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease (including Crohn’s disease).

**VALNI** ® XL

Decreased lumen diameter of gastro-intestinal tract - history of gastro-intestinal obstruction - history of oesophageal obstruction - ileostomy after proctocolectomy - inflammatory bowel disease

**CAUTIONS, FURTHER INFORMATION**

Dose form not appropriate for use where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, inflammatory bowel disease, or ileostomy after proctocolectomy.

- **INTERACTIONS**
  - Appendix 1: calcium channel blockers

- **SIDE-EFFECTS**
  - Common or very common Constipation - malaise - oedema - vasodilation

- **SIDE-EFFECTS, FURTHER INFORMATION**

Systemic absorption following rectal use is unknown, therefore consider the possibility of side-effects listed for oral use.

- **PREGNANCY**
  - With systemic use May inhibit labour; manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension. Use only if other treatment options are not indicated or have failed.

- **BREAST FEEDING**
  - With systemic use Amount too small to be harmful but manufacturers advise avoid.

- **HEPATIC IMPAIRMENT**
  - With oral use For once-daily preparations, manufacturers advise dose form not appropriate (owing to the duration of action of the formulation).

**DIRECTIONS FOR ADMINISTRATION**

**FORTIPINE** ® LA 40

Take with or just after food, or a meal.

**PRESCRIBING AND DISPENSING INFORMATION**

Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed.

**Palliative care**

For further information on the use of nifedipine in palliative care, see [www.medicinescomplete.com/#/content/palliative/nifedipine](http://www.medicinescomplete.com/#/content/palliative/nifedipine).

**PATIENT AND CARER ADVICE**

**ADALAT** ® LA

Tablet membrane may pass through gastrointestinal tract unchanged, but being porous has no effect on efficacy.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral drops

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Adalat LA** (Bayer Plc)
  - Nifedipine 20 mg 28 tablet POM £5.27 DT = £5.27
  - Nifedipine 30 mg 28 tablet POM £6.85 DT = £6.85
  - Nifedipine 60 mg 28 tablet POM £9.03 DT = £9.03
  - Adalafine XL (Advanz Pharma)
  - Nifedipine 30 mg 28 tablet POM £9.03 DT = £9.03
  - Nifedipine 60 mg 28 tablet POM £11.20 DT = £11.20
  - Adipine MR (Chiesi Ltd)
  - Nifedipine 10 mg 56 tablet POM £3.73 DT = £7.94
  - Nifedipine 20 mg 56 tablet POM £5.21 DT = £8.81
  - Adipine XL (Chiesi Ltd)
  - Nifedipine 30 mg 28 tablet POM £4.70 DT = £9.03
  - Nifedipine 60 mg 28 tablet POM £7.10 DT = £9.03

**BNF 78**

Cardiovascular system

www.getintopharma.com
\textbf{Verapamil hydrochloride}  
06-Aug-2018

- **Fortepine LA** (Advanz Pharma)  
  Nifedipine 40 mg Fortepine LA 40 tablets | 30 tablet [POM] £14.40  
  DT = £14.40

- **Nidel** (Morningidge Healthcare Ltd)  
  Nifedipine 30 mg Nidel 30mg modified-release tablets | 28 tablet [POM] £4.65 DT = £6.85

- **Nifedipine 60 mg** Nifed 60mg modified-release tablets | 28 tablet [POM] £8.77 DT = £9.03

- **Nifedipress MR** (Dexcel-Pharma Ltd)  
  Nifedipine 10 mg Nifedipress MR 10 tablets | 56 tablet [POM] £9.23
  DT = £7.34

- **Nifedipine 20 mg** Nifedipress MR 20 tablets | 56 tablet [POM] £10.06
  DT = £8.81

- **Tensipine MR** (Genus Pharmaceuticals Ltd)  
  Nifedipine 10 mg Tensipine MR 10 tablets | 56 tablet [POM] £4.30
  DT = £7.34

- **Nifedipine 20 mg** Tensipine MR 20 tablets | 56 tablet [POM] £5.49
  DT = £8.81

- **Valni Retard** (Tillomed Laboratories Ltd)  
  Nifedipine 20 mg Valni 20 Retard tablets | 56 tablet [POM] £10.06
  DT = £8.81

- **Valni XL** (Zentiva)  
  Nifedipine 30 mg Valni XL 30mg tablets | 28 tablet [POM] £9.14 DT = £6.85

- **Nifedipine 60 mg** Valni XL 60mg tablets | 28 tablet [POM] £11.85 DT = £9.03

\textbf{Modified-release capsule}

CAUTIONARY AND ADVISORY LABELS 25

- **Coracten SR** (UCB Pharma Ltd)  
  Nifedipine 10 mg Coracten SR 10mg capsules | 60 capsule [POM] £3.90 DT = £3.90

- **Nifedipine 20 mg** Coracten SR 20mg capsules | 60 capsule [POM] £5.41 DT = £5.41

- **Coracten XL** (UCB Pharma Ltd)  
  Nifedipine 30 mg Coracten XL 30mg capsules | 28 capsule [POM] £4.89 DT = £4.89

- **Nifedipine 60 mg** Coracten XL 60mg capsules | 28 capsule [POM] £7.34 DT = £7.34

\textbf{Oral drops}

- **Nifedipine (Non-proprietary)**  
  Nifedipine 20 mg per 1 ml Nifedipin-ratiopharm 20mg/ml oral drops | 30 ml [POM] £

Combinations available: Atenolol with nifedipine, p. 153

\section*{Blood pressure conditions}

\textbf{HALF SECURON ® SR}

\textbf{Hypertension (in patients new to verapamil)}

- **BY MOUTH**  
  - Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

\textbf{Hypertension}

- **BY MOUTH**  
  - Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

\textbf{Angina}

- **BY MOUTH**  
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

\textbf{Prophylaxis after myocardial infarction where beta-blockers not appropriate}

- **BY MOUTH**  
  - Adult: 360 mg daily in divided doses, started at least 1 week after infarction, given as either 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

\textbf{SECURON ® SR}

\textbf{Hypertension (in patients new to verapamil)}

- **BY MOUTH**  
  - Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

\textbf{Hypertension}

- **BY MOUTH**  
  - Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

\textbf{Angina}

- **BY MOUTH**  
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

\textbf{Prophylaxis after myocardial infarction where beta-blockers not appropriate}

- **BY MOUTH**  
  - Adult: 360 mg daily in divided doses, started at least 1 week after infarction, given as either 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

\textbf{VERAPRESS ® MR}

\textbf{Hypertension}

- **BY MOUTH**  
  - Adult: 240 mg daily, increased if necessary to 240 mg twice daily

\textbf{Angina}

- **BY MOUTH**  
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

\textbf{VERTAB ® SR 240}

\textbf{Mild to moderate hypertension}

- **BY MOUTH**  
  - Adult: 240 mg daily, increased if necessary to 240 mg twice daily

\textbf{Angina}

- **BY MOUTH**  
  - Adult: 240 mg twice daily, may sometimes be reduced to once daily

\textbf{UNLICENSED USE}

- With oral use. Prophylaxis of cluster headaches is an unlicensed indication.

\textbf{CONTRA-INDICATIONS}

- Acute porphyrias p. 1058 - atrial flutter or fibrillation associated with accessory conducting pathways (e.g. Wolff-Parkinson-White-syndrome).

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bradycardia - cardiogenic shock - history of heart failure (even if controlled by therapy) - history of significantly impaired left ventricular function (even if controlled by therapy) - hypotension - second- and third-degree AV block - sick sinus syndrome - sino-atrial block

**CAUTIONS** Acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure) - first-degree AV block

**INTERACTIONS** → Appendix 1: calcium channel blockers

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Common or very common
- Frequency not known

**INTERACTIONS**
- Common or very common

**SIDE-EFFECTS**
- Common or very common
- Frequency not known
- With intravenous use
- Uncommon
- Frequency not known
- With intravenous use
- Cardiac arrest - drowsiness - erythema - hepatic impairment - hypocalcaemia - hypokalaemia - hypothermia - increased movement, raising the legs, and support gravitational oedema (which will usually respond to continuous on a long-term basis to treat simple oedema.
- With oral use
- Overdose
- In overdose, verapamil has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.
- Pregnancy
- May reduce uterine blood flow with fetal hypoxia. Manufacturer advises avoid in first trimester unless absolutely necessary. May inhibit labour.
- Breast Feeding
- Amount too small to be harmful.
- Hepatic Impairment
- Dose adjustments

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 25**
- Half Securon (Mylan)
- Securon SR (Mylan)
- Vera-Til SR (Tillomed Laboratories Ltd, Actavis UK Ltd)
- Vera-Til SR (Dexcel-Pharma Ltd)
- Vera-Til SR (Mylan)
- Verta SR (Chiesi Ltd)

**Tablet**
- Verapamil hydrochloride (Non-proprietary)
- Verapamil hydrochloride 40 mg
- Verapamil hydrochloride 80 mg
- Verapamil hydrochloride 120 mg
- Verapamil hydrochloride 160 mg
- Verapamil hydrochloride 240 mg

**Solution for injection**
- Securon (Mylan) Verapamil hydrochloride 2.5 mg per 1 ml
- Securon IV 5mg/2ml

**Oral solution**
- Verapamil hydrochloride (Non-proprietary) Verapamil hydrochloride 8 mg per 1 ml

**Thiazides and related diuretics**

**Thiazides and Related Diuretics**

**CONTRA-INDICATIONS**
- Addison’s disease - hypercalcaemia - hypoponatraemia - refractory hypokalaemia - symptomatic hyperuricaemia

**CAUTIONS**
- Diabetes - gout - hyperaldosteronism - malnourishment - nephrotic syndrome - systemic lupus erythematosus

**CAUTIONS, FURTHER INFORMATION**
- Potassium loss
- Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.
- Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements.
- Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.
- In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis.
- Elderly
- Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).
- Existing conditions
- Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus.

**SIDE-EFFECTS**
- Common or very common
- Alkalosis hypochloraemic - constipation - diarrhoea - dizziness - electrolyte imbalance - headache - hyperuricaemia - nausea - postural hypotension - urticaria
- Uncommon
- Agranulocytosis - aplastic anaemia - leucopenia
- Alkalosis hypochloraemic - diabetes - electrocardiographic - electrolyte imbalance - pancreatitis - photosensitivity reaction - thrombocytopenia

**PREGNANCY**
- Thiazides and related diuretics should not be used to treat gestational hypertension. They may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

**HEPATIC IMPAIRMENT**
- General, manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT**
- Thiazides and related diuretics are ineffective if eGFR is less than 30 mL/minute/1.73 m² and should be avoided. Metolazone remains effective if eGFR is less than 30 mL/minute/1.73 m² but is associated with a risk of excessive diuresis.

**Monitoring**
- Electrolytes should be monitored in renal impairment.

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**Co-amilozide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrochlorothiazide below.

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
- Adult: Initially 2.5/25 mg daily, increased if necessary up to 5/50 mg daily

**Congestive heart failure**
- **BY MOUTH**
- Adult: Initially 2.5/25 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible

**Oedema and ascites in cirrhosis of the liver**
- **BY MOUTH**
- Adult: Initially 5/50 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible

**DOSE EQUIVALENCE AND CONVERSION**
- A mixture of amiloride hydrochloride and hydrochlorothiazide in the mass proportions of 1 part amiloride hydrochloride to 10 parts hydrochlorothiazide.

**Hydrochlorothiazide**

**INDICATIONS AND DOSE**

Indications listed in combination monographs (available in the UK only in combination with other drugs)
- **BY MOUTH**
- Adult: Doses listed in combination monographs

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVISE: HYDROCHLOROTHIAZIDE: RISK OF NON-MELANOMA SKIN CANCER, PARTICULARLY IN LONG-TERM USE (NOVEMBER 2018)

The MHRA advises healthcare professionals to:
- inform patients taking hydrochlorothiazide-containing products of the cumulative, dose-dependent increased risk of non-melanoma skin cancer, particularly in long-term use, and advise patients to regularly check for and report any new or changed skin lesions or moles;
- advise patients to limit exposure to sunlight and UV rays and use adequate sun protection;
- reconsider the use of hydrochlorothiazide in patients who have had previous skin cancer;
- examine all suspicious moles or skin lesions (potentially including histological examination of biopsies).

**INTERACTIONS** → Appendix 1: thiazide diuretics
## Indapamide

### DRUG ACTION
Indapamide is a thiazide-like diuretic with antihypertensive effects. At lower doses, vasodilatation is more prominent than diuresis; the diuretic effect becomes more apparent with higher doses.

### INDICATIONS AND DOSE

#### Essential hypertension

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 2.5 mg daily, dose to be taken in the morning
  - Adult: 1.5 mg daily, dose to be taken preferably in the morning

#### CAUTIONS
Acute porphyrias p. 1058

#### INTERACTIONS
Appendix 1: thiazide diuretics

### SIDE-EFFECTS

- **Common or very common** Hypersensitivity - skin reactions
- **Uncommon** Vomiting
- **Rare or very rare** Angioedema - arthralgias - dry mouth - fatigue - haemolytic anaemia - hepatic disorders - paraesthesia - renal failure - severe cutaneous adverse reactions (SCARs) - vertigo
- **Frequency not known** Hepatic encephalopathy - QT interval prolongation - syncope - systemic lupus erythematosus exacerbated - vision disorders
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of hypersensitivity to sulphonamides.
- **BREAST FEEDING** Present in milk—manufacturer advises avoid.

### MEDICINAL FORMS
Forms available from special-order manufacturers include: tablet, oral suspension, oral solution

<table>
<thead>
<tr>
<th>Combination</th>
<th>Dosage</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indapamide 1.5 mg</td>
<td>30 tablet</td>
<td>Torcent Pharma (UK) Ltd</td>
</tr>
<tr>
<td>Indapamide 1.5 mg</td>
<td>30 tablet</td>
<td>Servier Laboratories Ltd</td>
</tr>
<tr>
<td>Indapamide 1.5 mg</td>
<td>30 tablet</td>
<td>Sercn Laboratories Ltd</td>
</tr>
<tr>
<td>Indapamide 1.5 mg</td>
<td>30 tablet</td>
<td>Lyndal Healthcare Ltd</td>
</tr>
<tr>
<td>Indapamide 1.5 mg</td>
<td>30 tablet</td>
<td>Mylan</td>
</tr>
</tbody>
</table>

### DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

#### ACE INHIBITORS

- **CONTRA-INDICATIONS** The combination of an ACE inhibitor with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m² — the combination of an ACE inhibitor with aliskiren is contra-indicated in patients with diabetes mellitus.

- **CAUTIONS**
  - Afro-Caribbean patients (may respond less well to ACE inhibitors - concomitant diuretics - diabetes (may lower blood glucose) - first dose hypotension (especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure)
  - peripheral vascular disease or generalised atherosclerosis (risk of clinically silent renovascular disease) - primary aldosteronism (patients may respond less well to ACE inhibitors) - the risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended) - use with care (or avoid) in those with a history of idiopathic or hereditary angioedema - use with care (or avoid) in those with hypertrophic cardiomyopathy - use with care in patients with severe or symptomatic aortic stenosis (risk of hypotension)

- **CAUTIONS, FURTHER INFORMATION**
  - Anaphylactoid reactions - To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitisation with wap or bee venom.

### SIDE-EFFECTS

- **Common or very common** Alopecia - angina pectoris - angioedema (may be delayed; more common in Afro-Caribbean patients) - arthralgias - ashenia - chest pain - constipation - cough - diarrhoea - dizziness - drowsiness - dry mouth - dyspnoea - electrolyte imbalance - gastrointestinal discomfort - headache - hypotension - myalgia - nausea - palpitations - paraesthesia - renal impairment - rhinitis - skin reactions - sleep disorder - syncope - taste altered - tinnitus - vertigo - vomiting

- **Uncommon**

- **Rare or very rare**

- **Stevens-Johnson syndrome**
SIDE-EFFECTS, FURTHER INFORMATION

In light of reports of cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure, ACE inhibitors should be discontinued if marked elevation of hepatic enzymes or jaundice occur.

- **ALLERGY AND CROSS-SENSITIVITY** ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors (including angioedema).

- **PREGNANCY** ACE inhibitors should be avoided in pregnancy unless essential. They may adversely affect fetal renal function and control and renal function; skull defects and oligohydramnios have also been reported.

- **BREAST FEEDING** Information on the use of ACE inhibitors in breast-feeding is limited.

- **RENAL IMPAIRMENT**
  
  **Dose adjustments** Use with caution, starting with low dose, and adjust according to response. Hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced.

- **MONITORING REQUIREMENTS** Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if side effects mentioned are present).

- **DIRECTIONS FOR ADMINISTRATION** For hypertension the first dose should preferably be given at bedtime.

### Captopril

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  
  - Adult: Initially 12.5–25 mg twice daily, then increased if necessary up to 150 mg daily in 2 divided doses, doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken
  
  - Elderly: Initially 6.25 mg twice daily, then increased if necessary up to 150 mg daily in 2 divided doses, doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

**Essential hypertension if used in volume depletion, cardiac decompensation, or renovascular hypertension**

- **BY MOUTH**
  
  Adult: Initially 6.25–12.5 mg for 1 dose (under close medical supervision), then 6.25–12.5 mg twice daily; increased if necessary up to 100 mg daily in 1–2 divided doses, doses to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

**Heart failure**

- **BY MOUTH**
  
  Adult (under close medical supervision): Initially 6.25–12.5 mg 2–3 times a day, then increased if tolerated to up to 150 mg daily in divided doses, dose to be increased gradually at intervals of at least 2 weeks

**Short-term treatment within 24 hours of onset of myocardial infarction in clinically stable patients**

- **BY MOUTH**
  
  Adult: Initially 6.25 mg, then increased to 12.5 mg after 2 hours, followed by 25 mg after 12 hours; increased if tolerated to 50 mg twice daily for 4 weeks

**Prophylaxis of symptomatic heart failure after myocardial infarction in clinically stable patients with asymptomatic left ventricular dysfunction (starting 3–16 days after infarction) (under close medical supervision)**

- **BY MOUTH**
  
  - Adult: Initially 6.25 mg daily, then increased to 12.5 mg 3 times a day for 2 days, then increased if tolerated to 25 mg 3 times a day, then increased if tolerated to 75–150 mg daily in 2–3 divided doses, doses exceeding 75 mg per day to be increased gradually

**Diabetic nephropathy in type 1 diabetes mellitus**

- **BY MOUTH**
  
  - Adult: 75–100 mg daily in divided doses

**CAUTIONS**

- Children (efficacy and safety not fully established)

**INTERACTIONS** → Appendix 1: ACE inhibitors

**SIDE-EFFECTS**

- **Common or very common** Insomnia - peptic ulcer
  
  - Uncommon Appetite decreased - flushing - malaise - pallor - Raynaud’s phenomenon
  
  - Rare or very rare Anaemia - aplastic anaemia - autoimmune disorder - cardiac arrest - cardiogenic shock - cerebrovascular insufficiency - depression - gynaecomastia - hepatic disorders - hypoglycaemia - lymphadenopathy - nephrotic syndrome - oral disorders - proteinuria - urinary disorders - vision blurred

**BREAST FEEDING**

Avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.

**RENAL IMPAIRMENT**

**Dose adjustments** Reduce dose; max. initial dose 50 mg if eGFR above 40 mL/minute/1.73 m²; max. initial dose 25 mg daily (do not exceed 100 mg daily) if eGFR 20–40 mL/minute/1.73 m²; max. initial dose 12.5 mg daily (do not exceed 75 mg daily) if eGFR 10–20 mL/minute/1.73 m²; max. initial dose 6.25 mg daily (do not exceed 37.5 mg daily) if eGFR less than 10 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution

**Tablet**

- **Captopril (Non-proprietary)**
  
  - Captopril 12.5 mg: Captopril 12.5mg tablets | 56 tablet | £0.97 DT = £0.92
  
  - Captopril 25 mg: Captopril 25mg tablets | 56 tablet | £0.80 DT = £0.80
  
  - Captopril 50 mg: Captopril 50mg tablets | 56 tablet | £1.52 DT = £1.50

**Oral solution**

**ELECTROLYTES:** May contain Sodium

- **Captopril (Non-proprietary)**
  
  - Captopril 1 mg per 1 ml: Captopril 5mg/5ml oral solution sugar free | 100 ml | £93.30–£98.21 DT = £97.23
  
  - Captopril 2.5 mg per 1 ml: Captopril 25mg/5ml oral solution sugar free | 100 ml | £103.49–£108.94 DT = £107.85
  
  - Noyada (Martin-Dino Pharmaceuticals Ltd)
    
    - Captopril 1 mg per 1 ml: Noyada 5mg/5ml oral solution sugar-free | 100 ml | £98.21 DT = £97.23
    
    - Captopril 5 mg per 1 ml: Noyada 25mg/5ml oral solution sugar-free | 100 ml | £108.94 DT = £107.85

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Enalapril maleate

**INDICATIONS AND DOSE**

**Hypertension**
- By mouth
  - Adult: Initially 5 mg once daily, lower initial doses may be required when used in addition to diuretic or in renal impairment; maintenance 20 mg once daily; maximum 40 mg per day

**Heart failure**
- By mouth
  - Adult (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks

**Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction**
- By mouth
  - Adult (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks

**INTERACTIONS**
- Appendix 1: ACE inhibitors
- **SIDE-EFFECTS**
  - Common or very common: Depression, hypersensitivity, vision blurred
  - Uncommon: Anaemia, appetite decreased, asthma, bone marrow disorders, flushing, gastrointestinal disorders, hoarseness, hypoglycaemia, malaise, muscle cramps, nervousness, proteinuria, rhinorrhea, sleep disorders, throat pain
  - Rare or very rare: Autoimmune disorder, gynaecomastia, hepatic disorders, lymphadenopathy, oral disorders, Raynaud’s phenomenon, toxic epidermal necrolysis
  - Frequency not known: Arthritis, leucocytosis, myositis, serositis, Sjadih, vasculitis
- **BREAST FEEDING**: Avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.
- **HEPATIC IMPAIRMENT**: Enalapril is a prodrug.
- **RENAL IMPAIRMENT**: Dose adjustments: Max. initial dose 2.5 mg daily if eGFR less than 30 ml/minute/1.73 m².
- **DIRECTIONS FOR ADMINISTRATION**: Tablets may be crushed and suspended in water immediately before use.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Tablet**
  - **Enalapril maleate (Non-proprietary)**
    - Enalapril maleate 2.5 mg: Enalapril 2.5 mg tablets | 28 tablet | £5.63 DT = £5.15
    - Enalapril maleate 5 mg: Enalapril 5 mg tablets | 28 tablet | £4.13 DT = £3.74
    - Enalapril maleate 10 mg: Enalapril 10 mg tablets | 28 tablet | £5.64 DT = £5.11
    - Enalapril maleate 20 mg: Enalapril 20 mg tablets | 28 tablet | £6.63 DT = £6.16
  - **Innovace (Merck Sharp & Dohme Ltd)**
    - Enalapril maleate 2.5 mg: Innovace 2.5 mg tablets | 28 tablet | £5.35 DT = £5.15
    - Enalapril maleate 5 mg: Innovace 5 mg tablets | 28 tablet | £4.13 DT = £3.74
    - Enalapril maleate 10 mg: Innovace 10 mg tablets | 28 tablet | £5.64 DT = £5.11
    - Enalapril maleate 20 mg: Innovace 20 mg tablets | 28 tablet | £6.63 DT = £6.16

Enalapril with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, enalapril maleate above, hydrochlorothiazide p. 166.

**INDICATIONS AND DOSE**

**Mild to moderate hypertension in patients stabilised on the individual components in the same proportions**
- **BY MOUTH**
  - Adult: (consult product literature)

**INTERACTIONS**
- Appendix 1: ACE inhibitors - thiazide diuretics

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Enalapril with hydrochlorothiazide (Non-proprietary)
      - Hydrochlorothiazide 12.5 mg, Enalapril maleate 20 mg | Enalapril 20mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet | £20.00 DT = £19.98
      - Innovace (Merck Sharp & Dohme Ltd)
        - Hydrochlorothiazide 12.5 mg, Enalapril maleate 20 mg | Innovace 20mg/12.5mg tablets | 28 tablet | £13.90 DT = £13.98

Fosinopril sodium

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 10 mg daily for 4 weeks, then increased if necessary up to 40 mg daily, doses over 40 mg not shown to increase efficacy

**Congestive heart failure (adjunct) (under close medical supervision)**
- **BY MOUTH**
  - Adult: Initially 10 mg once daily, then increased if tolerated to 40 mg once daily, doses to be increased gradually

**INTERACTIONS**
- Appendix 1: ACE inhibitors

**SIDE-EFFECTS**
- Common or very common: Eye disorder, increased risk of infection, mood altered, oedema, pain, sexual dysfunction, urinary disorder, visual impairment
- Frequency not known: Appetite normal, arthritis, balance impaired, behaviour abnormal, cardiac arrest, cardiac conduction disorder, cerebrovascular insufficiency, depression, dysphagia, dysphonia, ear pain, fatigue, flushing, gout, haemorrhage, hypertensive crisis, lymphadenopathy, memory loss, muscle weakness, oral disorders, prostatic disorder, tremor, weight changes

**BREAST FEEDING**: Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT**: Fosinopril is a prodrug. Manufacturer advises caution (risk of increased exposure).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **Tablet**
    - Fosinopril sodium (Non-proprietary)
      - Fosinopril sodium 10 mg: Fosinopril 10mg tablets | 28 tablet | £5.73 DT = £4.07
      - Fosinopril sodium 20 mg: Fosinopril 20mg tablets | 28 tablet | £33.98 DT = £33.98
Cardiovascular system

170 Blood pressure conditions

Imidapril hydrochloride

**INDICATIONS AND DOSE**

**Essential hypertension**

- **BY MOUTH**
  - Adult: Initially 5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, doses to be increased at intervals of at least 3 weeks; maximum 20 mg per day
  - Elderly: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, doses to be increased at intervals of at least 3 weeks

**Essential hypertension in patients with heart failure, angina or cerebrovascular disease**

- **BY MOUTH**
  - Adult: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, dose to be increased at intervals of at least 3 weeks; maximum 20 mg per day

**INTERACTIONS** → Appendix 1: ACE inhibitors

**SIDE-EFFECTS**

- Uncommon: Cerebrovascular disorder - increased risk of infection - joint swelling - limb pain - oedema
- Rare or very rare: Anaemia

**HEPATIC IMPAIRMENT**

Imidapril is a prodrug. Manufacturer advises caution (risk of increased exposure).

**DOSE adjustments**

Manufacturer advises initial dose of 2.5 mg daily.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m².

**DOSE adjustments**

Initial dose 2.5 mg daily if eGFR 30–80 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Tanatril (Mitsubishi Tanabe Pharma Europe Ltd)
  - Imidapril hydrochloride 5 mg: Tanatril 5 mg tablets | 28 tablet | £6.40 DT = £6.40
  - Imidapril hydrochloride 10 mg: Tanatril 10 mg tablets | 28 tablet | £7.22 DT = £7.22
  - Imidapril hydrochloride 20 mg: Tanatril 20 mg tablets | 28 tablet | £8.67 DT = £8.67

Lisinopril

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 10 mg once daily; usual maintenance 20 mg once daily; maximum 80 mg per day

**Hypertension, when used in addition to diuretic, in cardiac decompensation or in volume depletion**

- **BY MOUTH**
  - Adult: Initially 2.5–5 mg once daily; usual maintenance 20 mg once daily; maximum 80 mg per day

**Short-term treatment following myocardial infarction in haemodynamically stable patients—systolic blood pressure over 120 mmHg**

- **BY MOUTH**
  - Adult: Initially 5 mg, taken within 24 hours of myocardial infarction, followed by 5 mg, to be taken 24 hours after initial dose, then 10 mg, to be taken 24 hours after second dose, then 10 mg once daily for 6 weeks (or continued if heart failure), temporarily reduce maintenance dose to 5 mg and if necessary 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs during treatment (systolic blood pressure less than 90 mmHg for more than 1 hour)

**Short-term treatment following myocardial infarction in haemodynamically stable patients—systolic blood pressure 100–120 mmHg**

- **BY MOUTH**
  - Adult: Initially 2.5 mg once daily, maintenance 5 mg once daily, increase to maintenance dose only after at least 3 days of the initial dose, should not be started after myocardial infarction if systolic blood pressure less than 100 mmHg, temporarily reduce maintenance dose to 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour)

**Renal complications of diabetes mellitus**

- **BY MOUTH**
  - Adult: Initially 2.5–5 mg once daily, adjusted according to response; usual dose 10–20 mg once daily

**Heart failure (adjunct) (under close medical supervision)**

- **BY MOUTH**
  - Adult: Initially 2.5 mg once daily; increased in steps of up to 10 mg at least every 2 weeks; maximum 35 mg per day

**INTERACTIONS** → Appendix 1: ACE inhibitors

**SIDE-EFFECTS**

- Common or very common: Joint pain - muscle pain - joint swelling - limb pain - oedema - peripheral oedema - SIADH
- Uncommon: Rheumatoid arthritis - vasculitis - drug fever
- Rare or very rare: Anaemia

**HEPATIC IMPAIRMENT**

Imidapril is a prodrug. Manufacturer advises caution (risk of increased exposure).

**DOSE adjustments**

Manufacturer advises initial dose of 2.5 mg daily.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m².

**DOSE adjustments**

Initial dose 2.5 mg daily if eGFR 30–80 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Tanatril (Mitsubishi Tanabe Pharma Europe Ltd)
  - Lisinopril (Non-proprietary)
    - Lisinopril 1 mg per 1 ml: Lisinopril 5 mg/5 ml oral solution sugar free | 150 ml | £15.41 DT = £15.41
  - Lisinopril 2.5 mg: Lisinopril 2.5 mg tablets | 28 tablet | £4.81 DT = £4.81
  - Lisinopril 5 mg: Lisinopril 5 mg tablets | 28 tablet | £7.54 DT = £7.54
  - Lisinopril 10 mg: Lisinopril 10 mg tablets | 28 tablet | £11.81 DT = £11.81
  - Lisinopril 5 mg: Lisinopril 5 mg tablets | 50 tablet | £10.93
  - Lisinopril 10 mg: Lisinopril 10 mg tablets | 50 tablet | £11.08
  - Lisinopril 20 mg: Lisinopril 20 mg tablets | 28 tablet | £10.42 DT = £10.42
  - Lisinopril 10 mg: Lisinopril 10 mg tablets | 50 tablet | £10.78
  - Lisinopril 20 mg: Lisinopril 20 mg tablets | 50 tablet | £12.75

- Zestril (AstraZeneca UK Ltd)
  - Lisinopril 5 mg: Zestril 5 mg tablets | 28 tablet | £3.92 DT = £3.92
  - Lisinopril 10 mg: Zestril 10 mg tablets | 28 tablet | £4.76 DT = £4.76
  - Lisinopril 20 mg: Zestril 20 mg tablets | 28 tablet | £13.02 DT = £13.02

- Tanatril (Mitsubishi Tanabe Pharma Europe Ltd)
  - Imidapril hydrochloride 5 mg: Tanatril 5 mg tablets | 28 tablet | £6.40 DT = £6.40
  - Imidapril hydrochloride 10 mg: Tanatril 10 mg tablets | 28 tablet | £7.22 DT = £7.22
  - Imidapril hydrochloride 20 mg: Tanatril 20 mg tablets | 28 tablet | £8.67 DT = £8.67

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### Lisinopril with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, lisinopril p. 170, hydrochlorothiazide p. 166.

#### INDICATIONS AND DOSE
- Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
- **INDICATIONS AND DOSE**
- **INTERACTIONS** 
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### MEDICINAL FORMS

- **Tablet**
  - Lisinopril with hydrochlorothiazide (Non-proprietary)
  - Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg  Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (PO) £2.80 DT = £2.69
  - Hydrochlorothiazide 12.5 mg, Lisinopril 20 mg  Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (PO) £2.45 DT = £2.41
  - Zestoretic (AstraZeneca UK Ltd)
    - Lisinopril 10 mg, Hydrochlorothiazide 12.5 mg  Zestoretic 10 tablets | 28 tablet (PO) £13.62 DT = £2.63
    - Hydrochlorothiazide 12.5 mg, Lisinopril 20 mg  Zestoretic 20 tablets | 28 tablet (PO) £13.82 DT = £2.41

### Perindopril arginine

#### INDICATIONS AND DOSE
- **Hypertension**
  - **INDICATIONS AND DOSE**
  - **INTERACTIONS** 
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Perindopril arginine with indapamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, perindopril arginine above, indapamide p. 167.

#### INDICATIONS AND DOSE
- **Hypertension not adequately controlled by perindopril alone**
- **INTERACTIONS** 
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Perindopril erbumine

#### INDICATIONS AND DOSE
- **Hypertension**
- **INTERACTIONS** 
- **SIDE-EFFECTS**
- **MEDICINAL FORMS**

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www.getintopharma.com
Prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease

▶ BY MOUTH
- Adult: Initially 4 mg once daily for 2 weeks, dose to be taken in the morning, then increased if tolerated to 8 mg once daily
- Elderly: Initially 2 mg once daily for 1 week, then increased if tolerated to 4 mg once daily for 1 week, then increased if tolerated to 8 mg once daily

INTERACTIONS → Appendix 1: ACE inhibitors
SIDE-EFFECTS
- Common or very common Muscle cramps - visual impairment
- Rare or very rare Cholestasis

BREAST FEEDING Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

HEPATIC IMPAIRMENT Perindopril is a prodrug. Manufacturer advises caution when used in combination with a diuretic.

RENAL IMPAIRMENT
Dose adjustments
- Max. initial dose 2.5 mg once daily if eGFR 30–60 mL/minute/1.73 m²; 2 mg once daily on alternate days if eGFR 15–30 mL/minute/1.73 m².

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Tablet
- CAUTIONARY AND ADVISORY LABELS 22

Perindopril erbumine (Non-proprietary)
- Perindopril erbumine 2 mg Perindopril erbumine 2mg tablets | 30 tablet PSM £12.09 DT = £2.04 | 56 tablet PSM £3.34 | 60 tablet PSM £13.90
- Perindopril erbumine 4 mg Perindopril erbumine 4mg tablets | 30 tablet PSM £12.39 DT = £2.33 | 56 tablet PSM £3.38 | 60 tablet PSM £27.80
- Perindopril erbumine 8 mg Perindopril erbumine 8mg tablets | 30 tablet PSM £12.99 DT = £2.53 | 56 tablet PSM £3.88 | 60 tablet PSM £40.00

Quinapril with hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, quinapril above, hydrochlorothiazide p. 166.

INDICATIONS AND DOSE
Hypertension in patients stabilised on the individual components in the same proportions
- BY MOUTH
- Adult: (consult product literature)

INTERACTIONS → Appendix 1: ACE inhibitors - thiazide diuretics

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Quinapril with hydrochlorothiazide (Non-proprietary)
  - Quinapril (Non-proprietary)
    - Quinapril (as Quinapril hydrochloride) 5 mg Quinapril 5mg tablets | 28 tablet PSM £8.59 DT = £8.60
    - Quinapril (as Quinapril hydrochloride) 40 mg Quinapril 40mg tablets | 28 tablet PSM £4.20 DT = £3.72
  - Accupro (Pfizer Ltd)
    - Quinapril (as Quinapril hydrochloride) 5 mg Accupro 5mg tablets | 28 tablet PSM £8.60 DT = £8.60
    - Quinapril (as Quinapril hydrochloride) 10 mg Accupro 10mg tablets | 28 tablet PSM £8.60 DT = £8.60
    - Quinapril (as Quinapril hydrochloride) 20 mg Accupro 20mg tablets | 28 tablet PSM £10.79 DT = £10.79
    - Quinapril (as Quinapril hydrochloride) 40 mg Accupro 40mg tablets | 28 tablet PSM £9.75 DT = £3.72

Rampiril

INDICATIONS AND DOSE
Hypertension
- BY MOUTH
- Adult: Initially 1.25–2.5 mg once daily, increased if necessary up to 10 mg once daily, dose to be increased at intervals of 2–4 weeks
**MEDICINAL FORMS**

**Breast feeding**

Frequency not known

- Uncommon
- Common or very common

**Side-effects**

- Gastrointestinal disorders - increased risk of infection - muscle spasms
- Anxiety - appetite decreased - asthma exacerbated - depressed mood - flushing - libido decreased - myocardiial ischaemia - nasal congestion - proteinuria aggravated - vision disorders
- Conjunctivitis - hearing impairment - hepatic disorders - hypoperfusion - movement disorders - onycholysis - oral disorders - tremor - vascular stenosis - vasculitis
- Altered smell sensation - bone marrow failure - cerebrovascular insufficiency - concentration impaired - enanthema - gynaecomastia - hypersensitivity - Raynaud’s phenomenon - SIADH - toxic epidermal necrolysis

**Breast Feeding**

- Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**Hepatic Impairment**

Ramipril is a prodrug: Manufacturer advises caution.

**Dose Adjustments**

Manufacturer advises maximum 2.5 mg daily.

**Renal Impairment**

Dose adjustments

- Max. daily dose 5 mg if eGFR 30–60 ml/minute/1.73 m²; max. initial dose 1.25 mg once daily (do not exceed 5 mg daily) if eGFR less than 30 ml/minute/1.73 m².

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral Solution**

- **Ramipril (Non-proprietary)**
  - Ramipril 500 microgram per 1 ml | 150 ml | £36.00 DT = £96.00

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**INDICATIONS AND DOSE**

**Hypertension in patients stabilised on the individual components in the same proportions**

- **By Mouth**
- Adult: (consult product literature)

**INTERACTIONS**

- Appendix 1: ACE inhibitors - calcium channel blockers

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

**Cautionary and Advisory Labels**

- **Triapin** (Sanofi)
- **Felodipine** 5 mg, **Ramipril** 2.5 mg

**Felodipine 5 mg, Ramipril 2.5 mg**

- 28 tablet | £24.55 DT = £48.05
- 28 tablet [PST] £17.00 DT = £34.00

**Felodipine 5 mg, Ramipril 10 mg**

- 28 tablet | £30.00 DT = £60.00
- 28 tablet [PST] £18.00 DT = £36.00

**Ramipril with felodipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ramipril p. 172, felodipine p. 160.

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**INDICATIONS AND DOSE**

**Mild to moderate hypertension**

- **By Mouth**
- Adult: Initially 500 micrograms once daily; increased to 1–2 mg once daily, dose to be increased at intervals of 2–4 weeks; maximum 4 mg per day

**Prophylaxis after myocardial infarction in patients with left ventricular dysfunction (starting as early as 3 days after infarction)**

- **By Mouth**
- Adult: Initially 500 micrograms once daily, then increased to up to 4 mg once daily, doses to be increased gradually
**SIDE-EFFECTS**

- **Uncommon** Feeling abnormal • gastrointestinal disorders • hot flush • increased risk of infection • insomnia • libido decreased • malaise • muscle spasms • pain • rhinorrhea
- **Rare or very rare** Anaemia • anxiety • appetite abnormal • azotaemia • cerebrovascular insufficiency • depression • enzyme abnormality • eye disorder • eye inflammation • gout • haemorrhage • hallucination • hyperbilirubinaemia • hyperglycaemia • hypersensitivity • hyperuricaemia • migraine • movement disorders • myocardial ischaemia • oedema • osteoarthritis • platelet disorder • throat irritation • urinary disorders • vascular disorders • visual impairment • white blood cell disorder
- **Frequency not known** Atrialventricular block • cardiac arrest • jaundice • proteinuria • toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION** If symptomatic hypotension develops during titration, do not increase dose further; if possible, reduce dose of any adjunctive treatment and if this is not effective or feasible, reduce dose of trandolapril.

**BREAST FEEDING** Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** Trandolapril is a prodrug. Manufacturer advises caution.

**Dose adjustments** Manufacturer advises consider initial dose of 20 mg in mild to moderate impairment.

**RENAL IMPAIRMENT** Dose adjustments Use with caution, starting with low dose, and adjust according to response.

**MONITORING REQUIREMENTS** Monitor plasma-potassium concentration, particularly in the elderly and in patients with renal impairment.

**Azilsartan medoxomil**

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult 18-74 years: Initially 40 mg once daily, increased if necessary to 80 mg once daily
  - Adult 75 years and over: Initially 20–40 mg once daily, increased if necessary to 80 mg once daily

**Hypertension with intravascular volume depletion**

- **BY MOUTH**
  - Adult: Initially 20–40 mg daily, increased if necessary to 80 mg daily

**CAUTIONS** Heart failure

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists

**SIDE-EFFECTS**

- **Uncommon** Angioedema • myalgia • skin reactions • thrombocytopenia
- **Rare or very rare** Arthralgia • hepatic function abnormal

**PREGNANCY** Angiotensin-II receptor antagonists should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; neonatal skull defects and oligohydramnios have also been reported.

**BREAST FEEDING** Information on the use of angiotensin-II receptor antagonists in breast-feeding is limited. They are not recommended in breast-feeding and alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** In general, manufacturers advise caution in mild to moderate impairment (limited information available); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Capsule**

- Trandolapril (Non-proprietary)
  - Trandolapril 500 microgram capsules 14 capsule £1.66 DT = £1.66
  - Trandolapril 1 mg capsules 28 capsule £20.21 DT = £20.21
  - Trandolapril 2 mg capsules 28 capsule £2.94 DT = £2.52
  - Trandolapril 4 mg capsules 28 capsule £11.39 DT = £11.39

**DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM**

**ANGIOTENSIN II RECEPTOR ANTAGONISTS**

**ANGIOTENSIN II receptor antagonists**

**CONTRA-INDICATIONS** The combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m² • the combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with diabetes mellitus

**CAUTIONS** Afro-Caribbean patients—particularly those with left ventricular hypertrophy (may not benefit from an angiotensin-II receptor antagonist) • aortic or mitral valve stenosis • elderly (lower initial doses may be appropriate) • hypertrophic cardiomyopathy • patients with a history of angiodema • patients with primary aldosteronism (may not benefit from an angiotensin-II receptor antagonist) • renal artery stenosis

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain • asthenia • back pain • cough • diarrhoea • dizziness • headache • hyperkalaemia • hypotension • nausea • postural

hypotension (more common in patients with intravascular volume depletion, e.g. those taking high-dose diuretics) • renal impairment • vertigo • vomiting

- **Uncommon** Angioedema • myalgia • skin reactions • thrombocytopenia

- **Rare or very rare** Arthralgia • hepatic function abnormal

**PREGNANCY** Angiotensin-II receptor antagonists should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; neonatal skull defects and oligohydramnios have also been reported.

**BREAST FEEDING** Information on the use of angiotensin-II receptor antagonists in breast-feeding is limited. They are not recommended in breast-feeding and alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** In general, manufacturers advise caution in mild to moderate impairment (limited information available); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**

**Dose adjustments** Use with caution, starting with low dose, and adjust according to response.

**MONITORING REQUIREMENTS** Monitor plasma-potassium concentration, particularly in the elderly and in patients with renal impairment.

**Azilsartan medoxomil**

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult 18-74 years: Initially 40 mg once daily, increased if necessary to 80 mg once daily
  - Adult 75 years and over: Initially 20–40 mg once daily, increased if necessary to 80 mg once daily

**Hypertension with intravascular volume depletion**

- **BY MOUTH**
  - Adult: Initially 20–40 mg daily, increased if necessary to 80 mg daily

**CAUTIONS** Heart failure

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists

**SIDE-EFFECTS**

- **Uncommon** Hyperuricaemia • muscle spasms • peripheral oedema

**HEPATIC IMPAIRMENT**

**Dose adjustments** Manufacturer advises consider initial dose of 20 mg in mild to moderate impairment.

**Monitoring** Manufacturer advises monitor closely in mild to moderate hepatic impairment (limited information available).

**RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Edarbi (Takeda UK Ltd)
  - Azilsartan medoxomil 20 mg Edarbi 20mg tablets 28 tablet £16.80 DT = £16.80
  - Azilsartan medoxomil 40 mg Edarbi 40mg tablets 28 tablet £16.80 DT = £16.80
  - Azilsartan medoxomil 80 mg Edarbi 80mg tablets 28 tablet £19.95 DT = £19.95
Candesartan cilexetil

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 8 mg once daily, increased if necessary up to 32 mg once daily, doses to be increased at intervals of 4 weeks; usual dose 8 mg once daily
  - **Hypertension with intravascular volume depletion**
    - **BY MOUTH**
      - Adult: Initially 4 mg once daily, increased if necessary up to 32 mg daily, doses to be increased at intervals of 4 weeks; usual dose 8 mg once daily
  - **Heart failure with impaired left ventricular systolic function when ACE inhibitors are not tolerated**
    - **BY MOUTH**
      - Adult: Initially 4 mg once daily, increased at intervals of at least 2 weeks to ‘target’ dose of 32 mg once daily or to maximum tolerated dose; maximum 32 mg per day

- **CONTRA-INDICATIONS**
- **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists
- **SIDE-EFFECTS**
  - Common or very common: Increased risk of infection
  - Rare or very rare: Agranulocytosis, hepatitis, hyponatraemia, leucopenia, neutropenia
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in severe impairment or cholestasis.
  - **Dose adjustments**
  - Manufacturer advises initial dose reduction to 4 mg once daily in mild to moderate impairment; adjust according to response.
- **RENAL IMPAIRMENT**
  - Use with caution if eGFR less than 30 mL/minute/1.73 m².
  - **Dose adjustments**
  - Initially 4 mg daily.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Candesartan cilexetil (Non-proprietary)
  - Candesartan cilexetil 2 mg: Candesartan 2mg tablets | 7 tablet (PO) £2.86 DT = £1.76
  - Candesartan cilexetil 4 mg: Candesartan 4mg tablets | 7 tablet (PO) £3.88 DT = £0.54 | 28 tablet (PO) £0.49–£3.78
  - Candesartan cilexetil 8 mg: Candesartan 8mg tablets | 28 tablet (PO) £9.89 DT = £0.99
  - Candesartan cilexetil 16 mg: Candesartan 16mg tablets | 28 tablet (PO) £12.72 DT = £1.78
  - Candesartan cilexetil 32 mg: Candesartan 32mg tablets | 28 tablet (PO) £16.13 DT = £1.76
  - Amias (Takeda UK Ltd)
    - Candesartan cilexetil 2 mg: Amias 2mg tablets | 7 tablet (PO) £3.58 DT = £1.76
    - Candesartan cilexetil 4 mg: Amias 4mg tablets | 7 tablet (PO) £3.88 DT = £0.54 | 28 tablet (PO) £9.78
    - Candesartan cilexetil 8 mg: Amias 8mg tablets | 28 tablet (PO) £9.89 DT = £0.99
    - Candesartan cilexetil 16 mg: Amias 16mg tablets | 28 tablet (PO) £12.72 DT = £1.78
    - Candesartan cilexetil 32 mg: Amias 32mg tablets | 28 tablet (PO) £16.13 DT = £1.76

Eprosartan

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult: 600 mg once daily
  - **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists
  - **SIDE-EFFECTS**
    - Common or very common: Gastrointestinal disorder, rhinitis
  - **RENAL IMPAIRMENT**
    - Dose adjustments: Caution if eGFR less than 30 mL/minute/1.73 m².

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 21
  - Eprosartan (Non-proprietary)
    - Eprosartan (as Eprosartan mesilate) 300 mg: Eprosartan 300mg tablets | 28 tablet (PO) £7.31 DT = £7.31
    - Eprosartan (as Eprosartan mesilate) 400 mg: Eprosartan 400mg tablets | 56 tablet (PO) £13.43 DT = £13.17
    - Eprosartan (as Eprosartan mesilate) 600 mg: Eprosartan 600mg tablets | 28 tablet (PO) £14.31 DT = £14.31
    - Teveten (Mylan)
      - Eprosartan (as Eprosartan mesilate) 300 mg: Teveten 300mg tablets | 28 tablet (PO) £7.31 DT = £7.31
      - Eprosartan (as Eprosartan mesilate) 600 mg: Teveten 600mg tablets | 28 tablet (PO) £14.31 DT = £14.31

Irbesartan

- **INDICATIONS AND DOSE**
  - **Hypertension**
    - **BY MOUTH**
      - Adult 18–74 years: Initially 150 mg once daily, increased if necessary to 300 mg once daily
      - Adult 75 years and over: Initially 75–150 mg once daily, increased if necessary to 300 mg once daily
  - **Renal disease in hypertensive type 2 diabetes mellitus**
    - **BY MOUTH**
      - Adult 18–74 years: Initially 150 mg once daily, increased if tolerated to 300 mg once daily
      - Adult 75 years and over: Initially 75–150 mg once daily, increased if tolerated to 300 mg once daily
  - **Renal disease in hypertensive type 2 diabetes mellitus in patients receiving haemodialysis**
    - **BY MOUTH**
      - Adult: Initially 75–150 mg once daily, increased if necessary to 300 mg once daily

- **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists
- **SIDE-EFFECTS**
  - Common or very common: Musculoskeletal pain
  - Uncommon: Chest pain, dyspepsia, flushing, hepatic disorders, sexual dysfunction, tachycardia
  - Frequency not known: Hypersensitivity vasculitis, muscle cramps, taste altered, tinnitus
**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **Irbesartan (Non-proprietary)**
  - **Irbesartan 75 mg** [Irbesartan 75mg tablets] | 28 tablet [PoM] £9.69 DT = £1.43
  - **Irbesartan 150 mg** [Irbesartan 150mg tablets] | 28 tablet [PoM] £11.84 DT = £2.18
  - **Irbesartan 300 mg** [Irbesartan 300mg tablets] | 28 tablet [PoM] £15.93 DT = £2.77
- **Aprovel** (Sanofi)
  - **Irbesartan 75 mg** [Aprovel 75mg tablets] | 28 tablet [PoM] £9.69 DT = £1.43
  - **Irbesartan 150 mg** [Aprovel 150mg tablets] | 28 tablet [PoM] £11.84 DT = £2.18
  - **Irbesartan 300 mg** [Aprovel 300mg tablets] | 28 tablet [PoM] £15.93 DT = £2.77
- **Ifirmasta** (Consilient Health Ltd)
  - **Irbesartan 75 mg** [Ifirmasta 75mg tablets] | 28 tablet [PoM] £8.23 DT = £1.43
  - **Irbesartan 150 mg** [Ifirmasta 150mg tablets] | 28 tablet [PoM] £10.06 DT = £2.18
  - **Irbesartan 300 mg** [Ifirmasta 300mg tablets] | 28 tablet [PoM] £13.54 DT = £2.77

**Chronic heart failure when ACE inhibitors are unsuitable or contra-indicated**
- **BY MOUTH**
  - **Adult:** Initially 12.5 mg once daily, increased if tolerated to up to 150 mg once daily, doses to be increased at weekly intervals

**Hypertension (including reduction of stroke risk in hypertension with left ventricular hypertrophy)**
- **BY MOUTH**
  - **Adult 18-75 years:** Initially 50 mg once daily for several weeks, then increased if necessary to 100 mg once daily
  - **Adult 76 years and over:** Initially 25 mg once daily for several weeks, then increased if necessary to 100 mg once daily

**Hypertension with intravascular volume depletion**
- **BY MOUTH**
  - **Adult 18-75 years:** Initially 25 mg once daily for several weeks, then increased if necessary up to 100 mg once daily

**Irbesartan with hydrochlorothiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, irbesartan p. 175, hydrochlorothiazide p. 166.

**INDICATIONS AND DOSE**

**Hypertension not adequately controlled with irbesartan alone**
- **BY MOUTH**
- **Adult:** (consult product literature)

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists · thiazide diuretics

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Irbesartan with hydrochlorothiazide (Non-proprietary)**
  - **Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg** [Irbesartan 150mg / Hydrochlorothiazide 12.5mg tablets] | 28 tablet [PoM] £7.92 DT = £1.46
  - **Hydrochlorothiazide 25 mg, Irbesartan 300 mg** [Irbesartan 300mg / Hydrochlorothiazide 25mg tablets] | 28 tablet [PoM] £8.24 DT = £1.66
  - **Hydrochlorothiazide 12.5 mg, Irbesartan 300 mg** [Irbesartan 300mg / Hydrochlorothiazide 12.5mg tablets] | 28 tablet [PoM] £10.37 DT = £1.67
- **CoAprovel** (Sanofi)
  - **Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg** [CoAprovel 150mg/12.5mg tablets] | 28 tablet [PoM] £11.84 DT = £2.47
  - **Hydrochlorothiazide 25 mg, Irbesartan 300 mg** [CoAprovel 300mg/25mg tablets] | 28 tablet [PoM] £15.93 DT = £3.47
  - **Hydrochlorothiazide 12.5 mg, Irbesartan 300 mg** [CoAprovel 300mg/12.5mg tablets] | 28 tablet [PoM] £15.93 DT = £3.47

**Losartan potassium**

**INDICATIONS AND DOSE**

**Diabetic nephropathy in type 2 diabetes mellitus**
- **BY MOUTH**
  - **Adult 18-75 years:** Initially 50 mg once daily for several weeks, then increased if necessary to 100 mg once daily
  - **Adult 76 years and over:** Initially 25 mg once daily for several weeks, then increased if necessary to 100 mg once daily

**CAUTIONS** Severe heart failure

**SIDE-EFFECTS**
- **Common or very common** Anaemia · hypoglycaemia · postural disorders
- **Uncommon** Angina pectoris · constipation · drowsiness · dyspnoea · oedema · palpitations · sleep disorder
- **Rare or very rare** Atrial fibrillation · hepatitis · hypersensitivity · paraesthesia · stroke · syncope · vasculitis
- **Frequency not known** Depression · erectile dysfunction · hynotonatrexia · influenza like illness · malaise · migraine · pancreatitis · photosensitivity reaction · rhabdomyolysis · taste altered · tinnitus · urinary tract infection

**HEPATIC IMPAIRMENT**

Dose adjustments
- Manufacturer advises consider dose reduction if history of impairment (risk of increased plasma concentrations).

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include berry-citrus.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral suspension**
- **Cozaar** (Merck Sharpe & Dohme Ltd)
  - **Losartan potassium 2.5 mg per 1 ml** [Cozaar 2.5mg/ml oral suspension sugar-free] | 200 ml [PoM] £53.68 DT = £53.68

**Tablet**
- **Losartan potassium (Non-proprietary)**
  - **Losartan potassium 12.5 mg** [Losartan 125mg tablets] | 28 tablet [PoM] £30.00 DT = £3.09
  - **Losartan potassium 25 mg** [Losartan 25mg tablets] | 28 tablet [PoM] £16.18 DT = £3.28
  - **Losartan potassium 50 mg** [Losartan 50mg tablets] | 28 tablet [PoM] £12.80 DT = £2.70
  - **Losartan potassium 100 mg** [Losartan 100mg tablets] | 28 tablet [PoM] £16.18 DT = £1.95
- **Cozaar** (Merck Sharp & Dohme Ltd)
  - **Losartan potassium 12.5 mg** [Cozaar 12.5mg tablets] | 28 tablet [PoM] £9.70 DT = £3.09
  - **Losartan potassium 25 mg** [Cozaar 25mg tablets] | 28 tablet [PoM] £16.18 DT = £3.28
  - **Losartan potassium 50 mg** [Cozaar 50mg tablets] | 28 tablet [PoM] £12.80 DT = £2.07
  - **Losartan potassium 100 mg** [Cozaar 100mg tablets] | 28 tablet [PoM] £16.18 DT = £1.95
Losartan with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, losartan potassium p. 176, hydrochlorothiazide p. 166.

**INDICATIONS AND DOSE**

**Hypertension not adequately controlled with losartan alone**

- **BY MOUTH**
- **Adult**: (consult product literature)

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists - thiazide diuretics

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Losartan with hydrochlorothiazide (Non-proprietary)**
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg
    - 50 mg: Losartan 50mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [POM] £12.80 DT = £1.21
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg
    - 100 mg: Losartan 100mg / Hydrochlorothiazide 25mg tablets | 28 tablet [POM] £16.18 DT = £1.29
- **Cozaar-Comp** (Merck Sharp & Dohme Ltd)
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg
    - 50 mg: Losartan 100mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [POM] £16.18 DT = £1.14
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg
    - 100 mg: Losartan 100mg / Hydrochlorothiazide 25mg tablets | 28 tablet [POM] £16.18 DT = £1.14

**Olmesartan medoxomil**

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
- **Adult**: Initially 10 mg daily, increased if necessary to 20 mg daily; maximum 40 mg per day

**CONTRA-INDICATIONS**

Biliary obstruction

**SIDE-EFFECTS**

- **Common or very common**
  - Arthritis - bone pain - chest pain - dyspepsia - haematuria - hypertriglyceridaemia - hypuricaemia - increased risk of infection - influenza like illness - oedema
- **Uncommon**
  - Angina pectoris - malaise
- **Rare or very rare**
  - Lethargy - muscle spasms - sprue-like enteropathy

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment; avoid in severe impairment (no information available).

**Dose adjustments**

Manufacturer advises maximum 20 mg daily in moderate impairment.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 20 mL/minute/1.73 m².

**Dose adjustments**

Max. 20 mg daily if eGFR 20–60 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Olmesartan medoxomil (Non-proprietary)**
  - Olmesartan medoxomil 10 mg: Olmesartan medoxomil 10mg tablets | 28 tablet [POM] £10.40 DT = £1.47
  - Olmesartan medoxomil 20 mg: Olmesartan medoxomil 20mg tablets | 28 tablet [POM] £12.30 DT = £1.52
  - Olmesartan medoxomil 40 mg: Olmesartan medoxomil 40mg tablets | 28 tablet [POM] £16.63 DT = £2.01
- **Olmetec** (Daiichi Sankyo UK Ltd)
  - Olmesartan medoxomil 10 mg: Olmetec 10mg tablets | 28 tablet [POM] £10.95 DT = £1.47
  - Olmesartan medoxomil 20 mg: Olmetec 20mg tablets | 28 tablet [POM] £12.95 DT = £1.52
  - Olmesartan medoxomil 40 mg: Olmetec 40mg tablets | 28 tablet [POM] £17.50 DT = £2.01

**Olmesartan with amlodipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil above, amlodipine p. 156.

**INDICATIONS AND DOSE**

**Hypertension in patients stabilised on the individual components in the same proportions**

- **BY MOUTH**
- **Adult**: (consult product literature)

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists - calcium channel blockers

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Sevikar** (Daiichi Sankyo UK Ltd)
  - Amlodipine (as Amlodipine besilate) 5 mg, Olmesartan medoxomil 20 mg: Sevikar 20mg/5mg tablets | 28 tablet [POM] £16.95 DT = £1.65
  - Amlodipine (as Amlodipine besilate) 10 mg, Olmesartan medoxomil 40 mg: Sevikar 40mg/10mg tablets | 28 tablet [POM] £16.95 DT = £1.65

**Olmesartan with amlodipine and hydrochlorothiazide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil above, amlodipine p. 156, hydrochlorothiazide p. 166.

**INDICATIONS AND DOSE**

**Hypertension in patients stabilised on the individual components in the same proportions, or for hypertension not adequately controlled with olmesartan and amlodipine**

- **BY MOUTH**
- **Adult**: (consult product literature)

**INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists - calcium channel blockers - thiazide diuretics

www.getintopharma.com
Blood pressure conditions

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Table
- Sevikar HCT (Daichii Sankyo UK Ltd)
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 20 mg
  - Sevikar HCT 20mg/5mg/12.5mg tablets | £16.95
- Amlodipine besilate 5 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg
  - Sevikar HCT 40mg/5mg/25mg tablets | £16.95
- Amlodipine besilate 10 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg
  - Sevikar HCT 40mg/10mg/25mg tablets | £16.95
- Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg
  - Sevikar HCT 40mg/5mg/12.5mg tablets | £16.95

Olmesartan with hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil p. 177, hydrochlorothiazide p. 166.

INDICATIONS AND DOSE
Hypertension not adequately controlled with olmesartan alone
  - BY MOUTH
  - Adult: (consult product literature)

INTERACTIONS
  → Appendix 1: angiotensin-II receptor antagonists - thiazide diuretics

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Table
  - Olmetec Plus (Daichii Sankyo UK Ltd)
    - Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 20 mg
      - Olmetec Plus 20mg/12.5mg tablets | £12.95
      - DT = £12.95
  - Hydrochlorothiazide 25 mg, Olmesartan medoxomil 20 mg
    - Olmetec Plus 20mg/12.5mg tablets | £12.95
      - DT = £12.95
    - Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg
      - Olmetec Plus 40mg/12.5mg tablets | £17.50
      - DT = £17.50

Telmisartan with hydrochlorothiazide
The properties listed below are those particular to the combination only. For the properties of the components please consider, telmisartan above, hydrochlorothiazide p. 166.

INDICATIONS AND DOSE
Hypertension not adequately controlled by telmisartan alone
  - BY MOUTH
  - Adult: (consult product literature)

INTERACTIONS
  → Appendix 1: angiotensin-II receptor antagonists - thiazide diuretics

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Table
  - Telmasrtan with hydrochlorothiazide (Non-proprietary)
    - Telmasrtan 20 mg Telmasrtan 20mg tablets | 28 tablet £10.55 DT = £2.26
    - Telmasrtan 40 mg Telmasrtan 40mg tablets | 28 tablet £12.93 DT = £5.17
    - Telmasrtan 80 mg Telmasrtan 80mg tablets | 28 tablet £16.15 DT = £4.90
  - Micards (Boehringer Ingelheim Ltd)
    - Micards 20 mg Micards 20mg tablets | 28 tablet £11.10 DT = £2.26
    - Micards 40 mg Micards 40mg tablets | 28 tablet £13.61 DT = £5.17
    - Micards 80 mg Micards 80mg tablets | 28 tablet £17.00 DT = £4.90
    - Tolura (Consilient Health Ltd)
      - Tolura 20 mg Tolura 20mg tablets | 28 tablet £11.10 DT = £2.26
      - Tolura 40 mg Tolura 40mg tablets | 28 tablet £13.61 DT = £5.17
      - Tolura 80 mg Tolura 80mg tablets | 28 tablet £17.00 DT = £4.90

Telmisartan

INDICATIONS AND DOSE
Hypertension
  - BY MOUTH
  - Adult: Initially 20–40 mg once daily for at least 4 weeks, increased if necessary up to 80 mg once daily

PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH ESTABLISHED Atherosclerotic Cardiovascular Disease, OR TYPE 2 DIABETES MELLITUS WITH TARGET-ORGAN DAMAGE
  - BY MOUTH
  - Adult: 80 mg once daily

CONTRA-INDICATIONS
  Biliary obstructive disorders - cholestasis

INTERACTIONS
  → Appendix 1: angiotensin-II receptor antagonists

SIDE-EFFECTS
  - Uncommon Anaemia - arthralgias - chest pain - cystitis - depression - dyspnoea - flatulence - gastrointestinal discomfort - hyperhidrosis - increased risk of infection - insomnia - muscle spasms - sciatia - syncope

Rare or very rare
  Anxiety - drowsiness - dry mouth - eosinophilia - hypoglycaemia - influenza-like illness - interstitial lung disease - liver disorder - pain in extremity - sepsis - taste altered - tendon pain - visual impairment

HEPATIC IMPAIRMENT
Dose adjustments Manufacturer advises maximum 40 mg daily in mild to moderate impairment.

RENAL IMPAIRMENT
Dose adjustments Manufacturer advises initial dose of 20 mg once daily in severe impairment.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Table
  - Micards Plus (Boehringer Ingelheim Ltd)
    - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
      - Micards Plus 12.5mg/40mg tablets | 28 tablet £13.61 DT = £3.61
    - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
      - Micards Plus 25mg/80mg tablets | 28 tablet £17.00 DT = £5.17
  - Actelors HCT (Actavis UK Ltd)
    - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
      - Actelors HCT 12.5mg/40mg tablets | 28 tablet £13.61 DT = £3.61
    - Hydrochlorothiazide 25 mg, Telmisartan 80 mg
      - Actelors HCT 25mg/80mg tablets | 28 tablet £17.00 DT = £5.17
  - MicardsPlus (Boehringer Ingelheim Ltd)
    - Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg
      - MicardsPlus 12.5mg/40mg tablets | 28 tablet £13.61 DT = £3.61
    - Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg
      - MicardsPlus 12.5mg/80mg tablets | 28 tablet £17.00 DT = £5.17
Valsartan

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 80 mg once daily, increased if necessary up to 320 mg daily, doses to be increased at intervals of up to 4 weeks

**Hypertension with intravascular volume depletion**
- **BY MOUTH**
  - Adult: Initially 40 mg once daily, increased if necessary up to 320 mg daily, doses to be increased at intervals of at least 2 weeks

**Heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used**
- **BY MOUTH**
  - Adult: Initially 40 mg twice daily, increased to up to 160 mg twice daily, doses to be increased at intervals of at least 2 weeks

**Myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct)**
- **BY MOUTH**
  - Adult: Initially 20 mg twice daily, increased if necessary up to 160 mg twice daily, doses to be increased over several weeks if tolerated

**CONTRA-INDICATIONS**
- Biliary cirrhosis - cholestasis

**INTERACTIONS**
- Appendix 1: angiotensin-II receptor antagonists - thiazide diuretics

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Valsartan with hydrochlorothiazide (Non-proprietary)
  - Hydrochlorothiazide 12.5 mg, Valsartan 80 mg: 28 tablet (BNF) £13.07 DT = £6.79
  - Hydrochlorothiazide 25 mg, Valsartan 160 mg: 28 tablet (BNF) £18.41 DT = £7.81

**DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM**

**Aliskiren**

**DRUG ACTION**
- Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I.

**INDICATIONS AND DOSE**
- Essential hypertension either alone or in combination with other antihypertensives
  - **BY MOUTH**
    - Adult: 150 mg once daily, increased if necessary to 300 mg once daily

**CONTRA-INDICATIONS**
- Concomitant treatment with an ACE inhibitor or an angiotensin-II receptor antagonist in patients with an eGFR less than 60 mL/minute/1.73 m² - concomitant treatment with an ACE inhibitor or an angiotensin-II receptor antagonist in patients with diabetes mellitus - hereditary angioedema - idiopathic angioedema

**CAUTIONS**
- Combination treatment with an ACE inhibitor - combination treatment with an angiotensin-II receptor antagonist - concomitant use of diuretics (first doses may cause hypotension - initiate with care) - history of angioedema - moderate to severe congestive heart failure - patients at risk of renal impairment - salt depletion (first doses may cause hypotension - initiate with care) - volume depletion (first doses may cause hypotension - initiate with care)
CAUTIONS, FURTHER INFORMATION

- Concomitant use of drugs affecting the renin-angiotensin system. Combination therapy with two drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin-II receptor antagonists, and aliskiren) is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment, compared to use of a single drug. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor with an angiotensin-II receptor antagonist. There is some evidence that the benefits of combination use of an ACE inhibitor with candesartan or valsartan may outweigh the risks in selected patients with heart failure for whom other treatments are unsuitable, however, the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended. For patients currently taking combination therapy, the need for continued combined therapy should be reviewed. If combination therapy is considered essential, it should be carried out under specialist supervision, with close monitoring of blood pressure, renal function, and electrolytes (particularly potassium); monitoring should be considered at the start of treatment, then monthly, and also after any change in dose or during intercurrent illness.

- INTERACTIONS ➔ Appendix 1: aliskiren

- SIDE-EFFECTS ➔ Appendix 2: aliskiren

- Common or very common Arthralgia • diarrhea • dizziness • electrolyte imbalance

- Uncommon Cough • oral disorder • palpitations • peripheral oedema • renal impairment • severe cutaneous adverse reactions (SCARs) • skin reactions

- Rare or very rare Angioedema • hypersensitivity

- Frequency not known Dyspnoea • hepatic disorders • nausea • vertigo • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

- If diuretics are severe or persistent discontinue treatment.

- PREGNANCY Manufacturer advises avoid—no information available; other drugs acting on the renin-angiotensin system have been associated with fetal malformations and neonatal death.

- BREAST FEEDING Present in milk in animal studies—manufacturer advises avoid.

- RENAL IMPAIRMENT Avoid if eGFR is less than 30 mL/minute/1.73 m²—no information available. Use with caution in renal artery stenosis—no information available.

- Monitoring Monitor plasma-potassium concentration in renal impairment.

- MONITORING REQUIREMENTS Monitor patients with a history of angioedema closely during treatment.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SMC No. 462/08

The Scottish Medicines Consortium has advised (February 2010) that aliskiren (Rasilez®) is not recommended for use within NHS Scotland for the treatment of essential hypertension as the economic case was not demonstrated.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

- Rasilez (Noden Pharma DAC) Aliskiren (as Aliskiren hemifumarate) 150 mg tablets | 28 tablet | £28.51 DT + £28.51 Aliskiren (as Aliskiren hemifumarate) 300 mg tablets | 28 tablet | £34.27 DT + £34.27

VASODILATORS ➔ VASODILATOR ANTIHYPERTENSIVES

Hydralazine hydrochloride [29-Mar-2017]

INDICATIONS AND DOSE

Moderate to severe hypertension (adjunct) ➔ BY MOUTH

- Adult: Initially 25 mg twice daily, increased if necessary up to 50 mg twice daily

Heart failure (with long acting nitrate) (initiated in hospital or under specialist supervision) ➔ BY MOUTH

- Adult: Initially 25 mg 3–4 times a day, subsequent doses to be increased every 2 days if necessary; usual maintenance 50–75 mg 4 times a day

Hypertensive emergencies (including during pregnancy) ➔ By intravenous infusion

- Adult: Initially 200–300 micrograms/minute; usual maintenance 50–150 micrograms/minute

- By slow intravenous injection

- Adult: 5–10 mg, to be diluted with 10 mL sodium chloride 0.9%; dose may be repeated after 20–30 minutes

CONTRA-INDICATIONS

Acute porphyrias p. 1058 • cor pulmonale • disseasing aortic aneurysm • high output heart failure • idiopathic systemic lupus erythematosus • myocardial insufficiency due to mechanical obstruction • severe tachycardia

CAUTIONS

Cerebrovascular disease • coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilised) • occasionally blood pressure reduction too rapid even with low parenteral doses

INTERACTIONS ➔ Appendix 1: hydralazine

SIDE-EFFECTS

- Common or very common Angina pectoris • diarrhea • dizziness • flushing • gastrointestinal disorders • headache • hypotension • joint disorders • lupus-like syndrome (after long-term therapy with over 100 mg daily (or less in women and in slow acetylator individuals)) • myalgia • nasal congestion • nausea • palpitations • tachycardia • vomiting

- Rare or very rare Acute kidney injury • agranulocytosis • anaemia • anxiety • appetite decreased • conjunctivitis • depression • dyspnoea • eosinophilia • eye disorders • fever • glomerulonephritis • haematuria • haemolytic anaemia • hallucination • heart failure • hepatic disorders • leucocytosis • leucopenia • lymphadenopathy • malaise • nerve disorders • neutropenia • oedema • pancytopenia • paradoxical pressor response • paraesthesia • pleuritic pain • proteinuria • skin reactions • splenomegaly • thrombocytopenia • urinary retention • vasculitis • weight decreased

SIDE-EFFECTS, FURTHER INFORMATION

The incidence of side-effects is lower if the dose is kept below 100mg daily, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

PREGNANCY

Neonatal thrombocytopenia reported, but risk should be balanced against risk of uncontrolled maternal hypertension. Manufacturer advises avoid before third trimester.

BREAST FEEDING

Present in milk but not known to be harmful.

Monitoring

Monitor infant in breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution (risk of accumulation).

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Dose adjustments Manufacturer advises adjust dose or dosing interval according to clinical response.

- **RENAI IMPAIRMENT**
  - **Dose adjustments** Reduce dose if eGFR less than 30 mL/minute/1.73 m².
  
- **MONITORING REQUIREMENTS** Manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose above 100 mg daily, but evidence of clinical value unsatisfactory.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Apresoline®) give continuously in Sodium chloride 0.9%. Suggested infusion volume 500 mL.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution.

- **Tablet**
  - **EXCIPIENTS:** May contain Gluten, propylene glycol
  
  **Hydralazine hydrochloride (Non-proprietary)**
  - Hydralazine hydrochloride 25 mg | 56 tablet | £0.37 DT = £15.18 | 84 tablet | £14.00
  - Hydralazine hydrochloride 50 mg | 56 tablet | £0.82 DT = £15.46
  - **Apresoline** (Advanz Pharma)
    - Hydralazine hydrochloride 25 mg | 84 tablet | £1.38
  
  **Powder for solution for injection**
  - **Hydralazine hydrochloride (Non-proprietary)**
    - Hydralazine hydrochloride 20 mg | Hydralazine 20mg powder for concentrate for solution for injection ampoules | 5 ampoule | £74.17

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Minoxidil

- **INDICATIONS AND DOSE**
  - **Severe hypertension, in addition to a diuretic and a beta-blocker**
    - **BY MOUTH**
      - **Adult:** Initially 5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day
      - **Elderly:** Initially 2.5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day

- **CONTRA-INDICATIONS**
  - Phaeochromocytoma
  - **CAUTIONS**
    - Acute porphyrias p. 1058 - after myocardial infarction (usually 3–4 weeks) - history of cerebrovascular accident
  
- **INTERACTIONS**
  - Appendix 1: minoxidil

- **SIDE-EFFECTS**
  - **Common or very common** Fluid retention - hair changes - oedema - cardiac disorders - pericarditis - tachycardia
  - **Rare or very rare** Leucopenia - skin reactions - Stevens-Johnson syndrome - thrombocytopenia
  
- **Frequency not known** Angina pectoris - breast tenderness - gastrointestinal disorder - pleural effusion - sodium retention - weight increased

- **PREGNANCY** Avoid - possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.

- **BREAST FEEDING** Present in milk but not known to be harmful.

- **RENAI IMPAIRMENT** Use with caution in significant impairment.

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4.1a Hypertension associated with phaeochromocytoma

Other drugs used for Hypertension associated with phaeochromocytoma

Propranolol hydrochloride, p. 150

**VASODILATORS > PERIPHERAL VASODILATORS**

**Phenoxybenzamine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Hypertension in phaeochromocytoma**
    - **BY MOUTH**
      - **Adult:** Initially 10 mg daily, increased in steps of 10 mg daily until hypertension controlled or treatment not tolerated; maintenance 1–2 mg/kg daily in 2 divided doses

- **CONTRA-INDICATIONS** During recovery period after myocardial infarction (usually 3–4 weeks) - history of cerebrovascular accident

- **CAUTIONS**
  - Avoid contact with skin (risk of contact sensitisation) - avoid in Acute porphyrias p. 1058 - carcinogenic in animals - cerebrovascular disease - congestive heart failure - elderly - severe ischaemic heart disease

- **SIDE-EFFECTS**
  - Abdominal distress - dizziness - ejaculation failure - fatigue - miosis - nasal congestion - postural hypotension - reflex tachycardia

- **PREGNANCY** Hypertension may occur in newborn.

- **BREAST FEEDING** May be present in milk.

- **RENAI IMPAIRMENT** Use with caution.

- **HANDLING AND STORAGE** Owing to risk of contact sensitisation healthcare professionals should avoid contamination of hands.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- **Capsule**
  - Phenoxybenzamine hydrochloride (Non-proprietary)
    - Phenoxybenzamine hydrochloride 10 mg | 10 mg capsules | 30 capsule | £106.61

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**Phentolamine mesilate**

- **INDICATIONS AND DOSE**
  - **Hypertensive episodes due to phaeochromocytoma e.g. during surgery**
    - **BY INTRAVENOUS INJECTION**
      - **Adult:** 2–5 mg, repeated if necessary

- **Diagnosis of phaeochromocytoma**
  - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  
  - **Adult:** (consult product literature)
CONTRA-INDICATIONS  Angina - coronary insufficiency - evidence of coronary artery disease - history of myocardial infarction - hypotension

CAUTIONS  Elderly - gastritis - peptic ulcer

SIDE-EFFECTS
- Common or very common  Arrhythmias - headache - hypertension - oral pain - post procedural pain
- Uncommon  Abdominal pain upper - diarrhoea - facial swelling - pain - paraesthesia - pruritus - vomiting

PREGNANCY  Use with caution—may cause marked decrease in maternal blood pressure with resulting fetal anoxia.

BREAST FEEDING  Manufacturer advises avoiding exposure to breast feeding.

RENA L IMPAIRMENT  Frequency not known
- Uncommon

SIDE-EFFECTS
- INTERACTIONS

CAUTIONS
- CONTRA-INDICATIONS

Medication forms
- FORMS  Forms available from special-order manufacturers include: solution for injection

INTERACTIONS
- ACTING

Vasodilators

182 Blood pressure conditions

MAP 40 mL/minute/

Antihypertensives

Sodium nitroprusside

Caution

UNLICENSED USE  Not licensed for use in the UK.

CONTRA-INDICATIONS  Compensatory hypertension - Leber’s optic atrophy - severe vitamin B12 deficiency

CAUTIONS  Elderly - hypotension - ischaemic heart disease - impair ed cerebral circulation - ischaemic heart disease

INTERACTIONS  Appendix 1: sodium nitroprusside

SIDE-EFFECTS
- Uncommon  Depression - dermatitis - dry mouth - heart failure - nausea - vision blurred - vomiting
- Rare or very rare  Alopecia - asthma - ischaemic heart disease - myalgia - parotid gland enlargement - tremor
- PREGNANCY  Postural hypotension and reduced uteroplacental perfusion. Should not be used to treat hypertension in pregnancy.
- REN AL IMPAIRMENT  Avoid if eGFR less than 40 mL/minute/1.73 m².
- Dose adjustments  Reduce dose if eGFR 40–65 mL/minute/1.73 m².
- LESS SUITABLE FOR PRESCRIBING  Guanethidine monosulfate is less suitable for prescribing.

Other drugs used for Hypertensive crises

Hydralazine hydrochloride, p. 180  Labetalol hydrochloride, p. 148

Cautions

Avoid if eGFR less than 40 mL/minute/1.73 m².

M edication forms

Sodium nitroprusside

Indications and Dose

Hypertensive crises
- Hypertensive crises (but no longer recommended)

Hypertensive emergencies
- By intravenous infusion

Adult: Initially 0.5–1.5 micrograms/kg/minute, increased in steps of 500 nanograms/kg/minute every 5 minutes, usual dose 0.5–8 micrograms/kg/minute, use lower doses if already receiving other antihypertensives, stop if response unsatisfactory with max. dose in 10 minutes, lower initial dose of 300 nanograms/kg/minute has been used

Maintenance of blood pressure at 30–40% lower than pretreatment diastolic blood pressure
- By intravenous infusion

Adult: 20–400 micrograms/min, use lower doses for patients being treated with other antihypertensives

Controlled hypotension in anaesthesia during surgery
- By intravenous infusion

Adult: To 1.5 micrograms/kg/minute

Acute or chronic heart failure
- By intravenous infusion

Adult: Initially 10–15 micrograms/minute, increased every 5–10 minutes as necessary; usual dose 10–200 micrograms/minute normally for max. 3 days

MONITORING REQUIREMENTS  Monitor blood pressure (including intra-arterial blood pressure) and blood-

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Pulmonary hypertension

4.1c Pulmonary hypertension

Other drugs used for Pulmonary hypertension
Epoprostenol, p. 115 · Sildenafil, p. 813 · Tadalafil, p. 814

ANTITHROMBOTIC DRUGS > ANTIPLATELET DRUGS

Selexipag

DRUG ACTION Selexipag is a selective prostacyclin (IP) receptor agonist.

INDICATIONS AND DOSE
Pulmonary arterial hypertension either as combination therapy (if insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type-5 inhibitor), or as monotherapy (initiated under specialist supervision)

BY MOUTH

Adult: Initially 200 micrograms twice daily, increased in steps of 200 micrograms twice daily at weekly intervals up to the highest tolerated dose. Usual maintenance 200–1600 micrograms twice daily. Initial dose and first dose after each dose increase should be taken in the evening. Maximum 3200 micrograms per day.

CONTRA-INDICATIONS Cerebrovascular event (within the last 3 months) congenital or acquired valvular defects with myocardial function disorders (not related to pulmonary hypertension) decompenated cardiac failure (unless under close medical supervision). Myocardial infarction (within last 6 months) severe arrhythmias severe coronary heart disease unstable angina.

CAUTIONS Elderly, limited information available.

INTERACTIONS Appendix 1: selexipag.

SIDE-EFFECTS

Common or very common Abdominal pain, anaemia, appetite decreased, arthralgia, diarrhoea, flushing, headache, hyperthyroidism, hypotension, myalgia, nasal congestion, nasopharyngitis, nausea, pain, skin reactions, vomiting, weight decreased.

Uncommon Sinus tachycardia.

PREGNANCY Manufacturer advises avoid—no information available.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises caution in moderate impairment (risk of increased exposure); avoid in severe impairment (no information available).

Dose adjustments Manufacturer advises initial dose reduction to 200 micrograms once daily in moderate impairment, increased in steps of 200 micrograms once daily at weekly intervals up to the highest tolerated dose.

RENAL IMPAIRMENT Manufacturer advises caution with dose titration in severe impairment.

PATIENT AND CARER ADVICE
Missed doses Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. If a dose is missed for 3 days or more, treatment should be restarted at a lower dose and then increased—consult product literature.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
SMC No. 1235/17 The Scottish Medicines Consortium has advised (updated May 2018) that selexipag (Uptravi®) is accepted for restricted use within NHS Scotland for the long-term treatment of pulmonary arterial hypertension in adults with WHO functional class III, as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and a phosphodiesterase type-5 inhibitor, and who would be considered for treatment with inhaled iloprost. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

All Wales Medicines Strategy Group (AWMSG) decisions
AWMSG No. 700
The All Wales Medicines Strategy Group has advised (June 2018) that selexipag (Uptravi®) is recommended as an option for restricted use within NHS Wales as a triple combination therapy for the treatment of pulmonary arterial hypertension (PAH) in adults with WHO functional class III as combination therapy in patients insufficiently controlled on dual therapy with an endothelin receptor antagonist and a phosphodiesterase type-5 inhibitor. Selexipag (Uptravi®) is not recommended for use within NHS Wales outside of this sub-population. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

Uptravi (Actelion Pharmaceuticals UK Ltd)

Selexipag 200 microgram Uptravi 200 microgram tablets | 60 tablet (Posm) £3,000.00 | 140 tablet (Posm) £7,000.00
Selexipag 400 microgram Uptravi 400 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 600 microgram Uptravi 600 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 800 microgram Uptravi 800 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 1 mg Uptravi 1,000 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 1.2 mg Uptravi 1,200 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 1.4 mg Uptravi 1,400 microgram tablets | 60 tablet (Posm) £3,000.00
Selexipag 1.6 mg Uptravi 1,600 microgram tablets | 60 tablet (Posm) £3,000.00
ANTITHROMBOTIC DRUGS > PROSTAGLANDINS, CARDIOVASCULAR

Iloprost

- **INDICATIONS AND DOSE**
  - Idiopathic or familial pulmonary arterial hypertension (initiated under specialist supervision)
  - By inhalation of nebulised solution
  - Adult: Initially 2.5 micrograms for 1 dose, increased to 5 micrograms for 1 dose, increased if tolerated to 5 micrograms 6–9 times a day, adjusted according to response; reduced if not tolerated to 2.5 micrograms 6–9 times a day, reduce to lower maintenance dose if high dose not tolerated

- **CONTRA-INDICATIONS**
  - Conditions which increase risk of haemorrhage: congenital or acquired valvular defects of the myocardium, decompensated cardiac failure (unless under close medical supervision), pulmonary veno-occlusive disease, severe arrhythmias, unstable angina, within 3 months of cerebrovascular events, within 6 months of myocardial infarction

- **CAUTIONS**
  - **GENERAL CAUTIONS**
    - Hypotension (do not initiate if systolic blood pressure below 85 mmHg), unstable pulmonary hypertension with advanced right heart failure
  - **SPECIFIC CAUTIONS**
    - Acute pulmonary infection, chronic obstructive pulmonary disease, severe asthma

- **INTERACTIONS**
  - Appendix 1: Iloprost

- **SIDE-EFFECTS**
  - Common or very common: Chest discomfort, cough, diarrhoea, dizziness, dysphonia, haemorrhage, headache, hypotension, nausea, oral disorders, pain, palpitations, rash, syncope, tachycardia, throat complaints, vasodilatation, vomiting
  - Frequency not known: Respiratory disorders, taste altered, thrombocytopenia

- **PREGNANCY**
  - Use if potential benefit outweighs risk.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Elimination reduced.
  - Dose adjustments: Initially 2.5 micrograms at intervals of 3–4 hours (max. 6 times daily), adjusted according to response (consult product literature).

- **DIRECTIONS FOR ADMINISTRATION**
  - For inhale treatment, to minimise accidental exposure use only with nebulisers listed in Ventavis product literature in a well ventilated room.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Delivery characteristics of nebuliser devices may vary—only switch devices under medical supervision.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
  - SMC No. 219/05
  - The Scottish Medicines Consortium has advised (December 2005) that iloprost (Ventavis®) is accepted for restricted use within NHS Scotland in patients in whom bosentan is ineffective or not tolerated, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Nebuliser liquid
    - **Ventavis** (Bayer Plc)
      - Iloprost (as iloprost trometamol) 10 microgram per 1 ml
      - Ventavis 10 micrograms/ml nebuliser solution 1ml ampoules (42 ampoule £560.27, 168 ampoule £2,241.08)
    - Iloprost (as iloprost trometamol) 20 microgram per 1 ml
      - Ventavis 20 micrograms/ml nebuliser solution 1ml ampoules (42 ampoule £560.27, 168 ampoule £2,241.08)

ENDOTHELIN RECEPTOR ANTAGONISTS

Ambrisentan

- **INDICATIONS AND DOSE**
  - Pulmonary arterial hypertension (initiated under specialist supervision)
  - By mouth
    - Adult: 5 mg once daily, increased if necessary to 10 mg once daily

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises max. dose 5 mg daily and close monitoring with concurrent use of ciclosporin.

- **CONTRA-INDICATIONS**
  - Idiopathic pulmonary fibrosis

- **CAUTIONS**
  - Not to be initiated in significant anaemia

- **INTERACTIONS**
  - Appendix 1: ambrisentan

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain, anaemia, asthenia, constipation, diarrhoea, dizziness, epistaxis, flushing, headaches, hypersensitivity, increased risk of infection, nasal congestion, nausea, palpitations, skin reactions, syncope, tinnitus, vision disorders, vomiting
  - Uncommon: Hepatic disorders, sudden hearing loss

- **CONCEPTION AND CONTRACEPTION**
  - Exclude pregnancy before treatment and ensure effective contraception during treatment. Monthly pregnancy tests advised.

- **PREGNANCY**
  - Avoid (teratogenic in animal studies).

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in severe impairment or if baseline serum transaminases exceed 3 times the upper limit of normal.

- **RENAL IMPAIRMENT**
  - Use with caution if eGFR less than 30 ml/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor haemoglobin concentration or haematocrit after observation (consult product literature).

- **Scottish Medicines Consortium (SMC) decisions**
  - SMC No. 511/08
  - The Scottish Medicines Consortium has advised (November 2008) that ambrisentan (Volibris®) is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity, when prescribed by specialists in the Scottish Pulmonary Vascular Unit or similar specialists.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Volibris (GlaxoSmithKline UK Ltd)
  - Ambrisentan 5 mg Volibris 5mg tablets | 30 tablet £1,618.08
  - Ambrisentan 10 mg Volibris 10mg tablets | 30 tablet £1,618.08

www.getintopharma.com
Bosentan

- INDICATIONS AND DOSE
  Pulmonary arterial hypertension (initiated under specialist supervision)
  > BY MOUTH
  > Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily (max. per dose 250 mg); maximum 500 mg per day

- Systemic sclerosis with ongoing digital ulcer disease (to reduce number of new digital ulcers)
  > BY MOUTH
  > Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily

- CONTRA-INDICATIONS
  Acute porphyrias p. 1058

- CAUTIONS
  Not to be initiated if systemic systolic blood pressure is below 85 mmHg

- INTERACTIONS
  > Appendix 1: bosentan

- SIDE-EFFECTS
  > Common or very common
    Anaemia - diarrhoea - flushing - gastrooesophageal reflux disease - headache - nasal congestion - palpitations - skin reactions - syncope
  > Uncommon
    Hepatic disorders - leucopenia - neutropenia - thrombocytopenia
  > Rare or very rare
    Angioedema
  > Frequency not known
    Vision blurred

- CONCEPTION AND CONTRACEPTION
  Effective contraception required during administration (hormonal contraception not considered effective). Monthly pregnancy tests advised.

- PREGNANCY
  Avoid (teratogenic in animal studies).

- BREAST FEEDING
  Manufacturer advises avoid—no information available.

- HEPATIC IMPAIRMENT
  Manufacturer advises avoid in moderate-to-severe impairment or if baseline serum transaminases exceed 3 times the upper limit of normal.

- MONITORING REQUIREMENTS
  > Monitor haemoglobin before and during treatment, monthly for first 4 months, then 3-monthly.
  > Monitor liver function before treatment, at monthly intervals during treatment, and 2 weeks after dose increase (reduce dose or suspend treatment if liver enzymes raised significantly)—discontinue if symptoms of liver impairment.

- TREATMENT CESSION
  Avoid abrupt withdrawal—withdraw treatment gradually.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Tablet
  > Bosentan (Non-proprietary)
    Bosentan (as Bosentan monohydrate) 62.5 mg 62.5 mg tablets | 56 tablet £112.50–£1,510.21
    Bosentan (as Bosentan monohydrate) 125 mg 125 mg tablets | 56 tablet £112.50–£1,510.21
  > Stayveer (Advanz Pharma)
    Bosentan (as Bosentan monohydrate) 62.5 mg Stayveer 62.5 mg tablets | 56 tablet £208.34
    Bosentan (as Bosentan monohydrate) 125 mg Stayveer 125 mg tablets | 56 tablet £208.34
  > Tracleer (Actelion Pharmaceuticals UK Ltd)
    Bosentan (as Bosentan monohydrate) 62.5 mg Tracleer 62.5 mg tablets | 56 tablet £1,510.21
    Bosentan (as Bosentan monohydrate) 125 mg Tracleer 125 mg tablets | 56 tablet £1,510.21

Macitentan

- INDICATIONS AND DOSE
  Pulmonary arterial hypertension (initiated under specialist supervision)
  > BY MOUTH
  > Adult: 10 mg daily

- CONTRA-INDICATIONS
  Severe anaemia

- CAUTIONS
  Patients over 75 years - pulmonary veno-occlusive disease

- INTERACTIONS
  > Appendix 1: macitentan

- SIDE-EFFECTS
  > Common or very common
    Anaemia - headache - increased risk of infection - nasal congestion
  > CONCEPTION AND CONTRACEPTION
    Manufacturer advises exclusion of pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment. Monthly pregnancy tests advised.
  > PREGNANCY
    Toxicity in animal studies.
  > BREAST FEEDING
    Manufacturer advises avoid—present in milk in animal studies.
  > HEPATIC IMPAIRMENT
    Manufacturer advises avoid in severe impairment or if hepatic transaminases are greater than 3 times the upper limit of normal.
  > RENAL IMPAIRMENT
    Manufacturer advises caution in severe impairment and avoid in patients undergoing dialysis (no information available).

- MONITORING
  In renal impairment consider monitoring blood pressure (risk of hypotension).

- MONITORING REQUIREMENTS
  > Monitor liver function before treatment, then monthly thereafter (discontinue if unexplained persistent raised serum transaminases or signs of hepatic injury—can restart on advice on hepatologist if liver function tests return to normal and no hepatic injury).
  > Monitor haemoglobin concentration before treatment and then as indicated.

- PATIENT AND CARER ADVICE
  Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as dark urine, nausea, vomiting, fatigue, abdominal pain, or pruritus develop.
  Patient card should be provided.

- NATIONAL FUNDING/ACCESS DECISIONS
  Scottish Medicines Consortium (SMC) decisions
  SMC No. 952/14
  The Scottish Medicines Consortium has advised (April 2014) that macitentan (Opsumit®) should be initiated and prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Tablet
  > Opsumit (Actelion Pharmaceuticals UK Ltd)
    Macitentan 10 mg Opsumit 10 mg tablets | 30 tablet £2,306.00
GUANYLATE CYCLASE STIMULATORS

Riociguat

21-Feb-2019

● INDICATIONS AND DOSE

**Chronic thromboembolic pulmonary hypertension that is recurrent or persistent following surgery, or is inoperable (initiated under specialist supervision)**

Monotherapy or in combination with an endothelin receptor antagonist for idiopathic or hereditary pulmonary arterial hypertension, or pulmonary arterial hypertension associated with connective tissue disease (initiated under specialist supervision)

- **BY MOUTH**
  - Adult: Initially 1 mg 3 times a day for 2 weeks, increased in steps of 0.5 mg 3 times a day, dose to be increased every 2 weeks, increased to up to 2.5 mg 3 times a day (max. per dose 2.5 mg 3 times a day), increase up to maximum dose only if systolic blood pressure > 95 mmHg and no signs of hypotension, if treatment interrupted for 3 or more days, restart at 1 mg three times daily for 2 weeks and titrate as before, during titration, reduce dose by 0.5 mg three times daily if systolic blood pressure falls below 95 mmHg and patient shows signs of hypotension

**CONTRA-INDICATIONS**

History of serious haemoptysis - previous bronchial artery embolisation - pulmonary hypertension associated with idiopathic interstitial pneumonias - pulmonary veno-occlusive disease

**CAUTIONS**

Autonomic dysfunction - elderly (risk of hypotension) - hypotension (do not initiate if systolic blood pressure below 95 mmHg) - hypovolaemia - severe left ventricular outflow obstruction

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment. Monthly pregnancy tests advised.

**PREGNANCY**

Avoid—toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment; avoid in severe impairment (no information available).

**Dose adjustments**

Manufacturer advises cautious dose titration in moderate impairment.

**RENASCENCE IMPAIRMENT**

Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m²—limited information available.

**Dose adjustments**

Titrate dose cautiously—risk of hypotension.

**DIRECTIONS FOR ADMINISTRATION**

Tablets may be crushed and mixed with water or soft foods and swallowed immediately.

**PATIENT AND CARER ADVICE**

Smoking cessation advised (response possibly reduced). Patients should inform prescriber if smoking started or stopped during treatment; dose adjustment may be necessary.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 1001/14

The Scottish Medicines Consortium has advised (December 2014) that riociguat (Adempas®) is accepted for restricted use within NHS Scotland for the treatment of chronic thromboembolic pulmonary hypertension in adults for whom a phosphodiesterase type-5 inhibitor is inappropriate, not tolerated, or ineffective, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1056/15

The Scottish Medicines Consortium has advised (July 2015) that riociguat (Adempas®) is accepted for restricted use within NHS Scotland for the treatment of pulmonary arterial hypertension in adults as specific monotherapy as an alternative treatment option to endothelin receptor antagonist monotherapy and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit or by similar specialists. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 5

- **Adempas** (Merck Sharp & Dohme Ltd)
  - Riociguat 500 microgram [Adempas 0.5mg tablets] [42 tablet £997.36]
  - Riociguat 1 mg [Adempas 1mg tablets] [42 tablet £997.36]
  - Riociguat 1.5 mg [Adempas 1.5mg tablets] [42 tablet £997.36]
  - Riociguat 2 mg [Adempas 2mg tablets] [42 tablet £997.36]
  - 84 tablet £1,994.72
  - Riociguat 2.5 mg [Adempas 2.5mg tablets] [42 tablet £997.36]
  - 84 tablet £1,994.72

4.2 Hypotension and shock

**Sympathomimetics**

**Inotropic sympathomimetics**

**Shock**

Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis, or myocardial insufficiency should be corrected. The profound hypotension of shock must be treated promptly to prevent tissue hypoxia and organ failure. Volume replacement is essential to correct the hypovolaemia associated with haemorrhage and sepsis but may be detrimental in cardiogenic shock. Depending on haemodynamic status, cardiac output may be improved by the use of sympathomimetic inotropes such as adrenaline/epinephrine p. 222, dobutamine p. 222 or dopamine hydrochloride p. 187. In septic shock, when fluid replacement and inotropic support fail to maintain blood
pressure, the vasoconstrictor noradrenaline/norepinephrine p. 188 may be considered. In cardiogenic shock peripheral resistance is frequently high and to raise it further it may worsen myocardial performance and exacerbate tissue ischaemia.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

See also advice on the management of anaphylactic shock in Anhistamines, allergen immunotherapy and allergic emergencies p. 277.

**Vasoconstrictor sympathomimetics**

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed.

The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension. Management may include intravenous fluids (which are usually given prophylactically), oxygen, elevation of the legs, and injection of a pressor drug such as ephedrine hydrochloride p. 272. As well as constricting peripheral vessels ephedrine hydrochloride also accelerates the heart rate (by acting on beta receptors). Use must be made of this dual action of ephedrine hydrochloride to manage associated bradycardia (although intravenous injection of atropine sulfate p. 1334 may also be required if bradycardia persists).

**SYMPATHOMIMETICS > INOTROPIC**

**Dopamine hydrochloride**

- **DRUG ACTION** Dopamine is a cardiac stimulant which acts on beta, receptors in cardiac muscle, and increases contractility with little effect on rate.

- **INDICATIONS AND DOSE**
  - **Cardiogenic shock in infarction or cardiac surgery**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 2–5 micrograms/kg/minute
  - **CONTRA-INDICATIONS** Phaeochromocytoma - tachyarrhythmia
  - **CAUTIONS** Correct hypovolaemia - hypertension (may raise blood pressure) - hyperthyroidism - low dose in shock due to acute myocardial infarction
  - **INTERACTIONS** → Appendix 1: sympathomimetics, inotrope
  - **SIDE-EFFECTS** Angina pectoris - anxiety - arrhythmias - azotaemia - cardiac conduction disorder - dyspnoea - gangrene - headache - hypertension - mydriasis - nausea - palpitations - piloerection - polyuria - tremor - vasoconstriction - vomiting
  - **PREGNANCY** No evidence of harm in animal studies—manufacturer advises use only if potential benefit outweighs risk.
  - **BREAST FEEDING** May suppress lactation—known to be harmful.
  - **DIRECTIONS FOR ADMINISTRATION** Dopamine concentrate for intravenous infusion to be diluted before use. For intravenous infusion give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to max. concentration of 3.2 mg/mL; incompatible with bicarbonate.

**SYMPATHOMIMETICS > VASOCONSTRICTOR**

**Metaraminol**

- **INDICATIONS AND DOSE**
  - **Acute hypotension**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 15–100 mg, adjusted according to response
  - **Emergency treatment of acute hypotension**
    - **INITIALLY BY INTRAVENOUS INJECTION**
      - Adult: Initially 0.5–5 mg, then (by intravenous infusion) 15–100 mg, adjusted according to response
  - **CONTRA-INDICATIONS** Hypertension
  - **CAUTIONS** Cirrhosis - coronary vascular thrombosis - diabetes mellitus - elderly - extravasation at injection site may cause necrosis - following myocardial infarction - hypercapnia - hypothyroidism - hypoxia - mesenteric vascular thrombosis - peripheral vascular thrombosis - Prinzmetal’s variant angina - uncorrected hypovolaemia
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for infusion**

- **Dopamine hydrochloride (Non-proprietary)**
  - Dopamine hydrochloride 40 mg per 1 ml Dopamine 200mg/5ml solution for infusion ampoules | 5 ampoule | £20.00 (Hospital only) | 5 ampoule | £20.00 | 10 ampoule | £4.04
  - Dopamine hydrochloride 160 mg per 1 ml Dopamine 800mg/5ml solution for infusion ampoules | 10 ampoule | £34.00

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for injection**

- **Metaraminol (Non-proprietary)**
  - Metaraminol (as Metaraminol tartrate) 10 mg per 1 ml Metaraminol 10mg/1ml solution for injection ampoules | 10 ampoule | £4.93

[www.getintopharma.com](http://www.getintopharma.com)
Midodrine hydrochloride

**DRUG ACTION** Midodrine hydrochloride is a pro-drug of desglymidodrine. Desglymidodrine is a sympathomimetic agent, which acts on peripheral alpha-adrenergic receptors to increase arterial resistance, resulting in an increase in blood pressure.

**INDICATIONS AND DOSE**

Severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate

- **BY MOUTH**
  - Adult: Initially 2.5 mg 3 times a day, increased if necessary up to 10 mg 3 times a day, dose to be increased at weekly intervals, according to blood pressure measurements; usual maintenance 10 mg 3 times a day, avoid administration at night; the last daily dose should be taken at least 4 hours before bedtime

- **CONTRA-INDICATIONS** Aortic aneurysm - blood vessel spasm - bradycardia - cardiac conduction disturbances - cerebrovascular occlusion - congestive heart failure - hypertension - hyperthyroidism - myocardial infarction - narrow-angle glaucoma - pheochromocytoma - proliferative diabetic retinopathy - serious obliterative blood vessel disease - serious prostate disorder - urinary retention

- **CAUTIONS** Atherosclerotic cardiovascular disease (especially with symptoms of intestinal angina or claudication of the legs) - autonomic dysfunction - elderly (manufacturer recommends cautious dose titration) - prostate disorders

- **INTERACTIONS** → Appendix 1: sympathomimetics, vasoconstrictor

- **SIDE-EFFECTS**
  - **Common or very common** Chills - flushing - gastrointestinal discomfort - headache - nausea - paraesthesia - piloerection - scalp pruritus - skin reactions - stomatitis - supine hypertension (dose-dependent) - urinary disorders
  - **Uncommon** Anxiety - arrhythmias - irritability - sleep disorders
  - **Rare or very rare** Hepatic function abnormal - palpitations
  - **Frequency not known** Confusion - diarrhea - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION** Manufacturer advises that treatment must be stopped if supine hypertension is not controlled by reducing the dose.

**CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception during treatment in women of childbearing potential.

**PREGNANCY** Manufacturer advises avoid—t响icity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**RENAI IMPAIRMENT** Manufacturer advises avoid in severe or acute impairment.

**MONITORING REQUIREMENTS**

- Manufacturer advises measure hepatic and renal function before treatment and at regular intervals during treatment.
- Manufacturer advises regular monitoring of supine and standing blood pressure due to the risk of hypertension in the supine position.

**PATIENT AND CARER ADVICE** Manufacturer advises that patients report symptoms of supine hypertension (such as chest pain, palpitations, shortness of breath, headache and blurred vision) immediately. The risk of supine hypertension at night can be reduced by raising the head of the bed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Midodrine hydrochloride (Non-proprietary)**
    - Midodrine hydrochloride 2.5 mg
      - 100 tablet [POM] £55.05 DT £55.05
    - Midodrine hydrochloride 5 mg
      - 100 tablet [POM] £75.05 DT £75.05
  - **Bramox (Brancaster Pharma Ltd)**
    - Midodrine hydrochloride 2.5 mg
      - 100 tablet [POM] £55.05 DT £55.05
    - Midodrine hydrochloride 5 mg
      - 100 tablet [POM] £75.05 DT £75.05
  - **Midotense (Transdermal Ltd)**
    - Midodrine hydrochloride 2.5 mg
      - 30 tablet [POM] £15.69

Noradrenaline/norepinephrine

**INDICATIONS AND DOSE**

**Acute hypotension [initial and on-going treatment]**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 0.16–0.33 mL/minute, adjusted according to response, dose applies to a solution containing noradrenaline 40 micrograms/base)/mL only; dilute the 1 mg/mL concentrate for infusion for this solution—consult product literature

**On-going treatment of acute hypotension [with escalating dose requirements]**

- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight 50 kg and above): Use the 0.08 mg/mL solution for infusion (consult product literature)

**DOSE EQUIVALENCE AND CONVERSION**

- 1 mg of noradrenaline base is equivalent to 2 mg of noradrenaline acid tartrate. **Doses expressed as the base.**

**IMPORTANT SAFETY INFORMATION**

**ASSOCIATION OF NORADRENALINE/NOREPINEPHRINE**

Healthcare professionals should be aware of the differences in strength and presentation between noradrenaline/norepinephrine products—manufacturer advises noradrenaline 0.08 mg/mL solution for infusion must not be diluted before use and should only be used for the on-going treatment of patients already established on noradrenaline therapy, whose dose requirements are clinically confirmed to be escalating.

**CONTRA-INDICATIONS** Hypertension

**CAUTIONS** Coronary vascular thrombosis - diabetes mellitus - elderly - extravasation at injection site may cause necrosis - following myocardial infarction - hypercapnia - hyperthyroidism - hypoxia - mesenteric vascular thrombosis - peripheral vascular thrombosis - Prinzmetal’s variant angina - uncorrected hypovolaemia

**INTERACTIONS** → Appendix 1: sympathomimetics, vasoconstrictor

**SIDE-EFFECTS** Anxiety - arrhythmias - dyspnoea - extravasation necrosis - headache - hypertension - hypovolaemia - peripheral ischaemia

**PREGNANCY** Manufacturer advises use if potential benefit outweighs risk—may reduce placental perfusion and induce fetal bradycardia.

**MONITORING REQUIREMENTS** Monitor blood pressure and rate of flow frequently.
Phenylephrine hydrochloride

<table>
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<th>INDICATIONS AND DOSE</th>
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<td>Acute hypotension</td>
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<tr>
<td>▶ BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION</td>
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<tr>
<td>Adult: Initially 2–5 mg, followed by 1–10 mg, after at least 15 minutes if required</td>
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<tr>
<td>Adult: 100–500 micrograms, repeated as necessary after at least 15 minutes</td>
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<tr>
<td>Adult: Initially up to 180 micrograms/minute, reduced to 30–60 micrograms/minute, adjusted according to response</td>
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<tr>
<td>CONTRA-INDICATIONS</td>
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<td>MONITORING REQUIREMENTS</td>
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<td>DIRECTIONS FOR ADMINISTRATION</td>
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5 Cardiovascular risk assessment and prevention

Cardiovascular disease risk assessment and prevention

Description of condition
Cardiovascular disease is a term that describes a group of disorders of the heart and blood vessels caused by atherosclerosis and thrombosis, which includes coronary heart disease, stroke, peripheral arterial disease, and aortic disease.

The risk of cardiovascular disease is greater in men, patients over 50 years of age, patients with a family history of cardiovascular disease, and in certain ethnic backgrounds such as South Asians. Cardiovascular disease also has several important, and potentially modifiable, risk factors such as hypertension, abnormal lipids, obesity, diabetes mellitus, and psychosocial factors such as depression, anxiety and social isolation. Low physical activity, poor diet, smoking, and excessive alcohol intake are also risk factors.

Aims of treatment
The overall aim of treatment is to prevent the occurrence of a cardiovascular event by reducing modifiable risk factors through lifestyle changes and drug management.

Cardiovascular risk assessment
Identifying patients who are at risk of cardiovascular disease should be based on their presenting risk factors, clinical judgement, and use of risk calculators. Cardiovascular risk assessment calculators are used to predict the likelihood of a cardiovascular event occurring over a given period of time.

Cardiovascular risk assessments should be offered every 5 years to all patients over 40 years of age with no history of cardiovascular disease, and to all patients, regardless of age, with a first-degree relative who has premature atherosclerotic cardiovascular disease or familial dyslipidaemia.

Risk assessment with a calculator is not required in patients who are at high risk of cardiovascular disease. High-
Cardiovascular system

Cardiovascular disease prevention

All patients at any risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet (such as increasing fruit and vegetable consumption, reducing saturated fat and dietary salt intake), increasing physical exercise, weight management, reducing alcohol consumption, and Smoking cessation p. 497.

Further preventative measures with drug treatment should be taken in individuals with a high risk of developing cardiovascular disease (primary prevention), and to prevent recurrence of events in those with established cardiovascular disease (secondary prevention).

Primary prevention

Antiplatelet therapy

Aspirin p. 121 is not recommended for primary prevention of cardiovascular disease due to the limited benefit gained versus risk of adverse effects such as bleeding.

Antihypertensive therapy

Antihypertensive drug treatment should be offered to patients who are at high risk of cardiovascular disease and have a sustained elevated blood pressure over 140/90 mmHg. For guidance on prescribing antihypertensive drugs, see Hypertension p. 140.

Lipid-lowering therapy

A statin is recommended as the lipid-lowering drug of choice for primary prevention of cardiovascular disease. All modifiable risk factors, comorbidities, and secondary causes of dyslipidaemia (e.g. uncontrolled diabetes mellitus, hepatic disease, nephrotic syndrome, excessive alcohol consumption, and hypothyroidism) should be managed before starting treatment with a statin. Correcting hypothyroidism itself may resolve the lipid abnormality, whereas untreated hypothyroidism, and nephrotic syndrome increase the risk of myositis with lipid-regulating drugs.

Treatment with low-dose atorvastatin p. 202 should also be offered to all patients who are at high risk of cardiovascular disease. Low-dose atorvastatin p. 202 should also be considered in all adults with type 1 diabetes mellitus.

Patients aged 85 years and over may also benefit from low-dose atorvastatin p. 202 to reduce their risk of non-fatal myocardial infarction, however, factors such as polypharmacy, frailty or comorbidities should be taken into account before starting statin therapy.

Specialist advice should be sought regarding alternative treatment options in patients at high risk of cardiovascular disease who are intolerant of three different statins.

Ezetimibe p. 198 and bile acid sequestrants such as colestevarmine p. 197 and colestipol hydrochloride p. 197 should only be considered for primary prevention in patients with an elevated cardiovascular risk in whom statin therapy is contra-indicated, and in patients with familial hypercholesterolaemia.

Although fibrates are generally not recommended for primary prevention of cardiovascular disease, they can be considered in patients with marked hypertriglyceridaemia and low HDL-cholesterol levels.

If cholesterol remains above target levels despite other tolerated lipid-lowering therapy in patients at high risk of vascular events, the use of PCSK9 inhibitors, such as alirocumab p. 206 and evolocumab p. 207, should be considered [unlicensed indication].

Lipid-lowering therapy recommendations from Joint British Societies’ consensus (2014), NICE Clinical guideline 181 (July 2014, updated September 2016), and SIGN Clinical guideline 149 (June 2017) all differ in certain respects for prevention of cardiovascular disease in patients with diabetes mellitus—see individual guidelines for further details.

For further information on lipid-lowering therapy, see Dyslipidaemias p. 196.
Heart failure 191

Heart failure 23-Oct-2018

Description of condition

Heart failure is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. It is characterised by symptoms such as shortness of breath, persistent coughing or wheezing, ankle swelling, reduced exercise tolerance, and fatigue. These symptoms may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles, and pulmonary oedema.

The risk of heart failure is greater in men, smokers and diabetic patients, and increases with age.

The most common cause of heart failure is coronary heart disease, however, patients of African or Afro-Caribbean origin are more likely to develop heart failure secondary to hypertension. In addition to coronary heart disease, heart failure often co-exists with other co-morbidities such as chronic kidney disease, atrial fibrillation, hypertension, dyslipidaemia, obesity, diabetes mellitus, and chronic obstructive pulmonary disease. Patients with co-morbidities have a worse prognosis, and the presence of atrial fibrillation or chronic kidney disease affects the management of heart failure in these patients. Complications of heart failure include chronic kidney disease, atrial fibrillation, depression, cachexia, sexual dysfunction, and sudden cardiac death.

Heart failure can be defined as either having a reduced or preserved ejection fraction. Both conditions present with signs and symptoms of heart failure. In heart failure with reduced ejection fraction, the left ventricle loses its ability to contract normally and therefore presents with an ejection fraction of less than 40%. In heart failure with preserved ejection fraction, the left ventricle loses its ability to relax normally therefore the ejection fraction is normal or only mildly reduced.

The New York Heart Association (NYHA) functional classification tool is used to define the progression of chronic heart failure according to severity of symptoms and limitation to physical activity. Heart failure is considered to be stable or chronic when symptoms remain unchanged for at least one month despite optimal management.

Advanced Pharmacy Services

Patients with, or at risk of cardiovascular disease may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Useful Resources


6 Heart failure

Chronic heart failure

Secondary prevention

Antiplatelet therapy

Antiplatelet therapy with low-dose daily aspirin p. 121 should be offered to patients with established atherosclerotic disease. Alternatively, clopidogrel p. 123 can be considered in patients who are intolerant of aspirin or in whom it is contra-indicated.

Clopidogrel p. 123 or a combination of dipyridamole with aspirin p. 124 should be considered to prevent recurrence of stroke and other vascular events in all patients with a history of stroke or transient ischaemic attack and who are in sinus rhythm. For further information, see Stroke p. 117.

Antihypertensive therapy

Antihypertensive drug treatment is recommended in patients with established cardiovascular disease and a sustained elevated blood pressure over 140/90 mmHg. For guidance on prescribing of antihypertensive drugs, see Hypertension p. 140.

Lipid-lowering therapy

A high-intensity statin, defined as the dose at which a reduction in LDL-cholesterol of greater than 40% is achieved, is the lipid-lowering therapy of choice for secondary prevention of cardiovascular disease. Treatment with high-dose atorvastatin p. 202 should be offered to all patients with established atherosclerotic cardiovascular disease. However, a lower dose can be used if the patient is at an increased risk of side effects or drug interactions. High-dose simvastatin p. 205 is generally avoided due to the risk of myopathy, unless the patient has been stable on this regimen for at least one year. Patients who are stable on a low- or medium-intensity statin should discuss the benefits and risks of switching to a high-intensity statin at their next medication review.

Total cholesterol, HDL-cholesterol, and non-HDL cholesterol concentrations should be checked 3 months after starting treatment with a high-intensity statin.

NICE Clinical Guideline 181 and SIGN 149 guideline recommend aiming for a reduction in non-HDL cholesterol concentration greater than 40%, whereas, JBS3 recommends a target non-HDL cholesterol concentration below 2.5 mmol/litre. If these targets are not achieved, adherence to drug treatment should be checked and lifestyle modifications optimised. In patients judged to be at a higher risk because of comorbidities, risk score, or clinical judgment, an increase in the statin dose (if started on less than maximum atorvastatin p. 202 dose) should be considered.

Specialist advice should be sought regarding alternative treatment options in patients with existing cardiovascular disease who are intolerant of three different statins.

If LDL-cholesterol remains inadequately controlled, ezetimibe p. 198 and bile acid sequestrants such as colestevamine and colestipol hydrochloride, can be considered for use in combination with a statin at the maximum tolerated dose.

Although fibrates are generally not recommended for secondary prevention of cardiovascular disease, they should be considered in patients with marked hypertriglyceridaemia, and low HDL-cholesterol levels.

For further information on lipid-lowering therapy, see Dyslipidaemias p. 196.

Psychological risk factors

Psychological treatment should be considered in patients with mood and anxiety disorders and comorbid cardiovascular disease; complex patients may require referral to a specialist. Selective serotonin re-uptake inhibitors (SSRIs) should be considered for treatment in patients with depression and coronary heart disease. For guidance on prescribing of antidepressant drugs see Antidepressant drugs p. 399.
Heart failure

**Aims of treatment**

The aims of treatment are to reduce mortality, relieve symptoms, improve exercise tolerance, and reduce the incidence of acute exacerbations.

**Non-drug treatment**

- Patients with heart failure should be advised to make lifestyle changes to reduce the risk of progression of their heart failure and associated co-morbidities. These include Smoking cessation p. 497, reducing alcohol consumption, increasing physical exercise if appropriate, weight control, and dietary changes such as increasing fruit and vegetable consumption and reducing saturated fat intake. Patients should be encouraged to weigh themselves daily at a set time of day and to report any weight gain of more than 1.5–2.0 kg in 2 days to their GP or heart failure specialist. Salt and fluid intake should only be restricted if these are high, and a salt intake of less than 6 g per day is advised. Patients with dilutional hyponatraemia should only restrict their fluid intake. Salt substitutes containing potassium should be avoided to reduce the risk of hyperkalaemia.

- Contraception and pregnancy should be discussed with women of childbearing potential and heart failure. Advice from a heart failure specialist and an obstetrician should be sought if pregnancy occurs or is being considered.

- Patients should be given the opportunity to join a personalised rehabilitation programme including education, psychological support, and exercise when appropriate.

- Implantable cardioverter defibrillators and cardiac resynchronisation therapy are treatment options recommended in patients with heart failure and a reduced ejection fraction of less than 35%. If symptoms remain severe and unresponsive despite optimal drug treatment, specialist referral should be considered.

**Drug treatment**

- The treatment of heart failure should include management of symptoms, risk factors and underlying causes and complications. Patients should have their medication reviewed, and any drugs that may cause or worsen their heart failure should be stopped if appropriate.

- Vaccination against pneumococcal disease, and annual influenza vaccination is recommended.

- Rate-limiting calcium-channel blockers (verapamil hydrochloride p. 1,64, and diltiazem hydrochloride p. 157) and short-acting dipyridamole (e.g. nifedipine p. 162, or nicardipine hydrochloride p. 161) should be avoided in patients who have heart failure with reduced ejection fraction as these drugs reduce cardiac contractility. Patients with heart failure and angina may safely be treated with amiodipine p. 156.

- Diuretics are recommended for the relief of breathlessness and oedema in patients with fluid retention. Loop diuretics such as furosemide p. 227, bumetanide p. 227, or torasemide p. 228 are usually the diuretics of choice. Thiazide diuretics may only be of benefit in patients with mild fluid retention and an eGFR greater than 30 ml/minute/1.73 m². Diuretic doses should be titrated according to clinical response and adjusted if needed following the initiation of subsequent heart failure treatments, to minimise the risk of dehydration, renal impairment or hypotension. If symptoms persist despite optimal titration, advice from a heart failure specialist should be sought.

- An angiotensin-converting enzyme (ACE) inhibitor (e.g. perindopril, ramipril p. 172, captopril p. 168, enalapril maleate p. 169, lisinopril p. 170, quinapril p. 172 or fosinopril sodium p. 169) and a beta-blocker licensed for heart failure (e.g. bisoprolol fumarate p. 153, carvedilol p. 148, or nebivolol p. 155) should be given as first-line treatment to reduce morbidity and mortality. Treatment with a beta-blocker should not be withheld because of age or the presence of diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, erectile dysfunction, or interstitial pulmonary disease. Patients who are already taking a beta-blocker for co-morbidities (e.g. angina or hypertension) and whose condition is stable should be switched to a beta-blocker licensed for heart failure. Clinical judgement should be used when deciding whether to start an ACE inhibitor or beta blocker first. The additional drug should only be initiated when the patient is stable on their existing treatment. Treatment should be initiated at a low dose and slowly titrated up to the maximum tolerated dose.

- An angiotensin II receptor blocker (ARB) licensed for heart failure (e.g. candesartan cilexetil p. 175, losartan potassium p. 176, or valsartan p. 179) can be considered if ACE inhibitors are not tolerated.

- Patients with heart failure and preserved ejection fraction (e.g. candesartan cilexetil p. 175, losartan potassium p. 176, or valsartan p. 179) can be considered if ACE inhibitors are not tolerated.

- If heart failure symptoms persist or worsen despite optimal first-line treatment, an aldosterone antagonist such as spironolactone p. 193 or eplerenone p. 193 should be offered as add-on therapy unless contra-indicated (e.g. due to hyperkalaemia or renal impairment). Hydralazine hydrochloride p. 180 combined with a nitrate can be considered under the advice of a heart failure specialist in patients who are intolerant of both ACE inhibitors and ARBs (in particular those of African or Caribbean origin with moderate to severe heart failure).

- Doses should only be increased if the patient is stable on their existing treatment. Treatment should be initiated at a low dose and slowly titrated up to the maximum tolerated dose.

**Monitoring drug treatment**

**Chronic heart failure with preserved ejection fraction**

- When initiating ACE inhibitors, ARBs and aldosterone antagonists, serum potassium and sodium, renal function, and blood pressure should be checked prior to starting treatment, 1-2 weeks after starting treatment, and at each dose increment. Once the target, or maximum tolerated dose is achieved, treatment should be monitored monthly for 3 months and then at least every 6 months, and if the patient becomes acutely unwell.

- When initiating beta blockers, heart rate, blood pressure and symptom control should be assessed at the start of treatment and after each dose change.

- In patients with chronic kidney disease, lower doses and slower dose titrations of ACE inhibitors, ARBs, aldosterone antagonists and digoxin should be considered. Advice from a renal specialist should be considered where appropriate.

**Chronic heart failure with preserved ejection fraction**

- Patients with heart failure and preserved ejection fraction should be managed under the care of a heart failure specialist. For the relief of fluid retention symptoms, a low to medium dose loop diuretic should be prescribed. If the patient fails to respond to treatment, advice from a heart failure specialist should be sought.

**Advanced heart failure**

Breathlessness is a common symptom in advanced heart failure and may occur even with optimal management and in the absence of clinical pulmonary oedema. Long-term oxygen therapy is not recommended in advanced heart failure, although it may be considered in patients with heart failure and additional co-morbidities that would benefit from...
oxygen therapy such as chronic obstructive pulmonary disease.

**Advanced Pharmacy Services**
Patients with heart failure may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

**Useful Resources**

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### DIURETICS > POTASSIUM-SPARING DIURETICS > ALDOSTERONE ANTAGONISTS

<table>
<thead>
<tr>
<th>Co-flumoxatone</th>
</tr>
</thead>
<tbody>
<tr>
<td>The properties listed below are those particular to the combination only. For the properties of the components please consider, spironolactone below.</td>
</tr>
<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
</tr>
<tr>
<td>Adult: Initially 100/100 mg daily; maintenance 25–250–200 mg daily, maintenance dose not recommended because spironolactone generally given in lower dose</td>
</tr>
<tr>
<td><strong>INTERACTIONS</strong> -&gt; Appendix 1: aldosterone antagonists - thiazide diuretics</td>
</tr>
<tr>
<td><strong>LESS SUITABLE FOR PRESCRIBING</strong> Co-flumoxatone tablets are less suitable for prescribing.</td>
</tr>
<tr>
<td><strong>MEDICINAL FORMS</strong> There can be variation in the licensing of different medicines containing the same drug.</td>
</tr>
<tr>
<td><strong>Tablet</strong></td>
</tr>
<tr>
<td>Aldactide (Pfizer Ltd)</td>
</tr>
<tr>
<td>Hydroflumethiazide 25 mg, Spironolactone 25 mg Aldactide 25 tablets</td>
</tr>
<tr>
<td>Hydroflumethiazide 50 mg, Spironolactone 50 mg Aldactide 50 tablets</td>
</tr>
</tbody>
</table>

### Eplerenone

| **INDICATIONS AND DOSE** |
| Adjunct in stable patients with left ventricular ejection fraction ≤40% with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event) Adjunct in chronic mild heart failure with left ventricular ejection fraction ≤30% |
| BY MOUTH |
| Adult: Initially 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment |
single dose or divided doses, maintenance dose adjusted according to response

Moderate to severe heart failure (adjunct)

- **BY MOUTH**
  - Adult: Initially 25 mg once daily, then adjusted according to response to 50 mg once daily

Resistant hypertension (adjunct)

- **BY MOUTH**
  - Adult: 25 mg once daily

Primary hyperaldosteronism in patients awaiting surgery

- **BY MOUTH**
  - Adult: 100–400 mg daily, may be used for long-term maintenance if surgery inappropriate, use lowest effective dose

- **UNLICENSED USE** Resistant hypertension (adjunct) unlicensed indication.

- **CONTRA-INDICATIONS** Addison’s disease • anuria • hyperkalaemia

- **CAUTIONS** Acute porphyrias p. 1058 • elderly • potential metabolic products carcinogenic in rodents

- **INTERACTIONS** → Appendix 1: aldosterone antagonists

- **SIDE-EFFECTS** Acidosis hyperchloremic • acute kidney injury • agranulocytosis • alopecia • breast neoplasms benign • breast pain • confusion • dizziness • electrolyte imbalance • gastrointestinal disorder • gynaecomastia • hepatic function abnormal • hyperkalaemia (discontinue) • hypertrichosis • leg cramps • leucopenia • libido disorder • malaise • menstrual disorder • nausea • severe cutaneous adverse reactions (SCARs) • skin reactions • thrombocytopenia

- **PREGNANCY** Use only if potential benefit outweighs risk—feminisation of male fetus in animal studies.

- **BREAST FEEDING** Metabolites present in milk, but amount probably too small to be harmful.

- **RENAI IMPAIRMENT** Avoid in acute renal insufficiency or severe impairment.

- **MONITORING** Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

- **MONITORING REQUIREMENTS** Monitor electrolytes—discontinue if hyperkalaemia occurs (in severe heart failure monitor potassium and creatinine 1 week after initiation and after any dose increase, monthly for first 3 months, then every 3 months for 1 year, and then every 6 months).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

**CAUTIONARY AND ADVISORY LABELS 21**

- Spironolactone (Non-proprietary)
  - Spironolactone 25 mg Spironolactone 25mg tablets
    - 28 tablet PPM £1.95 DT = £1.05 | 500 tablet PPM £17.86
  - Spironolactone 50 mg Spironolactone 50mg tablets
    - 28 tablet PPM £9.99 DT = £4.07
  - Spironolactone 100 mg Spironolactone 100mg tablets
    - 28 tablet PPM £2.96 DT = £1.85
  - Aldactone (Pfizer Ltd)
    - Spironolactone 25 mg Aldactone 25mg tablets | 100 tablet PPM £8.89
    - Spironolactone 50 mg Aldactone 50mg tablets | 100 tablet PPM £17.78
    - Spironolactone 100 mg Aldactone 100mg tablets | 28 tablet PPM £9.96 DT = £1.85 | 100 tablet PPM £35.56

## Drugs acting on the renin-angiotensin system → Angiotensin II receptor antagonists

### Sacubitril with valsartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, valsartan p. 179.

- **DRUG ACTION** Sacubitril (a prodrug) inhibits the breakdown of natriuretic peptides resulting in varied effects including increased diuresis, natriuresis, and vasodilation.

- **INDICATIONS AND DOSE** Symptomatic chronic heart failure with reduced ejection fraction (in patients not currently taking an ACE inhibitor or angiotensin II receptor antagonist, or stabilised on low doses of either of these agents)

  - **BY MOUTH**
    - Adult: Initially 24/26 mg twice daily for 3–4 weeks, increased if tolerated to 49/51 mg twice daily for 3–4 weeks, then increased if tolerated to 97/103 mg twice daily

Symptomatic chronic heart failure with reduced ejection fraction (in patients currently stabilised on an ACE inhibitor or angiotensin II receptor antagonist)

  - **BY MOUTH**
    - Adult: Initially 49/51 mg twice daily for 2–4 weeks, increased if tolerated to 97/103 mg twice daily, consider a starting dose of 24/26 mg if systolic blood pressure less than 110 mmHg

- **DOSE EQUIVALENCE AND CONVERSION**
  - → Entresto® tablets contain sacubitril and valsartan; the proportions are expressed in the form x/y where x and y are the strength in milligrams of sacubitril and valsartan respectively. Valsartan, in this formulation, is more bioavailable than other tablet formulations—26 mg, 51 mg, and 103 mg valsartan is equivalent to 40 mg, 80 mg and 160 mg, respectively. Furthermore, note that the 24/26 mg, 49/51 mg and 97/103 mg strengths are sometimes referred to as a total of both drug strengths, that is, 50 mg, 100 mg and 200 mg, respectively.

- **CONTRA-INDICATIONS** Concomitant use with an ACE inhibitor (do not initiate until at least 36 hours after discontinuing ACE inhibitor—risk of angioedema) • concomitant use with an angiotensin II receptor antagonist • systolic blood pressure less than 100 mmHg

- **INTERACTIONS** → Appendix 1: angiotensin-II receptor antagonists • sacubitril

- **SIDE-EFFECTS**
  - Common or very common Anaemia • asthenia • cough • diarrhoea • dizziness • electrolyte imbalance • gastritis • headache • hypoglycaemia • hypotension • nausea • renal impairment • syncope • vertigo
  - Uncommon Angioedema • skin reactions

- **PREGNANCY** Manufacturer advises avoid—toxicity with sacubitril in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment or if hepatic transaminases exceed 2 times the upper limit of normal (limited information available); avoid in severe impairment, biliary cirrhosis or cholestasis (no information available).

- **Dose adjustments** Manufacturer advises initial dose reduction to 24/26 mg twice daily in moderate impairment or if hepatic transaminases exceed 2 times the upper limit of normal.

www.getintopharma.com
**PHOSPHODIESTERASE TYPE-3 INHIBITORS**

**Enoximone**

**DRUG ACTION** Enoximone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

**INDICATIONS AND DOSE** Congestive heart failure where cardiac output reduced and filling pressures increased

- **BY SLOW INTRAVENOUS INJECTION**
- Adult: Initially 0.5–1 mg/kg, rate not exceeding 12.5 mg minute, then 500 micrograms/kg every 30 minutes until satisfactory response or total of 3 mg/kg given; maintenance, initial dose of up to 3 mg/kg may be repeated every 3–6 hours as required
- **BY INTRAVENOUS INFUSION**
- Adult: Initially 90 micrograms/kg/minute, dose to be given over 10–30 minutes, followed by 5–20 micrograms/kg/minute, dose to be given as either a continuous or intermittent infusion; maximum 24 mg/kg per day

**CAUTIONS** Heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction

**SIDE-EFFECTS**
- Common or very common Headache, hypotension, insomnia
- Uncommon Arrhythmias, diarrhea, dizziness, nausea, vomiting
- Rare or very rare Chills, fever, fluid retention, myalgia, oliguria, urinary retention
- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk
- BREAST FEEDING Manufacturer advises caution—no information available

**Milrinone**

**DRUG ACTION** Milrinone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

**INDICATIONS AND DOSE** Short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy (not immediately after myocardial infarction) / Acute heart failure, including low output states following heart surgery

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 50 micrograms/kg, given over 10 minutes, followed by (by intravenous infusion) 375–750 micrograms/kg/minute usually given following surgery for up to 12 hours or in congestive heart failure for 48–72 hours; maximum 1.13 mg/kg per day

**CONTRA-INDICATIONS** Severe hypovolaemia

**CAUTIONS** Correct hypokalaemia - heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction

**SIDE-EFFECTS**
- Common or very common Arrhythmias, supraventricular (increased risk in patients with pre-existing arrhythmias) - atrhythmias, headache, hypotension
- Uncommon Angina pectoris, chest pain, hypokalaemia, thrombocytopenia, tremor
- Rare or very rare Anaphylactic shock, bronchospasm, skin eruption
- Frequency not known Renal failure

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk

**BREAST FEEDING** Manufacturer advises avoid—no information available

**RENAL IMPAIRMENT** Dose adjustments Reduce dose and monitor response if eGFR less than 50 mL/minute/1.73 m²—consult product literature for details.

**MONITORING REQUIREMENTS** Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

**DIRECTIONS FOR ADMINISTRATION** Avoid extravasation.

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**Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (April 2016) NICE TA388**

Sacubitril valsartan (Entresto®) is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in adults:

- with New York Heart Association class II to IV symptoms, and
- a left ventricular ejection fraction of 35% or less, and
- who are already taking a stable dose of an ACE inhibitor or angiotensin II receptor antagonist.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta388

**Sacubitril valsartan**

**INDICATIONS AND DOSE**
- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: 150 mg, given over 2 minutes (Hospital only)
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 50 mg, given over 1 minute (Hospital only)

**CONTRA-INDICATIONS**
- Anaphylactic shock
- Arrhythmia
- Cardiac output less than 40%, systolic blood pressure less than 90 mmHg
- Congestive heart failure
- Diabetic coma
- Hypotension
- Heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction
- History of anaphylaxis
- History of severe angioedema
- Hypovolaemia
- Severe renal impairment
- Severe thrombocytopenia

**CAUTIONS**
- Hypotension
- Hypovolaemia
- Renal failure

**SIDE-EFFECTS**
- Common or very common Arrhythmia, bronchospasm, diarrhea, dizziness, hyponatraemia, hypotension, insomnia, nausea, vomiting
- Uncommon Acute heart failure, including low output states following heart surgery
- Rare or very rare Anaphylaxis, bronchospasm, hypokalaemia, hyponatraemia, skin eruption
- Frequency not known Renal failure

**PRESCRIBING AND DISPENSING INFORMATION** Sustained haemodynamic benefit has been observed after administration of phosphodiesterase type-3 inhibitors, but there is no evidence of any beneficial effect on survival.
Hyperlipidaemia

7 Hyperlipidaemia

Dyslipidaemias

Hypercholesterolaemia and hypertriglyceridaemia

Statins are the drugs of first choice for treating hypercholesterolaemia and moderate hypertriglyceridaemia. Severe hypercholesterolaemia or hypertriglyceridaemia not adequately controlled with a maximal dose of a statin may require the use of an additional lipid-regulating drug such as ezetimibe p. 198; such treatment should generally be supervised by a specialist.

A number of conditions, some familial, are characterised by very high LDL-cholesterol concentration, high triglyceride concentration, or both. Although statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration, they are less effective than fibrates in reducing triglyceride concentration. Fenofibrate p. 199 may be added to statin therapy if triglycerides remain high even after the LDL-cholesterol concentration has been reduced adequately.

Familial hypercholesterolaemia

Patients with familial hypercholesterolaemia are at high risk of premature coronary heart disease. Lifelong lipid-modifying therapy and advice on lifestyle changes should be offered to all patients with familial hypercholesterolaemia.

A high-intensity statin, defined as the dose at which a reduction in LDL-cholesterol of greater than 40% is achieved, is recommended as first-line therapy in all patients with familial hypercholesterolaemia. The dose of the statin should be titrated to achieve a reduction in LDL-cholesterol concentration of greater than 50% from baseline.

Patients with primary heterozygous familial hypercholesterolaemia who have contra-indications to, or are intolerant of statins, can be considered for treatment with ezetimibe as monotherapy. A combination of a statin and ezetimibe is recommended if the maximum tolerated dose of a statin alone fails to provide adequate control of LDL-cholesterol, or a switch to an alternative statin is being considered. Treatment with a fibrate or a bile acid sequestrant (such as colestyramine p. 197 or colestipol hydrochloride p. 197) can be considered under specialist advice, in patients for whom statins or ezetimibe are inappropriate.

The combination of a statin with a fibrate carries an increased risk of muscle-related side-effects (including rhabdomyolysis) and should be used under specialist supervision. The concomitant administration of gemfibrozil with a statin increases the risk of rhabdomyolysis considerably—this combination should not be used. Alirocumab p. 206 and evolocumab p. 207 can be considered for patients with primary heterozygous familial hypercholesterolaemia whose LDL-cholesterol has not been adequately controlled on maximum tolerated lipid-lowering therapy. See National funding/access decisions information for alirocumab p. 206 and evolocumab p. 207.

The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken in a specialist centre.

Reduction in low-density lipoprotein cholesterol

<table>
<thead>
<tr>
<th>Therapy intensity</th>
<th>Drug</th>
<th>Daily dose (reduction in LDL cholesterol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-intensity</td>
<td>Atorvastatin</td>
<td>20 mg (43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg (49%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg (55%)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
<td>10 mg (43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg (48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg (53%)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>80 mg (42%)</td>
</tr>
<tr>
<td>Medium-intensity</td>
<td>Atorvastatin</td>
<td>10 mg (37%)</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
<td>80 mg (33%)</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
<td>5 mg (38%)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>20 mg (32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg (37%)</td>
</tr>
<tr>
<td>Low-intensity</td>
<td>Fluvastatin</td>
<td>20 mg (21%)</td>
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<tr>
<td></td>
<td></td>
<td>40 mg (27%)</td>
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<tr>
<td></td>
<td>Pravastatin</td>
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<td>40 mg (29%)</td>
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<td></td>
<td>Simvastatin</td>
<td>10 mg (27%)</td>
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</table>

Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

Advanced Pharmacy Services

Patients with dyslipidaemia may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Other drugs used for Hyperlipidaemia

inositol nicotinate, p. 233

LIPID MODIFYING DRUGS

Bile acid sequestrants

- **DRUG ACTION** Bile acid sequestrants act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma.

- **CAUTIONS** Interference with the absorption of fat-soluble vitamins (supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged).

www.getintopharma.com
Colestevelam hydrochloride

**INDICATIONS AND DOSE**

*Primary hypercholesterolaemia as an adjunct to dietary measures (monotherapy)*

- **BY MOUTH**
  - Adult: 3.75 g daily in 1–2 divided doses; maximum 4.375 g per day

*Primary hypercholesterolaemia as an adjunct to dietary measures, in combination with a statin* | Primary and familial hypercholesterolaemia, in combination with ezetimibe, either with or without a statin

- **BY MOUTH**
  - Adult: 2.5–3.75 g daily in 1–2 divided doses, may be taken at the same time as the statin and ezetimibe

**SIDE-EFFECTS**

- Common or very common: Constipation, gastrointestinal discomfort, headache, nausea, vomiting
- Uncommon: Appetite decreased, diarrhoea, gastrointestinal disorders
- PREGNANCY: Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.
- BREAST FEEDING: Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

**CONTRA-INDICATIONS**

- Biliary obstruction - bowel obstruction
- Gastro-intestinal motility disorders - inflammatory bowel disease - major gastro-intestinal surgery

**INTERACTIONS**

- Appendix 1: colestevelam

**SIDE-EFFECTS**

- Uncommon: Dysphagia, myalgia
- Rare or very rare: Pancreatitis

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution in hepatic failure (no information available).

**MONITORING REQUIREMENTS**

- Patients receiving ciclosporin should have their blood-ciclosporin concentration monitored before, during, and after treatment with colestevelam.

**PATIENT AND CARER ADVICE**

- Patient counselling on administration is advised for colestevelam hydrochloride tablets (avoid other drugs at same time).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Granules**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tbody>
<tr>
<td><em>Colestipol</em> (Pfizer Ltd)</td>
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<td><em>Colestipol hydrochloride 5 gram</em></td>
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<td><em>Colestipol hydrochloride 1 gram</em></td>
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**Colestipol hydrochloride**

**INDICATIONS AND DOSE**

**Hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures**

- **BY MOUTH**
  - Adult: Initially 5 g 1–2 times a day, increased in steps of 5 g every month if required, total daily dose may be given in 1–2 divided doses; maximum 30 g per day

**CONTRA-INDICATIONS**

- Complete biliary obstruction (not likely to be effective)

**INTERACTIONS**

- Appendix 1: colestipol

**SIDE-EFFECTS**

- Angina pectoris, arthralgia, arthritis, asthenia, burping, chest pain, dizziness, dyspnoea, gallbladder disorders, headaches, inflammation, insomnia, pain, peptic ulcer haemorrhage, tachycardia

**DIRECTIONS FOR ADMINISTRATION**

- The contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice or skimmed milk; alternatively it can be mixed with thin soups, cereals, yoghurt, or pulpy fruits ensuring at least 100 mL of liquid is provided.

**MEDICATIONS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Granules**

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</table>
Ezetimibe, alone, is recommended as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contra-indicated, or who are intolerant of initial statin therapy.

Ezetimibe, in combination with initial statin therapy, is also recommended as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults when:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, and
- a change from initial statin therapy to an alternative statin is being considered.

When prescribing ezetimibe in combination with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

www.nice.org.uk/guidance/ta385

**SIDE-EFFECTS**
- Uncommon Bleeding tendency - hypoprothrombinemia - night blindness - osteoporosis - skin reactions - tongue irritation - vitamin deficiencies

**DIRECTIONS FOR ADMINISTRATION** The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content.

**PATIENT AND CARER ADVICE** Patient counselling on administration is advised for colestyramine powder (avoid other drugs at same time).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution Powder

**CAUTIONARY AND ADVISORY LABELS** 13 EXCipients: May contain Aspartame, sucrose

- Questran (Bristol-Myers Squibb Pharmaceuticals Ltd)
- Colestyramine anhydrous 4 g
- Questran Light 4 g
- Questran Light 4 g oral powder sachets sugar-free | 50 sachet [PoS] £16.15 DT = £16.15

**INTERACTIONS**

- Lipid modifying drugs
- Cholesterol absorption inhibitors

**LIPID MODIFYING DRUGS**

**Ezetimibe**

**DRUG ACTION** Ezetimibe inhibits the intestinal absorption of cholesterol.

If used alone, it has a modest effect on lowering LDL-cholesterol, with little effect on other lipoproteins.

**INDICATIONS AND DOSE**

- Adjunct to dietary measures and statin treatment in primary hypercholesterolaemia
- Adjunct to dietary measures and statin in homozgyous familial hypercholesterolaemia
- Primary hypercholesterolaemia (if statin inappropriate or not tolerated)

**SIDE-EFFECTS**
- Uncommon Bleeding tendency - hypoprothrombinemia - night blindness - osteoporosis - skin reactions - tongue irritation - vitamin deficiencies

**PATIENT AND CARER ADVICE** Patient counselling on administration is advised for colestyramine powder (avoid other drugs at same time).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Ezetimibe (Non-proprietary) | Ezetimibe 10 mg | 28 tablet [PoS] £2.08–£26.31 DT = £2.17 |
| Ezetrol (Merck Sharp & Dohme Ltd) | Ezetimibe 10 mg | 28 tablet [PoS] £26.31 DT = £2.17 |

Combinations available: Simvastatin with ezetimibe, p. 205

**SIDE-EFFECTS**

- Uncommon Bleeding tendency - hypoprothrombinemia - night blindness - osteoporosis - skin reactions - tongue irritation - vitamin deficiencies

**PATIENT AND CARER ADVICE** Patient counselling on administration is advised for colestyramine powder (avoid other drugs at same time).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Bezafibrate (Non-proprietary) | Bezafibrate 100 mg | 30 tablet [PoS] £2.08–£26.31 DT = £2.17 |
| Bezafibrate (Non-proprietary) | Bezafibrate 200 mg | 30 tablet [PoS] £26.31 DT = £2.17 |

**SIDE-EFFECTS**

- Uncommon Bleeding tendency - hypoprothrombinemia - night blindness - osteoporosis - skin reactions - tongue irritation - vitamin deficiencies

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Bezafibrate (Non-proprietary) | Bezafibrate 100 mg | 30 tablet [PoS] £2.08–£26.31 DT = £2.17 |
| Bezafibrate (Non-proprietary) | Bezafibrate 200 mg | 30 tablet [PoS] £26.31 DT = £2.17 |

Combinations available: Simvastatin with bezafibrate, p. 205
● **Hepatic Impairment**: Manufacturer advises avoid—no information available.

● **Renal Impairment**: Avoid immediate-release preparations if eGFR less than 15 mL/minute/1.73 m². Avoid modified-release preparations if eGFR less than 60 mL/minute/1.73 m².

Myotoxicity: Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

Dose adjustments: Reduce dose to 400 mg daily if eGFR 40–60 mL/minute/1.73 m².

Reduce dose to 200 mg every 1–2 days if eGFR 15–40 mL/minute/1.73 m².

● **Monitoring Requirements**: Consider monitoring of liver function and creatine kinase when fibrates used in combination with a statin.

● **Prescribing and Dispensing Information**: Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

● **Medicinal Forms**: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension.

**Modified-release tablet**

- **Cautions and Advisory Labels**: 21, 25
  - Bezalip Mono (Teva UK Ltd)
  - Ciprofibrate 400 mg
  - Bezalip Mono 400 mg modified-release tablets
  - 30 tablet (POM) £76.37 DT = £76.37
  - Bezalip (Teva UK Ltd)
  - Fibrazate XL (Sandoz Ltd)
  - Ciprofibrate 400 mg
  - Fibrazate XL 400 mg tablets
  - 30 tablet (POM)
  - £6.87 DT = £76.37

**Tablet**

- **Cautions and Advisory Labels**: 21
  - Bezalip (Non-proprietary)
  - Ciprofibrate 200 mg
  - Bezalip 200 mg tablets
  - 100 tablet (POM)
  - £8.50 DT = £5.22
  - 30 tablet (POM)

- **Bezalip (Teva UK Ltd)
  - Bezafibrate 200 mg
  - Bezalip 200 tablets
  - 100 tablet (POM)
  - £8.63 DT = £5.22

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**Fenofibrate**

**Drug Action**: Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**Indications and Dose**: Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia. Adjunct to statin in mixed hyperlipidaemia if triglycerides and HDL-cholesterol inadequately controlled in patients at high cardiovascular risk.

- **By Mouth Using Capsules**
  - Adult: Initially 100 mg daily, then increased if necessary to 267 mg daily, maximum 200 mg daily with concomitant statin, 267 mg capsules not appropriate for initial dose titration.

- **By Mouth Using Tablets**
  - Adult: 160 mg daily

**Dose Adjustments Due to Interactions**

- Manufacturer advises max. dose 200 mg daily with concurrent use of a statin.

- **Contra-Indications**: Gall bladder disease, pancreatitis (unless due to severe hypertriglyceridaemia), photosensitivity to ketoprofen

- **Caution**: Correct hypothyroidism before initiating treatment.

**Interactions**

- Appendix 1: fibrates

**Side-effects**

- Common or very common: Abdominal pain, diarrhea, dizziness, drowsiness, fatigue, gastrointestinal discomfort, headache, myalgia, nausea, skin reactions, vertigo, vomiting.

- Frequency not known: Cholelithiasis, erectile dysfunction, hepatic disorders, leucopenia, myopathy.
myopathy · pancreatitis · sexual dysfunction · skin reactions

- Rare or very rare Alopecia · hepatic disorders · photosensitivity reaction

- Frequency not known Fatigue · interstitial lung disease · rhabdomyolysis (increased risk in renal impairment) · severe cutaneous adverse reactions (SCARs)

- PREGNANCY Avoid—embryotoxicity in animal studies.
- BREST FEEDING Manufacturers advise avoid—no information available.
- HEPATIC IMPAIRMENT Manufacturer advises avoid —no information available.
- RENAL IMPAIRMENT Manufacturer advises use with caution in mild-to-moderate impairment; avoid if eGFR less than 30 mL/minute/1.73 m². Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

- MONITORING REQUIREMENTS Manufacturer advises monitor hepatic transaminases every 3 months during the first 12 months of treatment and periodically thereafter—interrupt treatment if creatinine level is 50% above the upper limit of normal.

- PRESCRIBING AND DISPENSING INFORMATION Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

### Table

**CAUTIONARY AND ADVISORY LABELS 21**

- **Fenofibrate (Non-proprietary)**
  - Fenofibrate micronised 160 mg Fenofibrate micronised 160mg tablets | 28 tablet £6.69 DT £3.30
  - Supralip (Mylan) Fenofibrate micronised 160 mg Supralip 160mg tablets | 28 tablet £6.69 DT £3.30

- **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS 21**
  - **Fenofibrate (Non-proprietary)**
    - Fenofibrate micronised 67 mg Fenofibrate micronised 67mg capsules | 90 capsule £3.30 DT £2.11
    - Fenofibrate micronised 200 mg Fenofibrate micronised 200mg capsules | 28 capsule £11.98 DT £3.00
    - Fenofibrate micronised 267 mg Fenofibrate micronised 267mg capsules | 28 capsule £21.75 DT £3.58
  - Lipantil Micro (Mylan) Fenofibrate micronised 67 mg Lipantil Micro 67 capsules | 90 capsule £23.30 DT £12.31
  - Fenofibrate micronised 200 mg Lipantil Micro 200 capsules | 28 capsule £14.23 DT £3.00
  - Fenofibrate micronised 267 mg Lipantil Micro 267 capsules | 28 capsule £21.75 DT £3.58

**Combinations available:** Simvastatin with fenofibrate, p. 206

### Gemfibrozil

- **DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

- **INDICATIONS AND DOSE** Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in primary hypercholesterolaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia. Adjunct to diet and other appropriate measures in primary prevention of cardiovascular disease in men with hyperlipidaemias if statin contra-indicated or not tolerated.

- **BY MOUTH**
  - Adult: 1.2 g daily in 2 divided doses, maintenance 0.9–1.2 g daily

- **CONTRA-INDICATIONS** History of gall-bladder or biliary tract disease including gallstones · photosensitivity to fibrates

- **CAUTIONS** Correct hypothyroidism before initiating treatment · elderly

- **INTERACTIONS** → Appendix 1: fibrates

- **SIDE-EFFECTS**
  - Common or very common Constipation · diarrhoea · fatigue · flatulence · gastrointestinal discomfort · headache · nausea · skin reactions · vertigo · vomiting
  - Uncommon Atrial fibrillation
  - Rare or very rare Alopecia · anaemia · angioedema · appendicitis · bone marrow failure · depression · dizziness · drowsiness · eosinophilia · gallbladder disorders · hepatic disorders · joint disorders · laryngeal oedema · leucopenia · muscle weakness · myalgia · myopathy · pain in extremity · pancreatitis · paraesthesia · peripheral neuropathy · photosensitivity reaction · sexual dysfunction · thrombocytopenia · vision blurred

- **PREGNANCY** Manufacturers advise avoid unless essential— toxicity in animal studies.

- **BREST FEEDING** Manufacturers advise avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturers advise avoid.

- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m². Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

- **Dose adjustments** Initially 900 mg daily if eGFR 30–80 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor blood counts for thrombocytopenia for the first year.
  - Monitor liver-function (discontinue treatment if abnormalities persist).
  - Consider monitoring creatine kinase if used in combination with a statin.

- **PRESCRIBING AND DISPENSING INFORMATION** Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Table

**CAUTIONARY AND ADVISORY LABELS 22**

- **Gemfibrozil (Non-proprietary)**
  - Gemfibrozil 600 mg Gemfibrozil 600mg tablets | 56 tablet £35.57 DT £35.57

www.getintopharma.com
LIPID MODIFYING DRUGS > NICOTINIC ACID DERIVATIVES

Acipimox

- **INDICATIONS AND DOSE**
  
  Adjunct or alternative treatment in hyperlipidaemias of types IIb and IV in patients who have not responded adequately to other lipid-regulating drugs such as a statin or fibrate, and lifestyle changes (including diet, exercise, and weight reduction)
  
  - BY MOUTH
  - Adult: 250 mg 2–3 times a day

- **CONTRA-INDICATIONS**
  
  Peptic ulcer

- **SIDE-EFFECTS**
  
  - Common or very common
    - Asthenia, gastrointestinal discomfort, headache, skin reactions, vasodilatation
  
  - Uncommon
    - Angioedema, arthralgia, feeling hot, malaise, myalgia, myositis, nausea
  
  - Frequency not known
    - Bronchospasm, diarrhoea, dry eye, eye disorder – eyes gritty

- **PREGNANCY**
  
  Manufacturer advises avoid — no information available.

- **BREAST FEEDING**
  
  Manufacturer advises avoid — no information available.

- **RENAL IMPAIRMENT**
  
  - Avoid if eGFR less than 30 mL/minute/1.73 m².
  
  - Dose adjustments
    - Reduce dose to 250 mg 1–2 times daily if eGFR 30–60 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  
  Monitor hepatic and renal function.

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  
  CAUTIONARY AND ADVISORY LABELS 21
  
  - **Lopid** (Pfizer Ltd)
    - Acipimox 250 mg
      - 90 capsule [PO]
      - £46.33 DT + £46.33

Nicotinic acid

- **DRUG ACTION**
  
  In doses of 1.5 to 3 g daily, it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis; it also increases HDL-cholesterol.

- **INDICATIONS AND DOSE**
  
  Adjunct to statin in dyslipidaemia or used alone if statin not tolerated
  
  - BY MOUTH
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  
  Active peptic ulcer disease - arterial bleeding

- **CAUTIONS**
  
  - Acute myocardial infarction - diabetes mellitus - gout - history of peptic ulceration - unstable angina
  
  - INTERACTIONS
    - Appendix 1: nicotinic acid

- **SIDE-EFFECTS**
  
  - Common or very common
    - Diarrhoea - flushing - gastrointestinal discomfort - nausea - skin reactions - vomiting
Hyperlipidaemia

Before starting treatment with statins, at least one full monitoring requirement is necessary.

**MONITORING REQUIREMENTS**
- **Liver function**
  - There is little information available on a rational approach to liver-function monitoring; however, NICE suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity (NICE clinical guideline 181 [July 2014]). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease).
- **Creatine kinase** Before initiation of statin treatment, creatine kinase concentration should be measured in patients who have had persistent, generalised, unexplained muscle pain (whether associated or not with previous lipid-regulating drugs); if the concentration is more than 5 times the upper limit of normal, a repeat measurement should be taken after 7 days. If the repeat concentration remains above 5 times the upper limit, statin treatment should not be started; if concentrations are still raised but less than 5 times the upper limit, the statin should be started at a lower dose.
- **Diabetes** Patients at high risk of diabetes mellitus should have fasting blood-glucose concentration or HbA1c checked before starting statin treatment, and then repeated after 3 months.

**PATIENT AND CARER ADVICE** Advise patients to report promptly unexplained muscle pain, tenderness, or weakness.

### Atorvastatin

**INDICATIONS AND DOSE**
- **Primary hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures**
  - **BY MOUTH**
  - **Adult:** Usual dose 10 mg once daily; increased if necessary up to 80 mg once daily, dose to be increased at intervals of at least 4 weeks
- **Heterozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures**
  - **BY MOUTH**
  - **Adult:** 20 mg once daily, dose can be increased if necessary

**SIDE-EFFECTS**
- **Common or very common**
  - Epistaxis, hyperglycaemia, hyperglycaemia, laryngeal pain, muscle complaints, nasopharyngitis, pain
- **Uncommon**
  - Appetite decreased, burping, chest pain, fever, hypertrophic cardiovascular disease, malaise, numbness, peripheral oedema, taste altered, tinnitus, vision disorders, weight increased
- **Rare or very rare**
  - Angioedema, gynaecomastia, hearing loss, severe cutaneous adverse reactions (SCARs)
- **Breast feeding**
  - Manufacturer advises avoid—no information available.

**RENAI IMPAIRMENT**
- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises if concurrent use of ciclosporin is unavoidable, max. dose cannot exceed 10 mg daily.
  - Manufacturer advises max. dose 40 mg daily when combined with anion-exchange resin for heterozygous familial hypercholesterolaemia.
  - Manufacturer advises max. dose 20 mg daily with concurrent use of elbasvir with grazoprevir.
  - Manufacturer advises max. dose 20 mg daily with concurrent use of letemovir without ciclosporin.

**PATIENT AND CARER ADVICE**
- Advise patients to report promptly unexplained muscle pain, tenderness, or weakness.

**REFERENCES**
- [unlicensed starting dose in secondary prevention]
- [unlicensed starting dose in primary prevention]
- [unlicensed starting dose in secondary prevention], initially 20 mg once daily, increased if necessary up to 80 mg once daily, dose to be increased at intervals of at least 4 weeks

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Manufacturer advises if concurrent use of ciclosporin is unavoidable, max. dose cannot exceed 10 mg daily.
- Manufacturer advises max. dose 40 mg daily when combined with anion-exchange resin for heterozygous familial hypercholesterolaemia.
- Manufacturer advises max. dose 20 mg daily with concurrent use of elbasvir with grazoprevir.
- Manufacturer advises max. dose 20 mg daily with concurrent use of letemovir without ciclosporin.

**UNLICENSED USE**
- Not licensed for secondary prevention of cardiovascular events. Starting dose of 20 mg daily or more is not licensed for the primary prevention of cardiovascular events.

**CAUTIONS**
- Haemorrhagic stroke

**INTERACTIONS**
- Appendix 1: statins
Fluvastatin

08-Feb-2019

**INDICATIONS AND DOSE**

Adjunct to diet in primary hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to dietary control

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 20–40 mg daily, dose to be taken in the evening, increased if necessary up to 80 mg daily in 2 divided doses, dose to be adjusted at intervals of at least 4 weeks

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 80 mg daily

Prevention of coronary events after percutaneous coronary intervention

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 80 mg daily

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 80 mg daily, dose form is not appropriate for initial dose titration

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Max. dose 20 mg daily with concomitant elbasvir with grazoprevir.

**INTERACTIONS**

- Appendix 1: statins

**SIDE-EFFECTS**

- Rare or very rare Angioedema • face oedema • lupus-like syndrome • muscle weakness • sensation abnormal • vasculitis

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT**

  **Dose adjustments**

  Manufacturer advises doses above 40 mg daily should be initiated with caution if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Patient counselling is advised for fluvastatin tablets/capsules (muscle effects).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 76/04

The Scottish Medicines Consortium has advised (February 2004) that fluvastatin (Lescol 79) is accepted for restricted use for the secondary prevention of coronary events after percutaneous coronary angioplasty; if the patient has previously been receiving another statin, then there is no need to change the statin.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Lipitor** (Pfizer Ltd)
  - Atorvastatin (as Atorvastatin calcium trihydrate) 10 mg
  - Atorvastatin (as Atorvastatin calcium trihydrate) 20 mg
  - Atorvastatin (as Atorvastatin calcium trihydrate) 40 mg

- **Lescol** (Sandoz Ltd)
  - Fluvastatin (as Fluvastatin sodium) 20 mg
  - Fluvastatin (as Fluvastatin sodium) 40 mg

- **Lipitor** (Pfizer Ltd)
  - Atorvastatin (as Atorvastatin calcium trihydrate) 10 mg
  - Atorvastatin (as Atorvastatin calcium trihydrate) 20 mg

- **Lescol XL** (Novartis Pharmaceuticals UK Ltd)
  - Fluvastatin (as Fluvastatin sodium) 80 mg

- **Cadaff XL** (Teva UK Ltd)
  - Fluvastatin (as Fluvastatin sodium) 40 mg

- **Nandovar XL** (Sandzol Ltd)
  - Fluvastatin (as Fluvastatin sodium) 40 mg

- **Nandovar XL** (Sandzol Ltd)
  - Fluvastatin (as Fluvastatin sodium) 40 mg

Pravastatin sodium

08-Jun-2017

**INDICATIONS AND DOSE**

Adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control

- **BY MOUTH**
  - Adult: 10–40 mg daily, dose to be taken at night, dose to be adjusted at intervals of at least 4 weeks

Prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina

- **BY MOUTH**
  - Adult: 40 mg daily, dose to be taken at night

Reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation

- **BY MOUTH**
  - Adult: Initially 20 mg daily, then increased if necessary up to 40 mg daily, dose to be taken at night, close medical supervision is required if dose is increased to maximum dose

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises reduce dose by half with concurrent use of omibitasvir with paritaprevir and ritonavir.

- Manufacturer advises max. 20 mg daily with concurrent use of glecaprevir with pibrentavir.

- Manufacturer advises max. 40 mg daily with concurrent use of sofosbuvir with velpatasvir and voxilaprevir.
Cardiovascular system

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, tablets, capsules, film-coated tablets, injectable, and ointment.

Tablet
- Pravastatin sodium (Non-proprietary)
  - Pravastatin sodium 10 mg: Pravastatin 10mg tablets [D][P] 28 tablet [P] £2.68 DT = £0.77
  - Pravastatin sodium 20 mg: Pravastatin 20mg tablets [D][P] 28 tablet [P] £3.05 DT = £0.96
  - Pravastatin sodium 40 mg: Pravastatin 40mg tablets [D][P] 28 tablet [P] £3.82 DT = £1.18

Rosuvastatin

INDICATIONS AND DOSE

Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures and who have risk factors for myopathy or rhabdomyolysis

BY MOUTH

Adult: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased gradually at intervals of at least 4 weeks.

Severe primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb), or homozygous familial hypercholesterolaemia in patients with high cardiovascular risk who have not responded adequately to diet and other appropriate measures, and who have risk factors for myopathy or rhabdomyolysis

BY MOUTH

Adult: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased gradually at intervals of at least 4 weeks.

Prevention of cardiovascular events in patients at high risk of a first cardiovascular event

BY MOUTH

Adult: Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased gradually at intervals of at least 4 weeks.

Dose adjustments due to interactions

- Manufacturer advises initially 5 mg daily with concurrent use of bezafibrate, ciprofibrate, and fenofibrate—40 mg dose is contra-indicated.
- Manufacturer advises initially 5 mg daily with concurrent use of clodipogrel—max. dose 20 mg daily.
- Manufacturer advises initially 5 mg daily with concurrent use of simprevir—max. dose 10 mg daily.
- Manufacturer advises max. dose 5 mg daily with concurrent omibitasvir, paritaprevir, and ritonavir given with dasabuvir, but max. 10 mg daily with concurrent omibitasvir, paritaprevir, and ritonavir given without dasabuvir.
- Manufacturer advises max. dose 10 mg daily with concurrent use of sofosbuvir with velpatasvir, or elbasvir with grazoprevir.
- Manufacturer advises reduce dose by half with concurrent use of glecaprevir with pibrentasvir.

INTERACTIONS

Appendix 1: statins

SIDE-EFFECTS

- Rare or very rare: Arthralgia; gynaecomastia; haematuria; polyneuropathy
- Frequency not known: Cough; dyspnoea; oedema; proteinuria; Stevens-Johnson syndrome; tendon disorders

BREAST FEEDING

Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT

Avoid if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments

- Initially 5 mg once daily (do not exceed 20 mg daily) if eGFR 30–60 mL/minute/1.73 m².
Simvastatin

- **INDICATIONS AND DOSE**
  - Primary hypercholesterolaemia, or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures
    - **BY MOUTH**
      - Adult: 10–20 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications
  - Homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures
    - **BY MOUTH**
      - Adult: Initially 40 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications
  - Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus
    - **BY MOUTH**
      - Adult: Initially 20–40 mg once daily, increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises max. 10 mg daily with concurrent use of bezafibrate or ciprofibrate.
  - Manufacturer advises max. 20 mg daily with concurrent use of amiodarone, amiodipine, or ranolazine.
  - Manufacturer advises reduce dose with concurrent use of some moderate inhibitors of CYP3A4 (max. 20 mg daily with verapamil and diltiazem).
  - Manufacturer advises max. 40 mg daily with concurrent use of elabavir with grazoprevir.

- **INTERACTIONS**
  - Appendix 1: statins

- **SIDE-EFFECTS**
  - Rare or very rare: Acute kidney injury, anaemia, muscle cramps

- **PATIENT AND CARER ADVICE**
  - Patient counselling is advised for simvastatin tablets/oral suspension (muscle effects).

- **INTERACTIONS**
  - Appendix 1: statins

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  - **Tablet**
    - Rosuvastatin (Non-proprietary) (AstraZeneca UK Ltd)
      - Adult: 5 mg; 10 mg; 20 mg; 40 mg tablets | 28 tablet | £18.03 DT = £1.44
      - Manufacturer advises max. daily dose.
      - Manufacturer advises use with caution if eGFR less than 30 mL/minute/1.73 m².
      - Patient and carer advice: Patient counselling is advised for simvastatin tablets/oral suspension (muscle effects).

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Simvastatin 10 mg tablets can be sold to the public to reduce risk of first coronary event in individuals at moderate risk of coronary heart disease (approx. 10–15% risk of major event in 10 years), max. daily dose 10 mg and pack size of 28 tablets; treatment should form part of a programme to reduce risk of coronary heart disease.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  - **Oral suspension**
    - EXCIPIENTS: May contain Propylene glycol
      - Simvastatin (Non-proprietary)
        - Simvastatin 4 mg per 1 ml Simvastatin 20 mg/5 ml oral suspension sugar-free sugar-free | 150 PDP | £144.32
        - Simvastatin 8 mg per 1 ml Simvastatin 40 mg/5 ml oral suspension sugar-free | 150 PDP | £200.45

  - **Tablet**
    - Simvastatin (Non-proprietary)
      - Simvastatin 10 mg | 28 tablet | £14.42 DT = £0.64
      - Simvastatin 20 mg | 28 tablet | £23.75 DT = £0.75
      - Simvastatin 40 mg | 28 tablet | £23.75 DT = £0.87
      - Simvastatin 80 mg | 28 tablet | £6.00 DT = £1.49

      - Simvador (Discovery Pharmaceuticals)
        - Simvastatin 10 mg | 28 tablet | £0.52 DT = £0.64
        - Simvastatin 20 mg | 28 tablet | £0.67 DT = £0.75
        - Simvastatin 40 mg | 28 tablet | £0.65 DT = £0.87
        - Simvastatin 80 mg | 28 tablet | £1.31 DT = £1.49

      - Zocor (Merck Sharp & Dohme Ltd)
        - Simvastatin 10 mg | 28 tablet | £18.03 DT = £0.64
        - Simvastatin 20 mg | 28 tablet | £29.69 DT = £0.75
        - Simvastatin 40 mg | 28 tablet | £29.69 DT = £0.87
        - Simvastatin 80 mg | 28 tablet | £29.69 DT = £1.49

- **Simvastatin with ezetimibe**
  - The properties listed below are those particular to the combination only. For the properties of the components please consider, simvastatin above, ezetimibe p. 198.

  - **INDICATIONS AND DOSE**
    - Homozygous familial hypercholesterolaemia, primary hypercholesterolaemia, and mixed hyperlipidaemia in patients over 10 years stabilised on the individual components in the same proportions, or for patients not adequately controlled by statin alone
      - **BY MOUTH**
      - Adult: consult product literature

  - **INTERACTIONS**
    - Appendix 1: ezetimibe, statins
**LIPID MODIFYING DRUGS**

### Simvastatin with fenofibrate

The properties listed below are those particular to the combination only. For the properties of the components please consider, simvastatin p. 205, fenofibrate p. 199.

- **INDICATIONS AND DOSE**
  Adjunct to diet and exercise in mixed dyslipidaemia, when LDL-cholesterol levels are adequately controlled with the corresponding dose of simvastatin monotherapy in patients at high cardiovascular risk

  - **BY MOUTH**
    - Adult: 20/145 mg once daily, alternatively 40/145 mg once daily, dose should be based on previous simvastatin monotherapy dose

- **CAUTIONS**
  History of pulmonary embolism

- **INTERACTIONS**
  - Appendix 1: fibrates · statins

- **RENAI IMPAIRMENT**
  Manufacturer advises avoid if eGFR less than 60 mL/minute/1.73 m²; use with caution if eGFR 60–89 mL/minute/1.73 m²

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 25
- **EXCIPIENTS:** May contain Butylated hydroxyanisole, lecithin
  - **Cholib (Mylan)**
    - Simvastatin 20 mg, Fenofibrate 145 mg
    - 30 tablet (Pte) £3.42 DT + £33.42
    - Simvastatin 40 mg, Fenofibrate 145 mg
    - 30 tablet (Pte) £2.98 DT + £28.98

- **Ezetimibe 10 mg, Simvastatin 80 mg**
  - 28 tablet (Pte) £41.21 DT + £41.21

**Solution for injection**

- **Manufacturer advises store in a refrigerator (2–8 °C)–consult product literature for further information regarding storage outside refrigerator.**
- **Praluent (Sanofi)**
  - **Alirocumab 75 mg per 1 ml**
  - **Alirocumab 150 mg per 1 ml**

### Relevant Links

- **Scottish Medicines Consortium (SMC) decisions**
  - **SMC No. 1147/16**
  - The Scottish Medicines Consortium has advised (August 2016) that alirocumab (Praluent®) is accepted for restricted use within NHS Scotland for treatment of primary hypercholesterolaemia or mixed dyslipidaemia (alone or in combination with other lipid lowering therapies, as specified within it’s licence), for specialist use only and only in patients at high cardiovascular risk as follows:
    - patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥ 5.0mmol/L, for primary prevention of cardiovascular events, or
    - patients with HeFH and LDL-C ≥ 3.5mmol/L for secondary prevention of cardiovascular events, or
    - patients at high risk due to previous cardiovascular events and LDL-C ≥ 4.0mmol/L, or
    - patients with recurrent/polyvascular disease and LDL-C ≥ 3.5mmol/L.
  - This advice is contingent upon the continuing availability of the Patient Access Scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **EXCIPIENTS:** May contain Polysorbates
  - **Praluent (Sanofi)**
    - **Alirocumab 75 mg per 1 ml**
      - Praluent 75mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection £168.00 | 2 pre-filled disposable injection £336.00
    - **Alirocumab 150 mg per 1 ml**
      - Praluent 150mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection £168.00 | 2 pre-filled disposable injection £336.00
Evolocumab
08-Feb-2019

**DRUG ACTION**
Evolocumab binds to a pro-protein involved in the regulation of LDL receptors on liver cells; receptor numbers are increased, which results in increased uptake of LDL-cholesterol from the blood.

**INDICATIONS AND DOSE**

Primary hypercholesterolaemia or mixed dyslipidaemia in patients who have not responded adequately to other appropriate measures (in combination with a statin, or with a statin and other lipid-lowering therapies, or with other lipid-lowering therapies alone or if a statin contra-indicated or not tolerated) | Established atherosclerotic cardiovascular disease (in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies, or with other lipid-lowering therapies alone or if a statin contra-indicated or not tolerated)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 140 mg every 2 weeks, alternatively 420 mg every month, to be administered into the thigh, abdomen or upper arm

Homozygous familial hypercholesterolaemia | (in combination with other lipid-lowering therapies)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 420 mg every month; increased if necessary to 420 mg every 2 weeks, if inadequate response after 12 weeks of treatment, to be administered into the thigh, abdomen or upper arm

Homozygous familial hypercholesterolaemia in patients on apheresis | (in combination with other lipid-lowering therapies)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 420 mg every 2 weeks, to correspond with apheresis schedule, to be administered into the thigh, abdomen or upper arm

**SIDE-EFFECTS**

- Common or very common: Arthralgia - back pain - increased risk of infection - nausea - skin reactions
- Rare or very rare: Angioedema
- **PREGNANCY**: Manufacturer advises avoid unless essential—limited information available.
- **BREAST FEEDING**: Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT**: Manufacturer advises caution in moderate to severe impairment (risk of reduced efficacy; no information available in severe impairment).
- **RENAL IMPAIRMENT**: Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m²—no information available.
- **HANDLING AND STORAGE**: Manufacturer advises store in a refrigerator (2–8°C)—consult product literature for further information regarding storage outside refrigerator.
- **PATIENT AND CARER ADVICE**: Patients and their carers should be given training in subcutaneous injection technique.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE decisions**
  - Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016) NICE TA4394
  - Evolocumab (Repatha®) is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:
    - it is given at a dose of 140 mg every 2 weeks, and
    - low-density lipoprotein cholesterol (LDL-C) concentrations are persistently above the thresholds specified in the NICE documentation, and
  - the manufacturer provides evolocumab with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta4394

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1148/16
The Scottish Medicines Consortium has advised (February 2017) that evolocumab (Repatha®) is accepted for restricted use within NHS Scotland for the treatment of primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia and non-familial) or mixed dyslipidaemia (alone or in combination with other lipid lowering therapies, as specified within its license), for specialist use only when administered at a dose of 140 mg every 2 weeks and only in patients at high cardiovascular risk as follows:

- patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C 5 mmol/L or greater for primary prevention of cardiovascular events, or
- patients with HeFH and LDL-C 3.5 mmol/L or greater for secondary prevention of cardiovascular events, or
- patients with high risk due to previous cardiovascular events and LDL-C 4 mmol/L or greater, or
- patients with recurrent/polyvascular disease and LDL-C 3.5 mmol/L or greater.

This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Repatha SureClick (£60.98) | Evolocumab 140 mg per 1 ml
- Repatha SureClick 140mg/1ml solution for injection pre-filled pens | 2 pre-filled disposable injection vials £180.20

Lomitapide
01-Aug-2018

**DRUG ACTION**
Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids such as cholesterol and triglycerides.

**INDICATIONS AND DOSE**

Adjunct to dietary measures and other lipid-lowering drugs with or without low-density lipoprotein apheresis in homozygous familial hypercholesterolaemia (under expert supervision)

- **BY MOUTH**
  - Adult: Initially 5 mg daily for 2 weeks, dose to be taken at least 2 hours after evening meal, then increased if necessary to 10 mg daily, for at least 4 weeks, then increased to 20 mg daily for at least 4 weeks, then increased in steps of 20 mg daily, adjusted at intervals of at least 4 weeks; maximum 60 mg per day

**CONTRA-INDICATIONS**
Significant or chronic bowel disease

**CAUTIONS**
Concomitant use of hepatotoxic drugs - lomitapide can interfere with the absorption of fat-soluble nutrients and supplementation of vitamin E and fatty acids is required - patients over 65 years

**INTERACTIONS**
→ Appendix 1: lomitapide

**SIDE-EFFECTS**

- Common or very common: Nausea - headache - muscle pain - increased liver enzymes
- Uncommon or rare: Appetite abnormal - constipation - dizziness - haemorrhage - jaundice - peripheral neuropathy - peripheral oedema - photosensitivity - pruritus - venous thromboembolism

www.getintopharma.com
risk of infection · muscle complaints · nausea · skin reactions · vomiting · weight decreased

- **Uncommon** Anaemia · chest pain · chills · dehydration · drowsiness · dry mouth · eye swelling · fever · gait abnormal · hyperhidrosis · joint disorders · malaise · pain in extremity · paraesthesia · throat lesion · upper-airway cough syndrome · vertigo

- **Frequency not known** Alopecia

**SIDE-EFFECTS, FURTHER INFORMATION** Reduce dose if serum transaminases raised during treatment (consult product literature).

**CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before treatment and ensure effective contraception used.

**PREGNANCY** Avoid—teratogenicity and embryotoxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment, or if unexplained persistent abnormal liver function tests.

**Dose adjustments** Manufacturer advises max. 40 mg daily in mild impairment.

**RENAL IMPAIRMENT**

**Dose adjustments** Max. 40 mg daily in end-stage renal disease.

**MONITORING REQUIREMENTS**

- Monitor liver function tests before treatment, then at least monthly and before each dose increase for first year, then at least every 3 months and before each dose increase thereafter.
- Screen for hepatic steatosis and fibrosis before treatment, then annually thereafter.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Lojuxta** (Amryt Pharma) ▼
  - Lomitapide 5 mg Lojuxta 5mg capsules | 28 capsule POM
  - Lomitapide 10 mg Lojuxta 10mg capsules | 28 capsule POM
  - Lomitapide 20 mg Lojuxta 20mg capsules | 28 capsule POM

**Omega-3-acid ethyl esters**

- **INDICATIONS AND DOSE**
  - Adjunct to diet and statin in type IIb or III hypertriglyceridaemia | Adjunct to diet in type IV hypertriglyceridaemia
  - **BY MOUTH**
  - Adult: Initially 2 capsules daily, dose to be taken with food, increased if necessary to 4 capsules daily
  - Adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months
  - **BY MOUTH**
  - Adult: 1 capsule daily, dose to be taken with food

- **CAUTIONS** Anticoagulant treatment (bleeding time increased) · haemorrhagic disorders

- **INTERACTIONS** Appendix 1: omega-3-acid ethyl esters

- **SIDE-EFFECTS**
  - Common or very common Burping · constipation · diarrhea · gastrointestinal discomfort · gastrointestinal disorders · nausea · vomiting
  - Uncommon Dizziness · gout · haemorrhage · headache · hyperglycaemia · hypotension · skin reactions · taste altered
  - Rare or very rare Liver disorder

- **PREGNANCY** Manufacturers advise use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING** Manufacturers advise avoid—no information available.

- **HEPATIC IMPAIRMENT** Monitoring Monitor liver function in hepatic impairment.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) decisions**

  The Scottish Medicines Consortium has advised (November 2002) that omega-3-acid ethyl esters are not recommended for use within NHS Scotland for the treatment of hypertriglyceridaemia.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 21**

- **Omega-3-acid ethyl esters (Non-proprietary)**
  - Eicosapentaenoic acid 60 mg, Docosahexaenoic acid 300 mg | Omega-3 600mg capsules | 28 capsule POM
  - Omega 3 (Glennmark Pharmaceuticals Europe Ltd)
    - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid 460 mg | Omega 3-acid-ethyl esters 1000mg capsules | 28 capsule POM £14.24 | 100 capsule POM £21.00
  - Teromeg (Advanz Pharma)
    - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid 460 mg | Teromeg 1000mg capsules | 28 capsule POM £11.39 DT = £14.24 | 100 capsule POM £40.67

8 Myocardial ischaemia

Stable angina

**Description of condition**

Stable angina is characterised by predictable chest pain or pressure, often precipitated by physical exertion or emotional stress causing an increase in myocardial oxygen demand. Although pain typically occurs in the front of the chest, it may also radiate to the neck, shoulders, jaw or arms; the pain is relieved with rest. Stable angina usually results from atherosclerotic plaques in the coronary arteries that restrict blood flow and oxygen supply to the heart; it can lead to cardiovascular complications such as stroke, unstable angina, myocardial infarction, and sudden cardiac death. For information about unstable angina and myocardial infarction, see Acute coronary syndromes.

Prinzmetal’s or vasospastic angina is a rare form of angina caused by narrowing or occlusion of proximal coronary arteries due to spasm, in which pain is experienced at rest rather than during activity.

**Aims of treatment**

Antianginal drug therapy and revascularisation aims to prevent or minimise angina symptoms, in order to improve quality of life and long-term morbidity and mortality. The aim of drug therapy for secondary prevention is to minimise the risk of cardiovascular events such as myocardial infarction and stroke.

**Drug treatment**

Antianginal drug therapy

Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate p. 218, which can also be used as a preventative measure immediately before performing activities that are known to bring on an attack.

For long-term prevention of chest pain in patients with stable angina, a beta-blocker (such as atenolol p. 152, bisoprolol fumarate p. 153, metoprolol tartrate p. 154 or propranolol hydrochloride p. 150) should be given as first-line therapy. A rate-limiting calcium-channel blocker (such
as verapamil hydrochloride p. 164 or diltiazem hydrochloride p. 157) should be considered as an alternative if beta-blockers are contra-indicated, for example in patients with Prinzmetal’s angina or decompensated heart failure. Dihydropyridine derivative calcium-channel blockers (such as amlodipine p. 156) may be effective in patients with Prinzmetal’s angina.

If a beta-blocker alone fails to control symptoms adequately, a combination of a beta-blocker and a calcium-channel blocker should be considered. If this combination is not appropriate due to intolerance of, or contra-indication to, either beta-blockers or calcium-channel blockers, NICE CG126 recommends to consider addition of either a long-acting nitrate, isosorbide dinitrate p. 211, nicorandil p. 212, or ranolazine p. 211.

A long-acting nitrate, isosorbide dinitrate p. 211, nicorandil p. 212, or ranolazine p. 211, should also be considered as monotherapy in patients who cannot tolerate beta-blockers and calcium-channel blockers, if both are contra-indicated, or when they both fail to adequately control angina symptoms.

Response to treatment should be assessed every 2–4 weeks following initiation or change of drug therapy; drug doses should be titrated to the maximum tolerated effective dose.

If a combination of two drugs at a maximum therapeutic dose fails to control angina symptoms, patients should be considered for referral to a specialist.

Secondary prevention of cardiovascular events

All patients with angina are assumed to be at high-risk for cardiovascular events. The occurrence of cardiovascular events can be prevented by management of cardiovascular risk factors through lifestyle changes (such as smoking cessation, weight management, increased physical activity), psychological support, and drug treatment. See also Secondary prevention in Cardiovascular disease risk assessment and prevention p. 189 for further information.

Non-drug treatment

Revascularisation by coronary artery bypass graft or percutaneous coronary intervention should be considered for patients with stable angina who remain symptomatic whilst on optimal drug therapy. See also Antiplatelet drugs and coronary stents in Antiplatelet drugs p. 121.

Advanced Pharmacy Services

Patients with stable angina may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Useful Resources


www.sign.ac.uk/assets/sign151.pdf


www.nice.org.uk/guidance/cg126

Other drugs used for Myocardial ischaemia


间的羊村
**210 Myocardial ischaemia**

**ANTITHROMBOTIC DRUGS > GLYCOPROTEIN IIb/IIIa INHIBITORS**

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**Eptifibatide**

**INDICATIONS AND DOSE**

In combination with aspirin and unfractionated heparin for the prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 24 hours (specialist use only)

- Initially by intravenous injection
  - Adult: Initially 180 micrograms/kg, then (by intravenous infusion) 2 micrograms/kg for up to 72 hours (up to 96 hours if percutaneous coronary intervention during treatment)

**CONTRA-INDICATIONS**

Abnormal bleeding within 30 days - aneurysm - arteriovenous malformation - haemorrhagic diathesis - history of haemorrhagic stroke - increased INR - increased prothrombin time - intracranial disease - major surgery or severe trauma within 6 weeks - neoplasm - severe hypertension - stroke within last 30 days - thrombocytopenia

**CAUTIONS**

Discontinue if emergency cardiac surgery necessary - discontinue if intra-aortic balloon pump necessary - discontinue if thrombolytic therapy necessary - risk of bleeding - discontinue immediately if uncontrolled serious bleeding

**INTERACTIONS**

Appendix 1: eptifibatide

**SIDE-EFFECTS**

- Common or very common
  - Arrhythmias - atrioventricular block - cardiac arrest - congestive heart failure - haemorrhage - hypotension - intracranial haemorrhage - procedural complications - shock

- Uncommon
  - Cerebral ischaemia - thrombocytopenia

- Rare or very rare
  - Rash

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk — no information available.

**BREAST FEEDING**

Manufacturer advises avoid — no information available.

**HEPATIC IMPAIRMENT**

Avoid in severe liver disease — increased risk of bleeding.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m²

**Dose adjustments**

Reduce infusion to 1 microgram/kg/minute if eGFR 30–50 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Measure baseline prothrombin time, activated partial thromboplastin time, platelet count, haemoglobin, haematocrit and serum creatinine.

- Monitor haemoglobin, haematocrit and platelets within 6 hours after start of treatment, then at least once daily.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Eptifibatide (Non-proprietary)**

  | Eptifibatide 2 mg per 1 ml | Epifibatide 20mg/10ml solution for injection vials | 1 vial [PCE] | £5.14 (Hospital only) |

  | Integrisil (GlasoSmithKline UK Ltd) | Eptifibatide 2 mg per 1 ml | Integrisil 20mg/10ml solution for injection vials | 1 vial [PCE] | £13.61 (Hospital only) |

**Solution for infusion**

- **Eptifibatide (Non-proprietary)**

  | Eptifibatide 750 microgram per 1 ml | Eptifibatide 75mg/100ml solution for infusion vials | 1 vial [PCE] | £7.14 (Hospital only) |

  | Integrisil (GlasoSmithKline UK Ltd) | Eptifibatide 750 microgram per 1 ml | Integrisil 75mg/100ml solution for infusion vials | 1 vial [PCE] | £42.79 (Hospital only) |

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**Tirofiban**

**INDICATIONS AND DOSE**

In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) and with last episode of chest pain within 12 hours (with angiography planned for 4–48 hours after diagnosis) (initiated under specialist supervision)

- Initially by intravenous injection
  - Adult: Initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention), maximum duration of treatment 108 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI) and with last episode of chest pain within 12 hours (with angiography within 4 hours of diagnosis) (initiated under specialist supervision)

- Initially by intravenous injection
  - Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI) intended for primary percutaneous coronary intervention (PCI) (initiated under specialist supervision)

- Initially by intravenous injection
  - Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

**CONTRA-INDICATIONS**

Abnormal bleeding within 30 days - history of aneurysm - history of arteriovenous malformation - history of haemorrhagic stroke - history of intracranial disease - history of neoplasm - increased INR - increased prothrombin time - severe hypertension - stroke within 30 days - thrombocytopenia

**CAUTIONS**

- Active peptic ulcer (within 3 months) - acute pericarditis - anaemia - aortic dissection - cardiogenic shock - discontinue if intra-aortic balloon pump necessary - discontinue if thrombolytic therapy necessary - discontinue immediately if serious or uncontrollable bleeding occurs - discontinue if emergency cardiac surgery necessary - elderly - faecal occult blood - haematuria - haemorrhagic retinopathy - low body-weight - major surgery within 3 months (avoid if within 6 weeks) - organ biopsy or lithotripsy within last 2 weeks - puncture of non-compressible vessel within 24 hours - risk of bleeding (within 3 months) - severe heart failure - severe trauma within 3 months (avoid if within 6 weeks) - traumatic or protracted cardiopulmonary resuscitation within last 2 weeks - uncontrolled severe hypertension - vasculitis

**INTERACTIONS**

Appendix 1: tirofiban

**SIDE-EFFECTS**

- Common or very common

  - Ecchymosis - fever - haemorrhage - headache - nausea - thrombocytopenia

- Frequency not known

  - Intracranial haemorrhage

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk — no information available.

**BREAST FEEDING**

Manufacturer advises avoid — no information available.

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**HEPATIC IMPAIRMENT** Manufacturer advises avoid unless essential—no information available.

**RENAL IMPAIRMENT** Increased risk of bleeding.

- **Dose adjustments** Use half normal dose if eGFR less than 30 mL/minute/1.73 m².
- **Monitoring** Monitor carefully if eGFR less than 60 mL/minute/1.73 m².
- **MONITORING REQUIREMENTS** Monitor platelet count, haemoglobin and haematocrit before treatment, 2–6 hours after start of treatment and then at least once daily.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Aggrastat®), give continuously in Glucose 5% or Sodium chloride 0.9%. Withdraw 50 mL infusion fluid from 250 mL bag and replace with 50 mL tirofiban concentrate (250 micrograms/mL) to give a final concentration of 50 micrograms/mL.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **ELECTROLYTES:** May contain Sodium
  - Aggrastat (Correvio UK Ltd)
    - Tirofiban 250 microgram per 1 ml Aggrastat 12.5mg/50ml concentrate for solution for infusion vials | 1 vial (Hospital only)
  - Infusion
    - Tirofiban (Non-proprietary)
      - Tirofiban 50 microgram per 1 ml Tirofiban 12.5mg/250ml infusion bags | 1 bag (Hospital only)
      - Aggrastat (Correvio UK Ltd)
        - Tirofiban 50 microgram per 1 ml Aggrastat 12.5mg/250ml infusion bags | 1 bag (Hospital only)

**PIPERAZINE DERIVATIVES**

### Ranolazine

- **INDICATIONS AND DOSE**
  - As adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line antianginal therapies
  - **BY MOUTH**
    - Adult: Initially 375 mg twice daily for 2–4 weeks, then increased to 500 mg twice daily, then adjusted according to response to 750 mg twice daily; reduced if not tolerated to 375–500 mg twice daily

- **CAUTIONS** Body-weight less than 60 kg - elderly - moderate to severe congestive heart failure - QT interval prolongation

- **INTERACTIONS** → Appendix 1: ranolazine

- **SIDE-EFFECTS**
  - Common or very common
    - Asthenia - constipation - headache - vomiting
  - Uncommon
  - Rare or very rare
    - Acute kidney injury - altered smell sensation - angioedema - consciousness impaired - coordination abnormal - erectile dysfunction - gait abnormal - hearing impairment - hypotension - memory loss - oral hypoesthesia - pancreatitis - peripheral coldness

**PREGNANCY** Manufacturer advises avoid unless essential—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Use with caution in mild impairment; avoid in moderate and severe impairment.

**RENAL IMPAIRMENT** Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE** Patient alert card to be provided.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **Scottish Medicines Consortium (SMC) decisions**
  - The Scottish Medicines Consortium has advised (October 2012) that ranolazine (Ranexa®) is not recommended for use within NHS Scotland.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Modified-release tablet**
  - Tirofiban (Non-proprietary)
    - Tirofiban 50 microgram per 1 ml Tirofiban 12.5mg/250ml infusion bags | 1 bag (Hospital only)
  - Aggrastat (Correvio UK Ltd)
    - Tirofiban 50 microgram per 1 ml Aggrastat 12.5mg/250ml infusion bags | 1 bag (Hospital only)

**SELECTIVE SINUS NODE I1 INHIBITORS**

- **Ivabradine**
  - **INDICATIONS AND DOSE**
    - Treatment of angina in patients in normal sinus rhythm
      - **BY MOUTH**
        - Adult 18–74 years: Initially 2.5–5 mg twice daily for 3–4 weeks, then increased if necessary up to 7.5 mg twice daily, dose to be increased gradually; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute, discontinue treatment if no improvement in symptoms within 3 months
        - Adult 75 years and over: Initially 2.5 mg twice daily for 3–4 weeks, then increased if necessary up to 7.5 mg twice daily, dose to be increased gradually; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute, discontinue treatment if no improvement in symptoms within 3 months
  - **Mild to severe chronic heart failure**
    - **BY MOUTH**
      - Adult 18–74 years: Initially 5 mg twice daily for 2 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute
      - Adult 75 years and over: Initially 2.5 mg twice daily for 2 weeks, then increased if necessary up to 7.5 mg twice daily, dose to be increased gradually; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute
  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Manufacturer advises reduce initial dose to 2.5 mg twice daily with concurrent use of moderate CYP3A4 inhibitors (except diltiazem, erythromycin and verapamil where concurrent use is contra-indicated).

- **CONTRA-INDICATIONS** Acute myocardial infarction - cardiogenic shock - congenital QT syndrome - do not initiate for angina if heart rate below 70 beats per minute - do not initiate for chronic heart failure if heart rate below
Ivabradine for the treatment of chronic heart failure

CAUTIONS Atrial fibrillation or other arrhythmias (treatment ineffective) - elderly - in angina, consider stopping if there is no or limited symptom improvement after 5 months; intraventricular conduction defects - mild to moderate hypotension (avoid if severe). Retinitis pigmentosa

INTERACTIONS → Appendix 1: ivabradine

SIDE-EFFECTS

Common or very common Arrhythmias - atrioventricular block - diziness - headache - hypertension - vision disorders

Uncommon Abdominal pain - angioedema - constipation - diarrhoea - eosinophilia - hyperuricaemia - hypotension - muscle cramps - nausea - QT interval prolongation - skin reactions - syncope - vertigo

PREGNANCY Manufacturer advises avoid — toxicity in animal studies.

BREAST FEEDING Present in milk in animal studies — manufacturer advises avoid.

HEPATIC IMPAIRMENT Manufacturer advises caution in moderate impairment; avoid in severe impairment — no information available.

RENAL IMPAIRMENT Manufacturer advises use with caution if eGFR less than 45 mL/minute/1.73 m² — no information available.

MONITORING REQUIREMENTS

Monitor regularly for atrial fibrillation (consider benefits and risks of continued treatment if atrial fibrillation occurs). Monitor for bradycardia, especially after any dose increase, and discontinue if resting heart rate persistently below 50 beats per minute or continued symptoms of bradycardia despite dose reduction.

NICE decisions

Ivabradine for the treatment of chronic heart failure (November 2012) NICE TA267

Ivabradine, in combination with standard therapy including a beta-blocker (unless contra-indicated or not tolerated), an ACE inhibitor, and an aldosterone antagonist, is an option for treating mild to severe stable chronic heart failure in patients who:

- have a left ventricular ejection fraction of < 35%, and
- are in sinus rhythm with a heart rate of ≥75 beats per minute

Ivabradine should be initiated only by a heart failure specialist after 4 weeks of stable optimal standard therapy; monitoring and dose titration should be carried out by a heart failure specialist, or a GP with special interest in heart failure, or by a heart failure specialist nurse. www.nice.org.uk/TA267

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2012) that ivabradine (Procoralan®) is accepted for restricted use within NHS Scotland in accordance with its licensed indication for heart failure only if resting heart rate remains ≥75 beats per minute despite optimal standard therapy.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

Ivabradine (Non-proprietary)

Ivabradine (as ivabradine hydrochloride) 2.5 mg | 56 tablet pack £0.17-£3.26 DT = £0.92

Ivabradine (as ivabradine hydrochloride) 5 mg | 56 tablet pack £0.69-£4.10 DT = £6.09

Ivabradine (as ivabradine hydrochloride) 7.5 mg | 56 tablet pack £3.01-£4.10 DT = £5.01

Procoralan (Servier Laboratories Ltd) Ivabradine (as ivabradine hydrochloride) 5 mg | 56 tablet pack £4.10 DT = £6.09

Ivabradine (as ivabradine hydrochloride) 7.5 mg | 56 tablet pack £4.10 DT = £5.01

VASODILATORS → POTASSIUM-CHANNEL OPENERS

Nicorandil 24-Feb-2016

INDICATIONS AND DOSE

Prophylaxis and treatment of stable angina (second-line)

BY MOUTH

Adult: Initially 5–10 mg twice daily, then increased if tolerated to 40 mg twice daily; usual dose 10–20 mg twice daily, lower initial dose regimen if patient susceptible to headache

CONTRA-INDICATIONS Acute pulmonary oedema - cardiogenic shock - hypovolaemia - left ventricular failure with low filling pressures - severe hypotension

CAUTIONS Acute myocardial infarction with acute left ventricular failure and low filling pressures - diverticular disease - risk of fistula formation or bowel perforation - G6PD deficiency - heart failure (class III–IV) - hyperkalaemia - low systolic blood pressure

INTERACTIONS → Appendix 1: nicorandil

SIDE-EFFECTS

Common or very common Asthenia - dizziness - haemorrhage - headache (more common on initiation, usually transitory) - nausea - vasodilatation - vomiting

Rare or very rare Abdominal pain - angioedema - conjunctivitis - eye disorders - gastrointestinal disorders - genital ulceration - hepatic disorders - hyperkalaemia - mucosal ulceration - myalgia - oral disorders - skin reactions - skin ulcer

Frequency not known Diplopia

SIDE-EFFECTS, FURTHER INFORMATION Nicorandil can cause serious skin, mucosal, and eye ulceration; including gastrointestinal ulcers, which may progress to perforation, haemorrhage, fistula or abscess. Stop treatment if ulceration occurs and consider an alternative.

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk — no information available.

BREAST FEEDING No information available — manufacturer advises avoid.

PATIENT AND CARER ADVICE

Driving and skilled tasks Patients should be warned not to drive or operate machinery until it is established that their performance is unimpaired.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

Nicorandil (Non-proprietary)

Nicorandil 10 mg | 60 tablet pack £7.71 DT = £4.29

Nicorandil 20 mg | 60 tablet pack £14.64 DT = £5.93

Ikerel (Sanofi)

Nicorandil 10 mg | 10mg Tablets 60 tablet pack £7.71 DT = £4.29

Nicorandil 20 mg | 20mg Tablets 60 tablet pack £14.64 DT = £5.93

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8.1 Acute coronary syndromes

Acute coronary syndromes

Overview

Acute coronary syndromes encompass a spectrum of conditions which include unstable angina, and myocardial infarction with or without ST-segment elevation. Patients with different acute coronary syndromes may present similarly; definitive diagnosis is made on the basis of clinical presentation, ECG changes, and measurement of biochemical cardiac markers.

Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)

These are related acute coronary syndromes that fall between the classifications of stable angina and ST-segment elevation myocardial infarction (STEMI). They usually occur as a result of atheromatous plaque rupture, and are often characterised by stable angina that suddenly worsens, recurring or prolonged angina at rest, or new onset of severe angina. Patients with unstable angina have no evidence of myocardial necrosis, whereas in NSTEMI, myocardial necrosis (less significant than with STEMI) will be evident. There is a risk of progression to STEMI or sudden death, particularly in patients who experience pain at rest.

Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)

These conditions are managed similarly; the aims of management are to provide supportive care and pain relief during the acute attack and to prevent further cardiac events and death. For advice on the management of patients with acute ST-segment elevation myocardial infarction (STEMI), see below.

Initial management

Oxygen should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

Nitrates are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 218 is not effective, intravenous or buccal glyceryl trinitrate or intravenous isosorbide dinitrate p. 220 is given. If pain continues, diamorphine hydrochloride p. 456 or morphine p. 463 can be given by slow intravenous injection; an antiemetic such as metoclopramide hydrochloride p. 432 should also be given.

Aspirin p. 121 (chewed or dispersed in water) is given for its antiplatelet effect. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel p. 123 should also be given. Prasugrel p. 214 is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance). Ticagrelor p. 215 is also an alternative to clopidogrel (see NICE guidance). Patients should also receive either heparin (unfractionated) p. 133, a low molecular weight heparin, or fondaparinux sodium p. 127.

Patients without contra-indications should receive beta-blockers which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem hydrochloride p. 157 or verapamil hydrochloride p. 164 can be given.

The glycoprotein IIb/IIIa inhibitors eptifibatide p. 210 (in combination with heparin (unfractionated) and aspirin) and tirofiban p. 210 (in combination with heparin (unfractionated), aspirin, and clopidogrel) can be used for unstable angina or for NSTEMI in patients at a high risk of either myocardial infarction or death.

In intermediate- and high-risk patients, abciximab or eptifibatide (in combination with heparin (unfractionated) and aspirin), or tirofiban (in combination with heparin (unfractionated), aspirin, and clopidogrel) can also be used in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion. In intermediate- and high-risk patients in whom early intervention is planned, bivalirudin p. 136 can be considered as an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin.

Revascularisation procedures are often appropriate for patients with unstable angina or NSTEMI; see Antiplatelet drugs p. 121 for the use of antiplatelet drugs in patients undergoing coronary stenting.

Long-term management

The need for long-term angina treatment or for coronary angiography should be assessed. Most patients will require standard angina treatment to prevent recurrence of symptoms.

ST-segment elevation myocardial infarction (STEMI)

This is an acute coronary syndrome where atheromatous plaque rupture leads to thrombosis and myocardial ischaemia, with irreversible necrosis of the heart muscle, often leading to long-term complications. STEMI can also occasionally occur as a result of coronary spasm or embolism, arteritis, spontaneous thrombosis, or sudden severe elevation in blood pressure.

Management of ST-segment elevation myocardial infarction (STEMI)

These notes give an overview of the initial and long-term management of myocardial infarction with ST segment elevation (STEMI). For advice on the management of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina, see above. The aims of management of STEMI are to provide supportive care and pain relief, to promote reperfusion and to reduce mortality. Oxygen, nitrates, and diamorphine hydrochloride or morphine can provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolitics promote reperfusion; anticoagulants help to reduce re-occlusion and systemic embolisation; long-term use of aspirin, beta-blockers, ACE inhibitors, and statins help to reduce mortality further.

Local guidelines for the management of myocardial infarction should be followed where they exist.

Initial management

Oxygen should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of diamorphine hydrochloride or morphine; an antiemetic such as metoclopramide hydrochloride (or, if left ventricular function is not compromised, cyclizine p. 430) by intravenous injection should also be given.

Aspirin (chewed or dispersed in water) is given for its antplatelet effect. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel p. 123 should also be given. Prasugrel p. 214 is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance). Ticagrelor p. 215 is also an alternative to clopidogrel (see NICE guidance). Patients should also receive either heparin (unfractionated) p. 133, a low molecular weight heparin, or fondaparinux sodium p. 127.

Patients without contra-indications should receive beta-blockers which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem hydrochloride p. 157 or verapamil hydrochloride p. 164 can be given.

The glycoprotein IIb/IIIa inhibitors eptifibatide p. 210 (in combination with heparin (unfractionated) and aspirin) and tirofiban p. 210 (in combination with heparin (unfractionated), aspirin, and clopidogrel) can be used for unstable angina or for NSTEMI in patients at a high risk of either myocardial infarction or death.
high-risk patients. Patients undergoing percutaneous coronary intervention should also receive either heparin (unfractionated) or a low molecular weight heparin (e.g. enoxaparin sodium p. 132); bivalirudin is an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin (see also NICE guidance). In patients who cannot be offered percutaneous coronary intervention within 90 minutes of diagnosis, a thrombolytic drug should be administrated along with either heparin (unfractionated) (for maximum 2 days), a low molecular weight heparin (e.g. enoxaparin sodium), or fondaparinux sodium. See use of antiplatelet drugs in patients undergoing coronary stenting in Antiplatelet drugs p. 121.

Patients who do not receive reperfusion therapy (with percutaneous coronary intervention or a thrombolytic) should be treated with either fondaparinux sodium, enoxaparin sodium, or heparin (unfractionated). Prescribers should consult product literature and local protocols (where they exist) for details of anticoagulant dose and duration.

**Nitrates** are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 218 is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate p. 220 is given.

Early administration of some **beta-blockers** has been shown to be of benefit and should be given to patients within 24 hours of presentation.

**ACE inhibitors**, and angiotensin-II receptor antagonists if an ACE inhibitor cannot be used, are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor, or an angiotensin-II receptor antagonist, can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment). All patients should be closely monitored for hyperglycaemia; those with diabetes or raised blood-glucose concentration should receive insulin p. 712.

**Long-term management**

Long-term management following STEMI involves the use of several drugs which should ideally be started before the patient is discharged from hospital.

Aspirin p. 121 should be given to all patients, unless contra-indicated. The addition of clopidogrel p. 123 has been shown to reduce morbidity and mortality. Prasugrel below or ticagrelor p. 215 are alternatives to clopidogrel in certain patients. For those intolerant of clopidogrel, and who are at low risk of bleeding, the combination of warfarin sodium p. 140 and aspirin should be considered. In those intolerant of both aspirin and clopidogrel, warfarin sodium alone can be used. Warfarin sodium should be continued for those who are already being treated for another indication, such as atrial fibrillation, with the addition of aspirin if there is a low risk of bleeding. The combination of aspirin with clopidogrel or warfarin sodium increases the risk of bleeding. Low-dose rivaroxaban p. 128, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following STEMI—see Prevention of cardiovascular events. For details of antiplatelet drug duration following coronary stenting—see also Antiplatelet drugs and coronary stents in Antiplatelet drugs p. 121.

**Beta-blockers** should be given to all patients in whom they are not contra-indicated. Acebutolol p. 152, metoprolol tartrate p. 154, propranolol hydrochloride p. 150 and timolol maleate p. 151 are suitable; for patients with left ventricular dysfunction, carvedilol p. 148, bisoprolol fumarate p. 153, or long-acting metoprolol tartrate may be appropriate.

Diltiazem hydrochloride p. 157 [unlicensed] or verapamil hydrochloride p. 164 can be considered if a beta-blocker cannot be used; however, they are contra-indicated in those with left ventricular dysfunction. Other calcium-channel blockers have no place in routine long-term management after a myocardial infarction.

An **ACE inhibitor** should be considered for all patients, especially those with evidence of left ventricular dysfunction. If an ACE inhibitor cannot be used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

**Nitrates** are used for patients with angina.

Eplerenone p. 193 is licensed for use following a myocardial infarction in those with left ventricular dysfunction and evidence of heart failure.

See also the role of **statins** in preventing recurrent cardiovascular events in Dyslipidaemias p. 196.

**Prevention of cardiovascular events**

Patients with stable angina, unstable angina, or NSTEMI should be given advice and treatments to reduce their cardiovascular risk. The importance of life-style changes, especially stopping smoking, should be emphasised. Aspirin should be given indefinitely. Antihypertensive treatment should be initiated if appropriate, and a **statin** should also be given.

In patients with stable angina, addition of an **ACE inhibitor** should be considered for patients with diabetes (and should be continued if indicated for a co-morbidity).

In patients with unstable angina or NSTEMI, clopidogrel is given, in combination with aspirin, for up to 12 months—most benefit occurs during the first 3 months. Prasugrel or ticagrelor are alternatives to clopidogrel in certain patients. An ACE inhibitor should also be given.

Low-dose rivaroxaban, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers.

### Other drugs used for Acute coronary syndromes

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### ANTITHROMBOTIC DRUGS > ANTIPLATELET DRUGS

#### Prasugrel

- **INDICATIONS AND DOSE**
  - **In combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention**
  - **BY MOUTH**
    - Adult 18–74 years (body-weight up to 60 kg): Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months
    - Adult 18–74 years (body-weight 60 kg and above): Initially 60 mg for 1 dose, then 10 mg once daily usually for up to 12 months
    - Adult 75 years and over: Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months

- **Patients undergoing coronary angiography within 48 hours of admission for unstable angina or NSTEMI**
  - **BY MOUTH**
    - Adult: Loading dose 60 mg, not to be administered until the time of percutaneous coronary intervention in order to minimise the risk of bleeding, maintenance dose of 10 mg or 5 mg daily should then be selected as appropriate based on age and weight

- **CONTRA-INDICATIONS** Active bleeding · history of stroke or transient ischaemic attack
- **CAUTIONS** Body-weight less than 60 kg · discontinue at least 7 days before elective surgery if antiplatelet effect not
desirable - elderly - patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastro-intestinal bleeding, or active peptic ulcer disease)

- INTERACTIONS ➔ Appendix 1: prasugrel
- SIDE-EFFECTS
  - Common or very common Anaemia - haemorrhage - skin reactions
  - Uncommon Angioedema
  - Rare or very rare Thrombocytopenia
- ALLERGY AND CROSS-SENSITIVITY
  Caution in patients with history of hypersensitivity reactions to thienopyridines (e.g. clopidogrel).
- PREGNANCY
  Manufacturer advises use only if potential benefit outweighs risk.
- BREAST FEEDING
  Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT
  Manufacturer advises caution in moderate impairment (increased risk of bleeding, limited information available); avoid in severe impairment (no information available).
- RENAL IMPAIRMENT
  Use with caution—increased risk of bleeding.
- NATIONAL FUNDING/ACCESS DECISIONS
  NICE decisions
  - Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (July 2014) NICE TA317
  Prasugrel 10 mg in combination with aspirin, within its marketing authorisation, for preventing atherothrombotic events in adults with acute coronary syndrome (unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI)) having primary or delayed percutaneous coronary intervention. www.nice.org.uk/TA317
  Scottish Medicines Consortium (SMC) decisions
  The Scottish Medicines Consortium has advised (August 2009) that prasugrel (Efient®), in combination with aspirin, be accepted for restricted use within NHS Scotland for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention who are eligible to receive the 10 mg dose of prasugrel.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Tablet
  - Prasugrel (Non-proprietary)
    - Prasugrel 5 mg Prasugrel 5 mg tablets | 28 tablet POM £47.56 DT = £47.56
    - Prasugrel 10 mg Prasugrel 10 mg tablets | 28 tablet POM £47.56 DT = £47.56
  - Efient (Daichi Sankyo UK Ltd)
    - Prasugrel 5 mg Efient 5 mg tablets | 28 tablet POM £47.56 DT = £47.56
    - Prasugrel 10 mg Efient 10 mg tablets | 28 tablet POM £47.56 DT = £47.56

**Ticagrelor**

19-Oct-2018

- DRUG ACTION
  Ticagrelor is a P2Y12 receptor antagonist that prevents ADP-mediated P2Y12 dependent platelet activation and aggregation.

- INDICATIONS AND DOSE
  Prevention of atherothrombotic events in patients with acute coronary syndrome [in combination with aspirin]
  - BY MOUTH
    - Adult: Initially 180 mg for 1 dose, then 90 mg twice daily usually for up to 12 months

**Prevention of atherothrombotic events in patients with a history of myocardial infarction and a high risk of an atherothrombotic event [in combination with aspirin]**

- BY MOUTH
  - Adult: 60 mg twice daily, extended treatment may be started without interruption after the initial 12-month therapy for acute coronary syndrome. Treatment may also be initiated up to 2 years from the myocardial infarction, or within 1 year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of extended treatment beyond 3 years

- CONTRA-INDICATIONS
  Active bleeding - history of intracranial haemorrhage

- CAUTIONS
  Asthma - bradycardia (unless pacemaker fitted) - chronic obstructive pulmonary disease - discontinu
 along the [cerebral artery] — extensive information available. — moderate impairment (limited information available); avoid in severe impairment (no information available).

- PREGNANCY
  Manufacturer advises avoid—toxicity in animal studies.

- BREAST FEEDING
  Manufacturer advises avoid—present in milk in animal studies.

- HEPATIC IMPAIRMENT
  Manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

- MONITORING REQUIREMENTS
  Manufacturer advises monitor renal function 1 month after initiation in patients with acute coronary syndrome.

- NATIONAL FUNDING/ACCESS DECISIONS
  NICE decisions
  - Ticagrelor for the treatment of acute coronary syndromes (October 2011) NICE TA236
  Ticagrelor, in combination with low-dose aspirin, is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes, that is, people:
    - with ST-segment elevation myocardial infarction—defined as ST elevation or new left bundle branch block on electrocardiogram—that cardiologists intend to treat with primary percutaneous coronary intervention, or
    - with non-ST-segment elevation myocardial infarction (NSTEMI), or
  - admitted to hospital with unstable angina—defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined below. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist. Characteristics to be used in defining treatment with ticagrelor for unstable angina are:
    - age 60 years or older;
    - previous myocardial infarction or previous coronary artery bypass grafting;
    - coronary artery disease with stenosis of 50% or more in at least two vessels;
    - previous ischaemic stroke;
    - previous transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation;
Cardiovascular system

Thrombolytic drugs can possibly lead to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation) - elderly - external chest compression - hypertension - risk of bleeding (including that from venepuncture or invasive procedures).

**SIDE-EFFECTS**

- **Common or very common** Anaphylactic reaction - angina pectoris - cardiac arrest - cardiogenic shock - chills - CNS haemorrhage - echocardiography - fever - haemorrhage - haemorrhagic stroke - heart failure - hypotension - ischaemia recurrent (when used in myocardial infarction) - nausea - pericarditis - pulmonary oedema - vomiting
- **Uncommon** Aphasis - mitral valve incompetence - myocardial rupture - pericardial disorders - reperfusion arrhythmia (when used in myocardial infarction) - seizure

Fibrinolytic drugs

**Overview**

The value of thrombolytic drugs for the treatment of myocardial infarction has been established. Streptokinase p. 217 and alteplase below have been shown to reduce mortality. Retepase and tenecteplase p. 217 are also licensed for acute myocardial infarction. Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest in those with ECG changes that include ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients. Alteplase should be given within 6–12 hours of symptom onset, reteplase and streptokinase within 12 hours of symptom onset, but ideally all should be given within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase and urokinase p. 138 can be used for other thromboembolic disorders such as deep–vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke.

Urokinase is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.

Fibrinolytics

**DRUG ACTION** Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

**CONTRA-INDICATIONS** Active pulmonary disease with cavitiation - acute pancreatitis - aneurysm - aortic dissection - bacterial endocarditis - bleeding diatheses - coagulation defects - coma - heavy vaginal bleeding - history of cerebrovascular disease (especially recent events or with any residual disability) - oesophageal varices - pericarditis - recent haemorrhage - recent surgery (including dental extraction) - recent symptoms of possible peptic ulceration - recent trauma - severe hypertension

**CAUTIONS** Conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation) - elderly - external chest compression - hypertension - risk of bleeding (including that from venepuncture or invasive procedures)

**ANTITHROMBOTIC DRUGS**

- Brilique
- Ticagrelor
- P2Y12 inhibitors
- Dual antiplatelet therapy
- Antiplatelet drugs
- Antiplatelet drugs - cardiovascular indications
- Antiplatelet drugs - key points
- Antiplatelet drugs - syndrome and treatment
- Antiplatelet drugs - review
- Antiplatelet drugs - risk
- Antiplatelet drugs - pharmacokinetics
- Antiplatelet drugs - contraindications
- Antiplatelet drugs - precautions
- Antiplatelet drugs - adverse effects
- Antiplatelet drugs - effectiveness
- Antiplatelet drugs - drug interactions
- Antiplatelet drugs - costs
- Antiplatelet drugs - duration
- Antiplatelet drugs - patient information

**HEPATIC IMPAIRMENT**

- Brilique
- Ticagrelor
- P2Y12 inhibitors
- Dual antiplatelet therapy
- Antiplatelet drugs
- Antiplatelet drugs - cardiovascular indications
- Antiplatelet drugs - key points
- Antiplatelet drugs - syndrome and treatment
- Antiplatelet drugs - review
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- Antiplatelet drugs - precautions
- Antiplatelet drugs - adverse effects
- Antiplatelet drugs - effectiveness
- Antiplatelet drugs - drug interactions
- Antiplatelet drugs - costs
- Antiplatelet drugs - duration
- Antiplatelet drugs - patient information

**PREGNANCY**

- Brilique
- Ticagrelor
- P2Y12 inhibitors
- Dual antiplatelet therapy
- Antiplatelet drugs
- Antiplatelet drugs - cardiovascular indications
- Antiplatelet drugs - key points
- Antiplatelet drugs - syndrome and treatment
- Antiplatelet drugs - review
- Antiplatelet drugs - risk
- Antiplatelet drugs - pharmacokinetics
- Antiplatelet drugs - contraindications
- Antiplatelet drugs - precautions
- Antiplatelet drugs - adverse effects
- Antiplatelet drugs - effectiveness
- Antiplatelet drugs - drug interactions
- Antiplatelet drugs - costs
- Antiplatelet drugs - duration
- Antiplatelet drugs - patient information

**SIDE-EFFECTS**

- **Common or very common** Anaphylactic reaction - angina pectoris - cardiac arrest - cardiogenic shock - chills - CNS haemorrhage - echocardiography - fever - haemorrhage - haemorrhagic stroke - heart failure - hypotension - ischaemia recurrent (when used in myocardial infarction) - nausea - pericarditis - pulmonary oedema - vomiting
- **Uncommon** Aphasis - mitral valve incompetence - myocardial rupture - pericardial disorders - reperfusion arrhythmia (when used in myocardial infarction) - seizure

**INDICATIONS AND DOSE**

**Acute myocardial infarction, accelerated regimen**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult (body-weight up to 65 kg): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 0.75 mg/kg, to be given over 30 minutes, then (by intravenous infusion) 0.5 mg/kg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes
  - Adult (body-weight 65 kg and above): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 30 minutes, then (by intravenous infusion) 35 mg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes

**Acute myocardial infarction**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 10 mg, to be initiated within 6–12 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 60 minutes, then (by intravenous infusion) 10 mg for 4 infusions, each 10 mg infusion dose to be given over 30 minutes, total dose of 100 mg over 3 hours; maximum 1.5 mg/kg in patients less than 65 kg

**Pulmonary embolism**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 10 mg, to be given over 1–2 minutes, followed by (by intravenous infusion) 90 mg, to be given over 2 hours, maximum 1.5 mg/kg in patients less than 65 kg
Acute ischaemic stroke (under specialist neurology physician only)

- **BY INTRAVENOUS INFUSION**
- **Adult 18-79 years**: Initially 900 micrograms/kg (max. per dose 90 mg), treatment must begin within 4.5 hours of symptom onset, to be given over 60 minutes, the initial 10% of dose is to be administered by intravenous injection and the remainder by intravenous infusion

ACTILYSE CATHFLU®
Thrombolytic treatment of occluded central venous access devices (including those used for haemodialysis)
- **BY INTRAVENOUS INJECTION**
- **Adults**: (consult product literature)

### CONTRA-INDICATIONS
- When used for acute ischaemic stroke: Convulsion accompanying stroke, history of stroke in patients with diabetes, hyperglycaemia, hypoglycaemia, severe stroke, stroke in last 3 months

### INTERACTIONS
- Appendix 1: alteplase

### SIDE-EFFECTS
- Uncommon: Haemothorax
- Rare or very rare: Agitation, confusion, delirium, depression, epilepsy, psychosis, speech disorder
- Frequency not known: Brain oedema (caused by reperfusion)

### ALLERGY AND CROSS-SENSITIVITY
Contra-indicated if history of hypersensitivity to gentamicin (residue from manufacturing process).

### MONITORING REQUIREMENTS
- When used for acute ischaemic stroke: Monitor for intracranial haemorrhage, and monitor blood pressure (antihypertensive recommended if systolic above 180 mmHg or diastolic above 105 mmHg).

### DIRECTIONS FOR ADMINISTRATION
- For intravenous infusion (Actilyse®), give intermittently or continuously in Sodium Chloride 0.9%; dissolve in water for injections to a concentration of not less than 200 micrograms/mL; not to be infused in glucose solution.

### NATIONAL FUNDING/ACCESS DECISIONS

#### NICE decisions
- **Alteplase for treating acute ischaemic stroke (September 2012) NICE TA264**
  - Alteplase (Actilyse®) is recommended for the treatment of acute ischaemic stroke in adults in accordance with its licensed indication if:
    - treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and
    - intracranial haemorrhage has been excluded by appropriate imaging techniques.
  - www.nice.org.uk/guidance/ta264

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Powder and solvent for solution for injection**
- Actilyse (Boehringer Ingelheim Ltd)
  - Alteplase 10 mg Actilyse 10mg powder and solvent for solution for injection vials | 1 vial [PDP] £172.80
  - Alteplase 20 mg Actilyse 20mg powder and solvent for solution for injection vials | 1 vial [PDP] £259.20

**Powder and solvent for solution for infusion**
- Actilyse (Boehringer Ingelheim Ltd)
  - Alteplase 50 mg Actilyse 50mg powder and solvent for solution for infusion vials | 1 vial [PDP] £432.00

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Streptokinase

- **INDICATIONS AND DOSE**
  - Acute myocardial infarction
    - **BY INTRAVENOUS INFUSION**
      - Adult: 1 500 000 units, to be initiated within 12 hours of symptom onset, dose to be given over 60 minutes
  - Acute arterial thromboembolism: Central retinal venous or arterial thrombosis
    - **BY INTRAVENOUS INFUSION**
      - Adult: 250 000 units, dose to be given over 30 minutes, then 100 000 units every 1 hour for up to 12–72 hours, duration is adjusted according to condition with monitoring of clotting parameters (consult product literature)

- **INTERACTIONS**
  - Appendix 1: streptokinase

- **SIDE-EFFECTS**
  - Common or very common: Arrhythmias, asthenia, diarrhoea, epigastric pain, headache, malaise, pain
  - Uncommon: Respiratory arrest, splenic rupture
  - Rare or very rare: Arthritis, eye inflammation, hypersensitivity, nephritis, nerve disorders, neurological effects, pulmonary oedema non-cardiogenic (caused by reperfusion), shock, vasculitis

### ALLERGY AND CROSS-SENSITIVITY
Contra-indicated if previous allergic reaction to either streptokinase or anistreplase (no longer available). Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available) can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration of either streptokinase or anistreplase.

### DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Streptase®), give continuously or intermittently; reconstitute with sodium chloride 0.9%, then dilute further with Glucose 5% or Sodium Chloride 0.9% after reconstitution.

#### MEDICINAL FORMS
No licensed medicines listed.

Tenecteplase

- **INDICATIONS AND DOSE**
  - Acute myocardial infarction
    - **BY INTRAVENOUS INJECTION**
      - Adult: 30–50 mg (max. per dose 50 mg), dose to be given over 10 seconds and initiated within 6 hours of symptom onset, dose varies according to body weight—consult product literature

- **INTERACTIONS**
  - Appendix 1: tenecteplase

- **SIDE-EFFECTS**
  - Uncommon: Drowsiness, hemiparesis, venous thrombosis

- **BREAST FEEDING**
  - Manufacturer advises avoid breast-feeding for 24 hours after dose (express and discard milk during this time).

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- Metalysse (Boehringer Ingelheim Ltd)
  - Tenecteplase 10000 unit Metalysse 10,000 unit powder and solvent for solution for injection vials | 1 vial [PDP] £602.70
NITRATES

Nitrates

Overview
Nitrates have a useful role in angina. Although they are potent coronary vasodilators, their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates.

Sublingual glyceryl trinitrate below is one of the most effective drugs for providing rapid symptomatic relief of angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The aerosol spray provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by transdermal preparations (but tolerance may develop).

Isosorbide dinitrate p. 220 is active sublingually and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for modified-release preparations. The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate p. 220. Isosorbide mononitrate itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available.

Glyceryl trinitrate or isosorbide dinitrate may be tried by intravenous injection when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of congestive heart failure.

Nitrates

- **CONTRA-INDICATIONS** Aortic stenosis · cardiac tamponade · constrictive pericarditis · hypertrophic cardiomyopathy · hypotensive conditions · hypovolaemia · marked anemia · mitral stenosis · raised intracranial pressure due to cerebral haemorrhage · raised intracranial pressure due to head trauma · toxic pulmonary oedema

- **CAUTIONS** Heart failure due to obstruction · hypothermia · hypothyroidism · hypoxaemia · malnutrition · metal-containing transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy · recent history of myocardial infarction · susceptibility to angle-closure glaucoma · tolerance · ventilation and perfusion abnormalities

**CAUTIONS, FURTHER INFORMATION**

- **Tolerance** Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 12 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for 8 to 12 hours (usually overnight) in each 24 hours; in the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses should be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used; modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

**SIDE-EFFECTS**

- **Common or very common** Arrhythmias · asthenia · cerebral ischaemia · dizziness · drowsiness · flushing · headache · hypotension · nausea · vomiting

- **Uncommon** Circulatory collapse · diarrhoea · skin reactions · syncope

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in nitrate hypersensitivity.

- **BREAST FEEDING** No information available—manufacturers advise use only if potential benefit outweighs risk.

- **HEPATIC IMPAIRMENT** In general, manufacturers advise caution in severe impairment.

- **RENAL IMPAIRMENT** Manufacturers advise use with caution in severe impairment.

- **MONITORING REQUIREMENTS** Monitor blood pressure and heart rate during intravenous infusion.

- **TREATMENT CESSATION** Avoid abrupt withdrawal.

Glyceryl trinitrate

**INDICATIONS AND DOSE**

**Prophylaxis of angina**

- **BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS**
  - Adult: 1 tablet, to be administered prior to activity likely to cause angina

**Treatment of angina**

- **BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS**
  - Adult: 1 tablet, dose may be repeated at 5 minute intervals if required; if symptoms have not resolved after 3 doses, medical attention should be sought

**Prophylaxis of angina**

- **BY SUBLINGUAL ADMINISTRATION USING AEROSOL SPRAY**
  - Adult: 400–800 micrograms, to be administered under the tongue and then close mouth prior to activity likely to cause angina

**Treatment of angina**

- **BY SUBLINGUAL ADMINISTRATION USING AEROSOL SPRAY**
  - Adult: 400–800 micrograms, to be administered under the tongue and then close mouth, dose may be repeated at 5 minute intervals if required; if symptoms have not resolved after 3 doses, medical attention should be sought

**Control of hypertension and myocardial ischaemia during and after cardiac surgery**

- **Induction of controlled hypotension during surgery**
  - **Congestive heart failure**
  - **Unstable angina**

- **BY INTRAVENOUS INFUSION**
  - Adult: 10–200 micrograms/minute (max. per dose 400 micrograms/minute), adjusted according to response, consult product literature for recommended starting doses specific to indication

**Anal fissure**

- **BY RECTUM USING OINTMENT**
  - Adult: Apply 2.5 centimetres every 12 hours until pain stops. Max. duration of use 6 weeks, apply to anal canal, 2.5 cm of ointment contains 1.5 mg of glyceryl trinitrate

**DEPONIT ®**

**Prophylaxis of angina**

- **BY TRANSDERMAL APPLICATION**
  - Adult: One ‘5’ or one ‘10’ patch to be applied to lateral chest wall, upper arm, thigh, abdomen, or shoulder; increase to two ‘10’ patches every 24 hours if necessary, to be replaced every 24 hours, siting replacement patch on different area
MINITRAN ®

**Prophylaxis of angina**
- **By transdermal application**
  - Adult: One ‘5’ patch to be applied to chest or upper arm; replace every 24 hours, sitting replacement patch on different area, dose to be adjusted according to response.

**Maintenance of venous patency (‘5’ patch only)**
- **By transdermal application**
  - Adult: (consult product literature)

**NITRO-DUR ®**

**Prophylaxis of angina**
- **By transdermal application**
  - Adult: One ‘0.2mg/h’ patch to be applied to chest or outer upper arm and replaced every 24 hours, sitting replacement patch on different area, dose adjusted according to response; maximum 15 mg per day

**PERCUTOL ®**

**Prophylaxis of angina**
- **To the skin**
  - Adult: Usual dose 1–2 inches every 3–4 hours as required, to be measured on to Applipule ® and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, approx. 800 micrograms/hour absorbed from 1 inch of ointment.

**Prophylaxis of angina (to determine dose)**
- **To the skin**
  - Adult: ½ inch to be administered on first day then increased by ½ inch/day until headache occurs, then reduced by ½ inch, to be measured on to Applipule ® and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, approx. 800 micrograms/hour absorbed from 1 inch of ointment.

**TRANSIDERM-NITRO ®**

**Prophylaxis of angina**
- **By transdermal application**
  - Adult: One ‘5’ or one ‘10’ patch to be applied to lateral chest wall and replaced every 24 hours, sitting replacement patch on different area, max. two ‘10’ patches daily

**Prophylaxis of phlebitis and extravasation (‘5’ patch only)**
- **By transdermal application**
  - Adult: (consult product literature)

**SIDE-EFFECTS**
- Interactions → Appendix 1: nitrates
- **Uncommon**
  - With parenteral use Cardiac disorder · cyanosis
  - With rectal use Anorectal disorder · anorectal haemorrhage · gastrointestinal discomfort
  - With sublingual use Cyanosis
  - Rare or very rare
  - With parenteral use Methaemoglobinemia · respiratory disorder · restlessness
  - With sublingual use Methaemoglobinemia · respiratory disorder · restlessness
  - With topical use Dyspepsia
  - Frequency not known
  - With parenteral use Hyperhidrosis
  - With rectal use Vertigo
  - With sublingual use Tongue blistering
  - With transdermal use Palpitations

**PREGNANCY** Not known to be harmful.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous infusion (Nitrocine ®, Nitrenal ®), give continuously in Glucose 5% or Sodium Chloride 0.9%. For Nitrocine ®, suggested infusion concentration 100 micrograms/ml, incompatible with polyvinyl chloride infusion containers such as Vialflex ® or Steriflex ®; use glass or polyethylene containers or give via a syringe pump.
- With intravenous use Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used. Glycerol trinitrate 1 mg/ml to be diluted before use or given undiluted with syringe pump. Glycerol trinitrate 5 mg/ml to be diluted before use.

**PRESCRIBING AND DISPENSING INFORMATION**
- With sublingual use Glycerol trinitrate tablets are available in strengths of 300-· 500- and 600-micrograms—manufacturer advises tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, and containing no cotton wool wadding; they should be discarded after 8 weeks in use.

**PATIENT AND CARER ADVICE** Rectal ointment should be discarded 8 weeks after first opening.

**PERCUTOL ®** Patients or carers should be given advice on how to administer glyceryl trinitrate ointment.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (January 2008) that glyceryl trinitrate 0.4% ointment (Rectigosic ®) is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Solution for infusion**

**EXCIPIENTS:** May contain Ethanol, propylene glycol
- Glycerol trinitrate (Non-proprietary) 0
  - Glycerol trinitrate 1 mg per 1 ml Glycerol trinitrate 50mg/50ml solution for infusion vials | 1 vial (Pipet) £15.90
  - Glycerol trinitrate 5 mg per 1 ml Glycerol trinitrate 50mg/10ml solution for infusion ampoules | 5 ampoule (Pipet) £64.90 (Hospital only)
  - Glycerol trinitrate 25mg/5ml solution for infusion ampoules | 5 ampoule (Pipet) £32.45 (Hospital only)
  - Nitrocine (Aspire Pharma Ltd) Glycerol trinitrate 1 mg per 1 ml Nitrocine 10mg/10ml solution for infusion ampoules | 10 ampoule (Pipet) £58.75 (Hospital only)
  - Nitronal (intrapharm Laboratories Ltd) Glycerol trinitrate 1 mg per 1 ml Nitronal 5mg/5ml solution for infusion ampoules | 10 ampoule (Pipet) £18.04
  - Nitronal 50mg/50ml solution for infusion vials | 1 vial (Pipet) £14.76

**Sublingual tablet**

**EXCIPIENTS:** May contain Propyleneglycol, woolfat and related substances (including lanolin)

**Transdermal patch**

**EXCIPIENTS:** May contain Propylene glycol, woolfat and related substances (including lanolin)
**Isosorbide dinitrate**

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of angina**

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: 30–120 mg daily in divided doses
  - BY INTRAVENOUS INFUSION
    - Adult: 2–10 mg/hour, increased if necessary up to 20 mg/hour
  - BY SUBLINGUAL ADMINISTRATION USING AEROSOL SPRAY
    - Adult: 1–3 sprays, to be administered under tongue whilst holding breath, allow a 30 second interval between each dose

**Left ventricular failure**

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: 40–160 mg daily in divided doses, increased if necessary up to 240 mg daily in divided doses
- BY INTRAVENOUS INFUSION
  - Adult: Initially 2–10 mg/hour, increased if necessary up to 20 mg/hour

**Prophylaxis of angina**

- BY MOUTH USING MODIFIED-RELEASE MEDICINES
  - Adult: 40 mg daily in 1–2 divided doses, increased if necessary to 60–80 mg daily in 2–3 divided doses

**INTERACTIONS**

- Appendix 1: nitrates

**SIDE-EFFECTS**

- Common or very common
  - With oral use: Peripheral oedema
  - Rare or very rare
  - With oral use: Angioedema, angle closure glaucoma, hypoventilation, hypoxia, pituitary haemorrhage, Stevens-Johnson syndrome

**PREGNANCY**

- May cross placenta—manufacturers advise avoidance unless potential benefit outweighs risk.

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion (Isoket 0.05%, Isoket 0.1%), give continuously in Glucose 5% or Sodium chloride 0.9%. Adsorbed to some extent by polyvinyl chloride infusion containers; preferably use glass or polyethylene containers or give via a syringe pump; Isoket 0.05% can alternatively be administered undiluted using a syringe pump with a glass or rigid plastic syringe. Glass or polyethylene infusion apparatus is preferable; loss of potency if PVC used.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

- CAUTIONARY AND ADVISORY LABELS 25
  - Isoket Retard (Aspire Pharma Ltd)
    - Isosorbide dinitrate 20 mg: Isoket Retard 20 tablets | 56 tablet
    - £2.58 DT = £2.58
  - Isosorbide dinitrate 40 mg: Isoket Retard 40 tablets | 56 tablet
    - £6.36 DT = £6.36

**Tablet**

- Isosorbide dinitrate (Non-proprietary)
  - Isosorbide dinitrate 10 mg: Isosorbide dinitrate 10mg tablets | 56 tablet
    - £3.79 DT = £3.79
  - Isosorbide dinitrate 20 mg: Isosorbide dinitrate 20mg tablets | 56 tablet
    - £7.09 DT = £7.09

**Solution for injection**

- Isosorbide dinitrate (Non-proprietary)
  - Isosorbide dinitrate 1 mg per 1 ml: Isosorbide dinitrate 10mg/10ml concentrate for solution for injection ampoules | 10 ampoule
    - £27.00
  - Isoket (Aspire Pharma Ltd)
    - Isosorbide dinitrate 1 mg per 1 ml: Isoket 0.1% solution for injection 1ml ampoules | 10 ampoule
    - £26.93 (Hospital only)

**Solution for infusion**

- Isosorbide dinitrate (Non-proprietary)
  - Isosorbide dinitrate 500 microgram per 1 ml: Isosorbide dinitrate 25mg/50ml solution for infusion vials | 10 vial
    - £61.20
  - Isosorbide dinitrate 1 mg per 1 ml: Isosorbide dinitrate 50mg/50ml concentrate for solution for infusion vials | 10 vial
    - £79.10

**Isosorbide mononitrate**

**INDICATIONS AND DOSE**

**Prophylaxis of angina | Adjunct in congestive heart failure**

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: Initially 40 mg twice daily, then increased if necessary up to 120 mg daily in divided doses

**Prophylaxis of angina (for patients who have not previously had a nitrate) | Adjunct in congestive heart failure (for patients who have not previously had a nitrate)**

- BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  - Adult: Initially 10 mg twice daily, increased if necessary up to 120 mg daily in divided doses

**CHEMODYR ® 60XL**

**Prophylaxis of angina**

- BY MOUTH
  - Adult: Initially 0.5 tablet daily for 2–4 days, to minimise possibility of headache, then 1 tablet daily, increased if necessary to 2 tablets daily, dose to be taken in the morning

**ELANTAN ® LA**

**Prophylaxis of angina**

- BY MOUTH
  - Adult: 25–50 mg once daily, then increased if necessary to 50–100 mg once daily, dose to be taken in the morning, the lowest effective dose should be used

**IMDR ®**

**Prophylaxis of angina**

- BY MOUTH
  - Adult: Initially 0.5 tablet once daily, to minimise the occurrence of headache, then 1 tablet once daily, then increased if necessary to 2 tablets once daily, dose to be taken in the morning
**ISIB® 60XL**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

**ISMO RETARD®**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** 1 tablet once daily, dose to be taken in the morning

**ISODUR®**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** 25–50 mg once daily, then increased if necessary to 50–100 mg once daily, dose to be taken in the morning

**ISOTARD®**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

**MODISAL® XL**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise the occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, to be taken in the morning

**MONOMAX® XL**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, dose to be taken in the morning

**MONOMIL® XL**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise occurrence of headache, then 1 tablet once daily, increased if necessary to 2 tablets once daily, to be taken in the morning

**MONOSORB® XL 60**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 0.5 tablet daily for 2–4 days, to minimise possibility of headache, then 1 tablet daily, increased if necessary to 2 tablets once daily, to be taken in the morning

**ZEMON®**

**Prophylaxis of angina**

- **BY MOUTH**
- **Adult:** Initially 30 mg once daily for 2–4 days, to minimise the occurrence of headache, then 40–60 mg once daily, increased if necessary to 80–120 mg once daily, dose to be taken in the morning

**INTERACTIONS** → Appendix 1: nitrates

**SIDE-EFFECTS**

- Rare or very rare: Myalgia

**PREGNANCY** Manufacturers advise avoid unless potential benefit outweighs risk.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

#### Modified-release tablet

**CAUTIONARY AND ADVISORY LABELS** 25

- **Carmil XL** (Milpharm Ltd)
  - Isosorbide mononitrate 60 mg Carmil XL 60 mg tablets |
  - 28 tablet [P] £5.75 DT + £10.50
- **Chemydur 60XL** (Adavanz Pharma)
  - Isosorbide mononitrate 60 mg Chemydur 60XL 60 mg tablets |
  - 28 tablet [P] £3.49 DT + £10.50
- **Ismo Retard** (Intrapharm Laboratories Ltd)
  - Isosorbide mononitrate 60 mg Ismo Retard 60 mg modified-release tablets |
  - 28 tablet [P] £10.50 DT + £10.50
- **Ismo XL** (Alliance Pharmaceuticals Ltd)
  - Isosorbide mononitrate 60 mg Ismo XL 60 mg tablets |
  - 28 tablet [P] £8.15 DT + £10.50
- **Isotard XL** (Triumph Laboratories Ltd)
  - Isosorbide mononitrate 60 mg Isotard XL 60 mg tablets |
  - 28 tablet [P] £10.71
- **Isotard XL (Ishika Kirin Ltd)**
  - Isosorbide mononitrate 25 mg Isotard 25XL capsules |
  - 28 tablet [P] £6.75 DT + £6.75
- **Monomax XL** (Chiesi Ltd)
  - Isosorbide mononitrate 60 mg Monomax XL 60 mg tablets |
  - 28 tablet [P] £5.25 DT + £10.50
- **Monomil XL** (Teva UK Ltd)
  - Isosorbide mononitrate 60 mg Monomil XL 60 mg tablets |
  - 28 tablet [P] £15.53 DT + £10.50
- **Monosorb XL** (Dexcel-Pharma Ltd)
  - Isosorbide mononitrate 60 mg Monosorb XL 60 tablets |
  - 28 tablet [P] £15.53 DT + £10.50
- **Relosorb XL (Relonchem Ltd)**
  - Isosorbide mononitrate 60 mg Relosorb XL 60 mg tablets |
  - 28 tablet [P] £22.45 DT + £10.50
- **Tardisc XL** (Discovery Pharmaceuticals)
  - Isosorbide mononitrate 60 mg Tardisc XL 60 tablets |
  - 28 tablet [P] £3.49 DT + £10.50
- **Xismox XL** (Genus Pharmaceuticals Ltd)
  - Isosorbide mononitrate 60 mg Xismox XL 60 tablets |
  - 28 tablet [P] £5.51 DT + £10.50
- **Ximol XL Retard (Intrapharm Laboratories Ltd)**
  - Isosorbide mononitrate 40 mg Ximol 40 tablets |
  - 28 tablet [P] £14.25 DT + £18.75

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Isosorbide mononitrate (Non-proprietary)**
  - Isosorbide mononitrate 10 mg Isosorbide mononitrate 10 mg tablets |
  - 56 tablet [P] £0.40 DT + £1.07
  - Isosorbide mononitrate 20 mg Isosorbide mononitrate 20 mg tablets |
  - 56 tablet [P] £0.41 DT + £1.12
  - Isosorbide mononitrate 40 mg Isosorbide mononitrate 40 mg tablets |
  - 56 tablet [P] £0.34 DT + £1.30
  - Isosorbide mononitrate 60 mg Isosorbide mononitrate 60 mg tablets |
  - 56 tablet [P] £0.49 DT + £1.80
  - Isosorbide mononitrate 80 mg Isosorbide mononitrate 80 mg tablets |
  - 56 tablet [P] £0.75 DT + £2.40

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS** 25

- **Elantan LA** (Aspire Pharma Ltd)
  - Isosorbide mononitrate 25 mg Elantan LA25 capsules |
  - 28 capsule [P] £3.40 DT + £3.40
  - Isosorbide mononitrate 50 mg Elantan LA50 capsules |
  - 28 capsule [P] £3.69 DT + £3.69
- **Isodur XL** (Galen Ltd)
  - Isosorbide mononitrate 25 mg Isodur 25XL capsules |
  - 28 capsule [P] £4.63 DT + £3.40

www.getintopharma.com
Dobutamine

**DRUG ACTION** Dobutamine is a cardiac stimulant which acts on beta receptors in cardiac muscle, and increases contractility.

**INDICATIONS AND DOSE**

**Inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, cardiogenic shock, and during positive end expiratory pressure ventilation**

- **Adult:** Usual dose 2.5–10 micrograms/kg/minute, adjusted according to response, alternatively 0.5–40 micrograms/kg/minute

**Cardiac stress testing**

- **Adult:** (consult product literature)

**CONTRA-INDICATIONS** Phaeochromocytoma

**CAUTIONS** Acute heart failure, acute myocardial infarction - arrhythmias - correct hypercapnia before starting and during treatment - correct hypovolaemia before starting and during treatment - correct hypoxia before starting and during treatment - correct metabolic acidosis before starting and during treatment - diabetes mellitus - elderly - extravasation may cause tissue necrosis - extreme caution or avoid in marked obstruction of cardiac ejection (such as idiopathic hypertrophic subaortic stenosis) - hyperthyroidism - ischaemic heart disease - oclusive vascular disease - severe hypotension - susceptibility to angle-closure glaucoma - tachycardia - tolerance may develop with continuous infusions longer than 72 hours

**INTERACTIONS** → Appendix 1: sympathomimetics, inotropic

**SIDE-EFFECTS**

- **Common or very common** Arrhythmias - bronchospasm - chest pain - dyspnoea - eosinophilia - fever - headache - inflammation localised - ischaemic heart disease - nausea - palpitations - platelet aggregation inhibition (on prolonged administration) - skin reactions - urinary urgency - vasoconstriction

- **Uncommon** Myocardial infarction

- **Rare or very rare** Atrioventricular block - cardiac arrest - coronary vasospasm - hypotension exacerbated - hypokalaemia - hypotension exacerbated

- **Frequency not known** Anxiety - cardiomyopathy - feeling hot - myoclonus - paraesthesia - tremor

**PREGNANCY** No evidence of harm in animal studies — manufacturers advise use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturers advise avoid — no information available.

**MONITORING REQUIREMENTS** Monitor serum-potassium concentration.

**DIRECTIONS FOR ADMINISTRATION** Dobutamine injection should be diluted before use or given undiluted with syringe pump. Dobutamine concentrate for intravenous infusion should be diluted before use.

For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of 0.5–1 mg/mL and give via an infusion pump; give higher concentration (max. 5 mg/mL) through central venous catheter; incompatible with bicarbonate and other strong alkaline solutions.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for infusion**

- **EXCIPIENTS:** May contain Sulfites

  - Dobutamine (Non-proprietary)
  - Dobutamine (as Dobutamine hydrochloride) 5 mg per 1 ml Dobutamine 250mg/50ml solution for infusion vials | 1 vial (£50) £7.50
  - Dobutamine (as Dobutamine hydrochloride) 12.5 mg per 1 ml Dobutamine 250mg/20ml concentrate for solution for infusion ampoules | 5 ampoule (£50) £12.00-£29.25 | 10 ampoule (£50) £52.50

### 8.1 Cardiac arrest

**Cardiopulmonary resuscitation**

**Overview**

The algorithm for cardiopulmonary resuscitation (Life support algorithm (image) p. 1671) reflects the most recent recommendations of the Resuscitation Council (UK). These guidelines are available at [www.resus.org.uk](http://www.resus.org.uk).

Cardiac arrest can be associated with ventricular fibrillation, pulseless ventricular tachycardia, asystole, and pulseless electrical activity (electromechanical dissociation). Adrenaline/epinephrine 1 in 1000 (100 micrograms/mL) below is recommended by intravenous injection repeated every 3–5 minutes if necessary. Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL. Sodium Chloride 0.9% injection to aid entry into the central circulation. Intravenous injection of amiodarone hydrochloride p. 105 should be considered after adrenaline/epinephrine to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. An additional dose of amiodarone hydrochloride can be given if necessary, followed by an intravenous infusion of amiodarone hydrochloride.

Lidocaine hydrochloride p. 103, is an alternative if amiodarone hydrochloride is not available. Atropine sulfate p. 1166 is no longer recommended in the treatment of asystole or pulseless electrical activity.

During cardiopulmonary arrest if intravenous access cannot be obtained, the intraosseous route can be used instead. Drug administration via the endotracheal route is no longer recommended.

For the management of acute anaphylaxis, see allergic emergencies under Antihistamines, allergen immunotherapy and allergic emergencies p. 277.

**SYMPATHOMIMETICS**

**Vasocostrictor**

**Adrenaline/epinephrine**

**DRUG ACTION** Acts on both alpha and beta receptors and increases both heart rate and contractility (beta₂ effects); it can cause peripheral vasodilation (a beta₁ effect) or vasoconstriction (an alpha effect).

**INDICATIONS AND DOSE**

**Cardiopulmonary resuscitation**

- **BY INTRAVENOUS INJECTION**
  - **Adult:** 1 mg every 3–5 minutes as required, a 1 in 10 000 (100 micrograms/mL) solution is recommended
Acute hypotension
► BY CONTINUOUS INTRAVENOUS INFUSION
  ► Neonate: Initially 100 nanograms/kg/minute, adjusted according to response, higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension.
  ► Child: Initially 100 nanograms/kg/minute, adjusted according to response, higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension.

Emergency treatment of acute anaphylaxis (under expert supervision) Angioedema (if laryngeal oedema is present) (under expert supervision)
► BY INTRAMUSCULAR INJECTION
  ► Child 1 month–5 years: 150 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, to be injected preferriably into the anterolateral aspect of the middle third of the thigh
  ► Child 6–11 years: 300 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, to be injected preferriably into the anterolateral aspect of the middle third of the thigh
  ► Child 12–17 years: 500 micrograms, to be injected preferriably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, 300 micrograms (0.3 mL) to be administered if child small or prepubertal
  ► Adult: 500 micrograms, to be injected preferriably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, 300 micrograms/kg, to be administered if child large or adult

Acute anaphylaxis when there is doubt as to the adequacy of the circulation (specialist use only) Angioedema (if laryngeal oedema is present) (specialist use only)
► BY SLOW INTRAVENOUS INFUSION
  ► Adult: 50 micrograms, using 0.5 mL of the dilute 1 in 10 000 adrenaline injection, dose to be repeated according to response, if multiple doses required, adrenaline should be given as a slow intravenous infusion stopping when a response has been obtained

Control of bradycardia in patients with arrhythmias after myocardial infarction, if there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine
► BY INTRAVENOUS INFUSION
  ► Adult: 2–10 micrograms/minute, adjusted according to response

EMERADE® 150 MICROGRAMS
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
  ► Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

EMERADE® 300 MICROGRAMS
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required
  ► Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

EMERADE® 500 MICROGRAMS
Acute anaphylaxis (for self-administration for patients at risk of severe anaphylaxis)
► BY INTRAMUSCULAR INJECTION
  ► Child 12–17 years: 500 micrograms, then 500 micrograms after 5–15 minutes as required
  ► Adult: 500 micrograms, then 500 micrograms after 5–15 minutes as required

EPIPEN® AUTO-INJECTOR 0.3MG
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required
  ► Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

EPIPEN® JR AUTO-INJECTOR 0.15MG
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
  ► Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

JEXT® 150 MICROGRAMS
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
  ► Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

JEXT® 300 MICROGRAMS
Acute anaphylaxis (for self-administration)
► BY INTRAMUSCULAR INJECTION
  ► Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required
  ► Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

атель
> With intramuscular use for acute anaphylaxis in children Auto-injectors delivering 150-microgram dose of adrenaline may not be licensed for use in children with body-weight under 15 kg.
> With intravenous use for acute hypotension in children Adrenaline 1 in 1000 (1 mg/mL) solution is not licensed for intravenous administration.

IMPORTANT SAFETY INFORMATION
SAFE PRACTICE
Intravenous route should be used with extreme care by specialists only.

MHRA/CHM ADVICE: ADRENALINE AUTO-INJECTORS: UPDATED ADVICE AFTER EUROPEAN REVIEW (AUGUST 2017)
Following a European review of all adrenaline auto-injectors approved in the EU, the MHRA recommend that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times. This is particularly important for patients with allergic asthma, who are at increased risk of a severe anaphylactic reaction. Patients with allergies and their carers should be trained to use the particular auto-injector they have been prescribed and encouraged to practise using a trainer device. Patients are advised to check the expiry date of the adrenaline auto-injectors and obtain replacements before they expire.
Cardiovascular system

DIRECTIONS FOR ADMINISTRATION

1. With intramuscular use in adults
   - Administer through a central line if possible.
   - The recommended dose is 1 mg/kg body weight or a maximum dose of 1 mg/kg body weight if the individual is over 60 kg or 0.5 mg/kg body weight if the individual is under 60 kg.
   - Do not exceed a maximum dose of 1 mg/kg body weight.

2. With intravenous use in adults
   - Administer through a central line if possible.
   - The recommended dose is 1 mg/kg body weight or a maximum dose of 1 mg/kg body weight if the individual is over 60 kg or 0.5 mg/kg body weight if the individual is under 60 kg.
   - Do not exceed a maximum dose of 1 mg/kg body weight.

MONITORING REQUIREMENTS

1. Monitor blood pressure and ECG continuously.
2. Monitor the patient for signs of shock or hypotension.
3. Monitor the patient for signs of cardiac arrest or respiratory arrest.
4. Monitor the patient for signs of arrhythmias.
5. Monitor the patient for signs of peripheral ischaemia.

INTERACTIONS

1. Adrenaline is a potent vasoconstrictor and can cause hypertension, tachycardia, and myocardial ischaemia.
2. Adrenaline can cause vasoconstriction in the peripheral circulation, leading to peripheral ischaemia.
3. Adrenaline can cause vasoconstriction in the cerebral circulation, leading to cerebral ischaemia.
4. Adrenaline can cause vasoconstriction in the coronary circulation, leading to myocardial ischaemia.

CAUTIONS

1. Arteriosclerosis (in adults) - arrhythmias, cerebrovascular disease, cor pulmonale, diabetes mellitus, elderly, hypercalcaemia, hyperreflexia, hypertension, hyperthyroidism, hypokalaemia, ischaemic heart disease, obstructive cardiomyopathy, oclusive vascular disease, organic brain damage, phaeochromocytoma, prostate disorders, psychoneurosis, severe angina, susceptibility to angle-closure glaucoma.

CAUTIONS, FURTHER INFORMATION

1. Cautions listed are only for non-life-threatening situations.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

1. Rare or very rare Cardiomyopathy
2. Frequency not known Angina pectoris, angle closure glaucoma, anxiety, appetite decreased, arrhythmias, asthenia, CNS haemorrhage, confusion, dizziness, dry mouth, dyspnoea, headache, hepatic necrosis, hyperglycaemia, hyperhidrosis, hypersalivation, hypertension (increased risk of cerebral haemorrhage), hypokalaemia, injection site necrosis, insomnia, intestinal necrosis, metabolic acidosis, mydriasis, myocardial infarction, nausea, pallor, palpitations, peripheral coldness, psychosis, pulmonary oedema (on excessive dosage or extreme sensitivity), renal necrosis, soft tissue necrosis, tremor, urinary disorders, vomiting.

SPECIFIC SIDE-EFFECTS

1. With intramuscular use
   - Muscle necrosis, necrotising fasciitis, peripheral ischaemia.
2. With intravenous use
   - Hemiplegia, muscle rigidity.

PREGNANCY

1. With intramuscular use or intravenous use
   - May reduce placental perfusion and cause tachycardia, cardiac irregularities, and extrasystoles in fetus. Can delay second stage of labour. Manufacturers advise use only if benefit outweighs risk.

BREAST FEEDING

1. Present in milk but unlikely to be harmful as poor oral bioavailability.

RENAL IMPAIRMENT

1. Manufacturers advise use with caution in severe impairment.

MONITORING REQUIREMENTS

1. Monitor blood pressure and ECG.

DIRECTIONS FOR ADMINISTRATION

1. Acute hypotension
   - With intravenous use in adults
     - Adju administration through a central line if possible.
     - The recommended dose is 1 mg/kg body weight or a maximum dose of 1 mg/kg body weight if the individual is over 60 kg or 0.5 mg/kg body weight if the individual is under 60 kg.
     - Do not exceed a maximum dose of 1 mg/kg body weight.

2. With intravenous use in adults
   - Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL.
   - Sodium Chloride 0.9% injection to aid entry into the central circulation.

PRESCRIBING AND DISPENSING INFORMATION

1. With intramuscular use
   - It is important, in acute anaphylaxis where intramuscular injection might still succeed, time should not be wasted seeking intravenous access. Great vigilance is needed to ensure that the correct strength of adrenaline injection is used; anaphylactic shock kits need to make a very clear distinction between the 1 in 10 000 strength and the 1 in 1000 strength. Patients with severe allergy should be instructed in the self-administration of adrenaline by intramuscular injection. Packs for self-administration need to be clearly labelled with instructions on how to administer adrenaline (intramuscularly, preferably at the midpoint of the outer thigh, through light clothing if necessary) so that in the case of rapid collapse someone else is able to give it. It is important to ensure individuals at risk and their carers understand that:
     - two injection devices should be carried at all times to treat symptoms until medical assistance is available; if, after the first injection, the individual does not start to feel better, the second injection should be given 5 to 15 minutes after the first;
     - an ambulance should be called after every administration, even if symptoms improve;
     - the individual should lie down with their legs raised (unless they have breathing difficulties, in which case they should sit up) and should not be left alone.
   - Adrenaline for administration by intramuscular injection is available in ‘auto-injectors’ (e.g. Emerade®, EpiPen®, or Jext®), pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available); injection technique is device specific.
   - To ensure patients receive the auto-injector device that they have been trained to use, prescribers should specify the brand to be dispensed.

PATIENT AND CARER ADVICE

1. With intramuscular use
   - Individuals at considerable risk of anaphylaxis need to carry (or have available) adrenaline at all times and the patient, or their carers, need to be instructed in advance when and how to inject it.
   - With intramuscular use
     - The MHRA has produced an advice sheet on the use of adrenaline auto-injectors, which should be provided to patients and their carers.

JEXT® 300 MICROGRAMS

1. 1.1 mL of the solution remains in the auto-injector device after use.

JEXT® 150 MICROGRAMS

1. 0.5 mL of the solution remains in the auto-injector device after use.

EMERADE® 150 MICROGRAMS

1. 0.35 mL of the solution remains in the auto-injector device after use.

EPIPEN® JR AUTO-INJECTOR 0.15MG

1. 1.7 mL of the solution remains in the auto-injector device after use.

EMERADE® 500 MICROGRAMS

1. No solution remains in the auto-injector device after use.

EMERADE® 300 MICROGRAMS

1. 0.2 mL of the solution remains in the auto-injector device after use.

EXCEPTIONS TO LEGAL CATEGORY

1. With intramuscular use
   - POM restriction does not apply to the intramuscular administration of up to 1 mg of adrenaline injection 1 in 1000 (1 mg/mL) for the emergency treatment of anaphylaxis.

MEDICINAL FORMS

1. There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection.

Solution for injection

EXCIPIENTS: May contain Sulphites

Adrenaline/epinephrine (Non-proprietary)

1. Adrenaline 100 microgram per 1 ml
2. Adrenaline (base) 100 micrograms/ml (1 in 10,000) dilute solution for injection

ampoules | 10 ampoule | £67.34
Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection pre-filled syringes | 1 pre-filled disposable injection (PN) £6.87 | 1 pre-filled disposable injection (PN) £18.00 (Hospital only) | 10 pre-filled disposable injection (PN) £180.00 (Hospital only)
Adrenaline (as Adrenaline acid tartrate) 100 microgram per 1 ml Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (PN) £8.48
Adrenaline (base) 500micrograms/5ml (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (PN) £81.33
Adrenaline 1 mg per 1 ml Adrenaline (base) 10mg/10ml (1 in 1,000) solution for injection ampoules | 10 ampoule (PN) £96.38
Adrenaline (base) for anaesthesia 1mg/1ml (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (PN) £11.88 DT + £11.71
Adrenaline (base) 1mg/1ml (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (PN) £11.88 DT + £11.71
Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 ml Adrenaline (base) 5mg/5ml (1 in 1,000) solution for injection ampoules | 10 ampoule (PN) £93.59
Adrenaline (base) 500micrograms/0.5ml (1 in 1,000) solution for injection ampoules | 10 ampoule (PN) £76.73 DT + £76.73
Adrenaline (base) 1mg/1ml (1 in 1,000) solution for injection ampoules | 10 ampoule (PN) £5.95 DT + £6.01
Emerade (Bausch & Lomb UK Ltd)
Adrenaline 1 mg per 1 ml Emerade 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £22.99 DT + £26.45
Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 ml Emerade 150micrograms/0.15ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £23.99 DT + £23.99
Emerade 500micrograms/0.5ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £26.99 DT + £26.99
EpiPen (Meda Pharmaceuticals Ltd)
Adrenaline 500 microgram per 1 ml EpiPen Jr.
150micrograms/0.3ml (1 in 2,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £26.45 DT + £26.45 | 2 pre-filled disposable injection (PN) £52.90 DT + £52.90
Adrenaline 1 mg per 1 ml EpiPen 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £26.45 DT + £26.45 | 2 pre-filled disposable injection (PN) £52.90 DT + £52.90
Jext (ALK-Abello Ltd)
Adrenaline 1 mg per 1 ml Jext 300micrograms/0.3ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £23.99 DT + £26.45
Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 ml Jext 150micrograms/0.15ml (1 in 1,000) solution for injection auto-injectors | 1 pre-filled disposable injection (PN) £23.99 DT + £23.99

9 Oedema

Diuretics

Overview
Thiazides are used to relieve oedema due to chronic heart failure and, in lower doses, to reduce blood pressure.

Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure.

Combination diuretic therapy may be effective in patients with edema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

Thiazides and related diuretics
Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuretic does not interfere with sleep.

In the management of hypertension a low dose of a thiazide produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. Chlortalidone p. 230 and indapamide p. 167 are the preferred diuretics in the management of hypertension. Thiazides also have a role in chronic heart failure.

Bendroflumethiazide p. 166 can be used for mild or moderate heart failure; it is licensed for the treatment of hypertension but is no longer considered the first-line diuretic for this indication, although patients with stable and controlled blood pressure currently taking bendroflumethiazide can continue treatment.

Chlortalidone, a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike the altered pattern of micturition caused by other diuretics. Chlortalidone can also be used under close supervision for the treatment of ascites due to cirrhosis in stable patients.

Xipamide p. 231 and indapamide are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

Metolazone p. 231 is particularly effective when combined with a loop diuretic (even in renal failure); profound diuresis can occur and the patient should therefore be monitored carefully.

The thiazide diuretics benzthiazide, clopamide, hydrochlorothiazide, and hydroflumethiazide do not offer any significant advantage over other thiazides and related diuretics.

Loop diuretics
Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces the need for load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide or metolazone).

If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure.

Loop diuretics can exacerbate diabetes (but hyperglycaemia is less likely than with thiazides) and gout. If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially.

Furosemide p. 227 and bumetanide p. 227 are similar in activity; both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration furosemide has a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.

Torasemide p. 228 has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

Potassium-sparing diuretics and aldosterone antagonists
Amiloride hydrochloride p. 229 and triamterene p. 220 on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements. See compound preparations with thiazides or loop diuretics.
Potassium supplements must not be given with potassium-sparing diuretics. Administration of a potassium sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

**Aldosterone antagonists**
Spironolactone p. 193 potentiates thiazide or loop diuretics by antagonising aldosterone; it is a potassium-sparing diuretic. Spironolactone is of value in the treatment of oedema and ascites caused by cirrhosis of the liver; furosemide can be used as an adjunct. Low doses of spironolactone are beneficial in moderate to severe heart failure and when used in resistant hypertension [unlicensed indication].

Spironolactone is also used in primary hyperaldosteronism (Conn’s syndrome). It is given before surgery or if surgery is not appropriate, in the lowest effective dose for maintenance.

Eplerenone p. 193 is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction; it is also licensed as an adjunct in chronic mild heart failure with left ventricular systolic dysfunction. Potassium supplements must not be given with aldosterone antagonists

**Potassium-sparing diuretics with other diuretics**
Although it is preferable to prescribe thiazides and potassium-sparing diuretics separately, the use of fixed combinations may be justified if compliance is a problem.

Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops.

**Other diuretics**
Mannitol p. 229 is an osmotic diuretic that can be used to treat cerebral oedema and raised intra-ocular pressure.

Mercurial diuretics are effective but are now almost never used because of their nephrotoxicity.

The carbonic anhydrase inhibitor acetazolamide p. 1181 is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness [unlicensed indication] but is not a substitute for acclimatisation.

Eye drops of dorzolamide p. 1182 and brinzolamide p. 1181 inhibit the formation of aqueous humour and are used in glaucoma.

**Diuretics with potassium**
Many patients on diuretics do not need potassium supplements. For many of those who do, the amount of potassium in combined preparations may not be enough, and for this reason their use is to be discouraged.

Diuretics with potassium and potassium-sparing diuretics should not usually be given together. Diuretics and potassium supplements should be prescribed separately for children.

**Advanced Pharmacy Services**
Patients taking diuretics may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

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**SIDE-EFFECTS**
- **Common or very common** Dizziness · electrolyte imbalance · fatigue · headache · metabolic alkalosis · muscle spasms · nausea
- **Uncommon** Diarrhoea
- **Rare or very rare** Bone marrow depression · photosensitivity reaction
- **Frequency not known** Deafness (more common in renal impairment) · leucopenia · paraesthesia · rash · severe cutaneous adverse reactions (SCARs) · thrombocytopenia · tinnitus (more common with rapid intravenous administration, and in renal impairment) · vomiting
- **HEPATIC IMPAIRMENT** Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma—potassium-sparing diuretics can be used to prevent this. Diuretics can increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias.

**RENAL IMPAIRMENT** High doses or rapid intravenous administration can cause tinnitus and deafness.

**Dose adjustments** High doses of loop diuretics may occasionally be needed in renal impairment.

**MONITORING REQUIREMENTS** Monitor electrolytes during treatment.
Bumetanide

- **INDICATIONS AND DOSE**
  - **Oedema**
    - **BY MOUTH**
    - Adult: 1 mg, dose to be taken in the morning, then 1 mg after 6–8 hours if required
    - Elderly: 500 micrograms daily, this lower dose may be sufficient in elderly patients
  - **Oedema, severe cases**
    - **BY MOUTH**
    - Adult: Initially 5 mg daily, increased in steps of 5 mg every 12–24 hours, adjusted according to response

- **INTERACTIONS** → Appendix 1: loop diuretics
- **SIDE-EFFECTS**
  - **Common or very common** Dehydration, hypotension, skin reactions
  - **Uncommon** Breast pain, chest discomfort, ear pain, vertigo
  - **Rare or very rare** Hearing impairment
  - **Frequency not known** Arthralgia, encephalopathy, gastrointestinal discomfort, gynaecomastia, hyperglycaemia, hyperuricaemia, muscle cramps, musculoskeletal pain, (with high doses in renal failure)
  - **PREGNANCY** Bumetanide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.
  - **BREAST FEEDING** No information available. May inhibit lactation.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **Oral solution**
    - **Bumetanide (Non-proprietary)**
      - Bumetanide 200 microgram per 1 ml Bumetanide 1mg/5ml oral solution sugar free sugar-free | 150 ml (POS) £198.00 DT + £198.00
  - **Tablet**
    - **Bumetanide (Non-proprietary)**
      - Bumetanide 1 mg Bumetanide 1mg tablets | 28 tablet (POS) £7.35 DT £11.31
      - Bumetanide 5 mg Bumetanide 5mg tablets | 28 tablet (POS) £6.98 DT £16.98
    - Combinations available: Amiloride with bumetanide, p. 230
  - **Co-amilofruse**

Furosemide

(Frusemide)

- **INDICATIONS AND DOSE**
  - **Oedema**
    - **BY MOUTH**
    - Adult: Initially 40 mg daily, dose to be taken in the morning, then maintenance 20–40 mg daily
    - Initially by Intramuscular injection, or by slow intravenous injection, or by intravenous infusion
    - Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day
  - **Resistant oedema**
    - **BY MOUTH**
    - Adult: 80–120 mg daily
    - Initially by Intramuscular injection, or by slow intravenous injection, or by intravenous infusion
    - Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day
  - **Resistant hypertension**
    - **BY MOUTH**
    - Adult: 40–80 mg daily
    - Initially by Intramuscular injection, or by slow intravenous injection, or by intravenous infusion
    - Adult: Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

- **INTERACTIONS** → Appendix 1: loop diuretics
- **SIDE-EFFECTS**
  - **Common or very common** Dehydration, hypotension, skin reactions
  - **Uncommon** Breast pain, chest discomfort, ear pain, vertigo
  - **Rare or very rare** Hearing impairment
  - **Frequency not known** Arthralgia, encephalopathy, gastrointestinal discomfort, gynaecomastia, hyperglycaemia, hyperuricaemia, muscle cramps, musculoskeletal pain, (with high doses in renal failure)
  - **PREGNANCY** Furosemide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.
  - **BREAST FEEDING** No information available. May inhibit lactation.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **Tablet**
    - **Co-amilofruse (Non-proprietary)**
      - Amiloride hydrochloride 2.5 mg, Furosemide 20 mg Co-amilofruse 2.5mg/20mg tablets | 28 tablet (POS) £7.50 DT + £5.95 | 56 tablet (POS) £11.90–£14.50
      - Amiloride hydrochloride 5 mg, Furosemide 40 mg Co-amilofruse 5mg/40mg tablets | 28 tablet (POS) £9.13 DT + £5.29 | 56 tablet (POS) £10.58–£18.26
      - Amiloride hydrochloride 10 mg, Furosemide 80 mg Co-amilofruse 10mg/80mg tablets | 28 tablet (POS) £18.40 DT + £15.52
      - Frumil (Sanofi)
        - Amiloride hydrochloride 5 mg, Furosemide 20 mg Frumil L5 20mg/2.5mg tablets | 28 tablet (POS) £4.32 DT + £5.95
        - Amiloride hydrochloride 5 mg, Furosemide 40 mg Frumil 40mg/5mg tablets | 28 tablet (POS) £5.29 DT + £5.29

- **CONTRA-INDICATIONS** Addison’s disease, anuria, comatose or precomatose states associated with liver cirrhosis, dehydration, hyperkalaemia, hypovolaemia, renal failure, severe hypokalaemia, severe hypoproteinaemia
- **CAUTIONS** Correct hypovolaemia before using in oliguria, diabetes mellitus, elderly, gout, hepatorenal syndrome, hypoproteinaemia, hypotension, impaired micturition, prostatic enlargement
- **INTERACTIONS** → Appendix 1: loop diuretics
- **PREGNANCY** Not used to treat hypertension in pregnancy.

- **BREAST FEEDING** Manufacturers advise avoid — no information regarding amiloride component available. Amount of furosemide in milk too small to be harmful. Furosemide may inhibit lactation.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in hepatic cirrhosis with renal impairment.
- **RENAL IMPAIRMENT** Risk of hyperkalaemia in renal impairment but may need higher doses. Avoid if eGFR less than 30 mL/minute/1.73 m².
  - **MONITORING** Monitor plasma-potassium concentration.
  - **MONITORING REQUIREMENTS** Monitor electrolytes.

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**Furosemide with triamterene**

The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide p. 227, triamterene p. 230.

### INDICATIONS AND DOSE

**Oedema**

- **BY MOUTH**
  - Adult: 0.5–2 tablets daily, to be taken in the morning

**CONTRA-INDICATIONS** Anuria – dehydration – hyperkalaemia – hypovolaemia – renal failure – severe hypokalaemia – severe hyponatraemia

**CAUTIONS** Diabetes mellitus – elderly – gout – hepatorenal syndrome – hypotension – impaired micturition – may cause blue fluorescence of urine – prostatic enlargement

**INTERACTIONS** → Appendix 1: loop diuretics – potassium-sparring diuretics

**BREAST FEEDING** Triamterene present in milk—manufacturer advises avoid. Furosemide may inhibit lactation.

**HEPATIC IMPAIRMENT** Manufacturer advises caution; avoid in severe hepatic failure or hepatic coma.

**Dose adjustments** Manufacturer advises initial dose reduction.

**RENAI IMPAIRMENT** Avoid in severe impairment. Dose adjustments May need high doses. Monitoring Monitor plasma-potassium concentration in renal impairment (high risk of hyperkalaemia).

**MONITORING REQUIREMENTS** Monitor electrolytes.

**PATIENT AND CARER ADVICE** Urine may look slightly blue in some lights.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

- **Furosemide (Non-proprietary)**
  - Furosemide 20 mg  [F] 28 tablet  **POT** £2.62 DT = £1.48 | 250 tablet  **POT** £5.08-$13.21
  - Furosemide 40 mg  [F] 28 tablet  **POT** £2.84 DT = £2.09 | 250 tablet  **POT** £5.50-$18.66 | 1000 tablet  **POT** £28.21-$92.15
  - Furosemide 500 mg  [F] 28 tablet  **POT** £7.00 DT = £3.94
  - Diureal (Emmogen Pharma Ltd)  Furosemide 500 mg  [tablet]  **POT** £0.99 DT = £3.94

### Solution for injection

- **Furosemide (Non-proprietary)**
  - Furosemide 10 mg per 1 ml  [F] 28 ampoule  **POT** £3.00-40.00
  - Furosemide 50 mg/5ml solution for injection ampoules  | 10 ampoule  **POT** £2.38-$50.00
  - Furosemide 20mg/2ml solution for injection ampoules  | 10 ampoule  **POT** £4.00 DT = £13.42

### Oral solution

- **Furosemide (Non-proprietary)**
  - Furosemide 4 mg per 1 ml  [F] 150 ml (PO) £14.81 DT = £14.81
  - Furosemide 8 mg per 1 ml  [F] 150 ml (PO) £19.53 DT = £19.53
  - Furosemide 10 mg per 1 ml  [F] 150 ml (PO) £20.21 DT = £20.21
  - Frusol (Rosemont Pharmaceuticals Ltd)  Furosemide 4 mg per 1 ml  [F] 150 ml (PO) £12.07 DT = £14.81
  - Frusol 8 mg per 1 ml  [F] 150 ml (PO) £15.58 DT = £19.53
  - Frusol 10 mg per 1 ml  [F] 150 ml (PO) £16.84 DT = £20.21

Combinations available: **Spironolactone with furosemide**, p. 229

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**Torasemide**

### INDICATIONS AND DOSE

**Oedema**

- **BY MOUTH**
  - Adult: 5 mg once daily, to be taken preferably in the morning, then increased if necessary to 20 mg once daily; maximum 40 mg per day

**Hypertension**

- **BY MOUTH**
  - Adult: 2.5 mg daily, then increased if necessary to 5 mg once daily

**INTERACTIONS** → Appendix 1: loop diuretics

**SIDE-EFFECTS**

- **Common or very common** Asthenia – gastrointestinal disorder
- **Uncommon** Bladder dilatation – urinary retention
- **Rare or very rare** Allergic dermatitis

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.
DIURETICS > OSMOTIC DIURETICS

Mannitol

21-Feb-2019

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Torasemide (Non-proprietary)
    - Torasemide 5 mg | 28 tablet [POD] £14.50 DT + £5.53
    - Torasemide 10 mg | 28 tablet [POD] £18.50 DT + £8.14
  - Torem (Meda Pharmaceuticals Ltd)
    - Torasemide 2.5 mg | 28 tablet [POD] £3.78 DT + £3.78
    - Torasemide 5 mg | 28 tablet [POD] £5.53 DT + £5.53
    - Torasemide 10 mg | 28 tablet [POD] £8.14 DT + £8.14

DIURETICS > POTASSIUM-SPARING DIURETICS > ALDOSTERONE ANTAGONISTS

Spironolactone with furosemide

The properties listed below are those particular to the combination only. For the properties of the components please consider, spironolactone p. 193, furosemide p. 227.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Lasilactone (Sanofi)
    - Furosemide 20 mg, Spironolactone 50 mg | 28 capsule [POD] £7.97 DT + £7.97

DIURETICS > POTASSIUM-SPARING DIURETICS > OTHER

Amiloride hydrochloride

- **INDICATIONS AND DOSE**
  - Oedema (monotherapy)
    - By mouth
      - Adult: Initially 10 mg daily, alternatively initially 5 mg twice daily, adjusted according to response; maximum 20 mg per day

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension or congestive heart failure

- By mouth
  - Adult: Initially 5–10 mg daily

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hepatic cirrhosis with ascites

- By mouth
  - Adult: Initially 5 mg daily

- **CONTRA-INDICATIONS** Addison’s disease · anuria · hyperkalaemia
- **CAUTIONS** Diabetes mellitus · elderly
- **INTERACTIONS** → Appendix 1: potassium-sparing diuretics
- **SIDE-EFFECTS** Alopecia · angina pectoris · aplastic anaemia · appetite decreased · arrhythmia · arthralgia · asthenia · atrioventricular block exacerbated · bladder spasm · chest pain · confusion · constipation · cough · depression · diarrhoea · dizziness · drowsiness · dry mouth · dyspnoea · dysuria · electrolyte imbalance · encephalopathy · gastrointestinal discomfort · gastrointestinal disorders ·
gastrointestinal haemorrhage · gout · headache · insomnia · jaundice · muscle cramps · nasal congestion · nausea · nervousness · neutropenia · pain · palpitations · paraesthesia · postural hypotension · sexual dysfunction · skin reactions · tinnitus · tremor · vertigo · visual impairment · vomiting

- **PREGNANCY** Not to be used to treat gestational hypertension.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **RENAI L IMPAIRMENT** Manufacturers advise avoid in severe impairment.
- **MONITORING** Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).
- **MONITORING REQUIREMENTS** Monitor electrolytes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
  - **Oral solution**
    - EXCIPIENTS: May contain Propylene glycol
      - Amiloride hydrochloride (Non-proprietary)
        - Amiloride hydrochloride 1 mg per 1 ml Amiloride 5mg/5ml oral solution sugar free sugar-free
          - 150 ml [Para] £42.35 DT = £42.33
    - **Tablet**
      - Amiloride hydrochloride (Non-proprietary)
        - Amiloride hydrochloride 5 mg Amiloride 5mg tablets
        - 28 tablet [Para] £27.68 DT + £3.29
  - Combinations available: Co-amilfruse, p. 227

### Amiloride with bumetanide

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiloride hydrochloride p. 229, bumetanide p. 227.

- **INDICATIONS AND DOSE**
  - **Oedema**
    - **BY MOUTH**
      - Adult: 1–2 tablets daily
- **INTERACTIONS** → Appendix 1: loop diuretics · potassium-sparing diuretics

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Amiloride with bumetanide (Non-proprietary)
      - Bumetanide 1 mg, Amiloride hydrochloride 5 mg Amiloride 5mg / Bumetanide 1mg tablets
        - 28 tablet [Para] £56.00 DT = £56.00

### Triamterene

- **INDICATIONS AND DOSE**
  - **Oedema**
    - **BY MOUTH**
      - Adult: Initially 150–250 mg daily for 1 week, lower initial dose when given with other diuretics, then reduced to 150–250 mg daily on alternate days, to be taken in divided doses after breakfast and lunch

- **CONTRA-INDICATIONS** Addison’s disease · anuria · hyperkalaemia
- **CAUTIONS** Diabetes mellitus · elderly · gout · may cause blue fluorescence of urine
- **INTERACTIONS** → Appendix 1: potassium-sparing diuretics

- **SIDE-EFFECTS**
  - Common or very common Diarrhoea · hyperkalaemia · nausea · vomiting
  - Uncommon Dry mouth · headache · hyperuricaemia · renal failure (reversible on discontinuation) · skin reactions
  - Rare or very rare Megaloblastic anaemia · nephritis tubulointerstitial · pancytopenia · photosensitivity reaction · serum sickness · urolithiasis
  - Frequency not known Asthenia · jaundice · metabolic acidosis

- **PREGNANCY** Not used to treat gestational hypertension. Avoid unless essential.
- **BREAST FEEDING** Present in milk—manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution; avoid in progressive impairment.
- **RENAI L IMPAIRMENT** Avoid in progressive impairment.
- **MONITORING** Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).
- **MONITORING REQUIREMENTS** Monitor electrolytes.
- **PATIENT AND CARER ADVICE** Urine may look slightly blue in some lights.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - CAUTIONARY AND ADVISORY LABELS 14, 21
      - Triamterene (Non-proprietary)
        - Triamterene 50 mg Triamterene 50mg capsules
        - 30 capsule [Para] £41.90 DT = £41.90
  - Combinations available: Co-triamterzide, p. 231 · Furosemide with triamterene, p. 228

### Triamterene with chlortalidone

The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene above, chlortalidone below.

- **INDICATIONS AND DOSE**
  - **Hypertension / Oedema**
    - **BY MOUTH**
      - Adult: 50/50–100/100 mg once daily, dose to be taken in the morning

- **DOSE EQUIVALENCE AND CONVERSION**
  - Dose expressed as $x/y$ mg of triamterene/chlortalidone.

- **INTERACTIONS** → Appendix 1: potassium-sparing diuretics · thiazide diuretics

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 14, 21
      - Kalspare (DHP Healthcare Ltd)
        - Chlortalidone 50 mg, Triamterene 50 mg
        - Kalspare tablets
        - 28 tablet [Para] £9.90

### Diuretics >thiazides and related diuretics

### Chlortalidone

(Chlortalidone)

- **INDICATIONS AND DOSE**
  - **Aspects due to cirrhosis in stable patients (under close supervision)** Oedema due to nephrotic syndrome
    - **BY MOUTH**
      - Adult: Up to 50 mg daily

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### Hypertension

- **BY MOUTH**
  - Adult: 25 mg daily, dose to be taken in the morning, then increased if necessary to 50 mg daily

### Mild to moderate chronic heart failure

- **BY MOUTH**
  - Adult: 25–50 mg daily, dose to be taken in the morning, then increased if necessary to 100–200 mg daily, reduce to lowest effective dose for maintenance

### Nephrogenic diabetes insipidus | Partial pituitary diabetes insipidus

- **BY MOUTH**
  - Adult: Initially 100 mg twice daily, then reduced to 50 mg daily

### INTERACTIONS

- Common or very common Appetite decreased · erectile dysfunction · gastrointestinal discomfort · hyperglycaemia · rash
- Uncommon Gout
- Rare or very rare Arrhythmia · diabetes mellitus exacerbated · eosinophilia · glycosuria · hepatic disorders · nephritis · tubulointerstitial · paraesthesia · pulmonary oedema · respiratory disorder · vomiting

### BREAST FEEDING

The amount present in milk is too small to be harmful. Large doses may suppress lactation.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

#### Tablet

- **Chlortalidone (Non-proprietary)**
  - Chlortalidone 25 mg (Meda Pharmaceuticals Ltd)
  - 100 tablet £0.55 DT £8.04
  - Chlortalidone 50 mg (Meda Pharmaceuticals Ltd)
  - 30 tablet £0.55 DT £8.04

#### Combinations available:

- **Triamterene with chlortalidone**, p. 230

### Co-trimaterzide

The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene p. 230, hydrochlorothiazide p. 166.

#### INDICATIONS AND DOSE

- **Hypertension**
  - **BY MOUTH**
    - Adult: 50/25 mg daily, increased if necessary up to 200/100 mg daily, dose to be taken after breakfast
- **Oedema**
  - **BY MOUTH**
    - Adult: 50/25 mg twice daily, to be taken after breakfast and after midday meal, increased if necessary to 150/75 mg daily, to be taken as 100/50 mg after breakfast and 50/25 mg after midday meal; maintenance 50/25 mg daily, alternatively maintenance 100/50 mg once daily on alternate days; maximum 200/100 mg per day

#### DOSE EQUIVALENCEN AND CONVERSION

- Dose expressed as ×/y mg of triamterene/hydrochlorothiazide.

#### INTERACTIONS

- Appendix 1: potassium-sparing diuretics · thiazide diuretics

#### PATIENT AND CARER ADVICE

Urine may look slightly blue in some lights.

### Metolazone

#### INDICATIONS AND DOSE

- **Oedema**
  - **BY MOUTH**
    - Adult: 5–10 mg daily, dose to be taken in the morning; increased if necessary to 20 mg daily, dose increased in resistant oedema; maximum 80 mg per day
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 5 mg daily, dose to be taken in the morning; maintenance 5 mg once daily on alternate days

#### CAUTIONS

Acute porphyrias p. 1058

#### INTERACTIONS

Appendix 1: thiazide diuretics

#### SIDE-EFFECTS

Chest pain · chills

#### BREAST FEEDING

The amount present in milk is too small to be harmful. Large doses may suppress lactation.

#### DIRECTIONS FOR ADMINISTRATION

Tablets may be crushed and mixed with water immediately before use.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution

#### Tablet

- **Zaroxolyn (Imported (Canada))**
  - Metolazone 2.5 mg Zaroxolyn 2.5mg tablets | 100 tablet £0.04 DT £9.58
  - Metolazone 5 mg Zaroxolyn 5mg tablets | 50 tablet £0.04 DT £9.58

### Xipamide

#### INDICATIONS AND DOSE

- **Oedema**
  - **BY MOUTH**
    - Adult: 50 mg per day, to be used in resistant cases; maintenance 20 mg daily, dose to be taken in the morning
  - **Hypertension**
    - **BY MOUTH**
      - Adult: Initially 40 mg daily, dose to be taken in the morning, increased if necessary to 80 mg daily, higher dose to be used in resistant cases; maintenance 20 mg daily, dose to be taken in the morning

#### CAUTIONS

Acute porphyrias p. 1058

#### INTERACTIONS

Appendix 1: thiazide diuretics

#### SIDE-EFFECTS

- Common or very common Anxiety · dry mouth · fatigue · gastrointestinal discomfort · gouty arthritis · hyperhidrosis · lethargy · muscle complaints · palpitations
  - Rare or very rare Cholecystitis acute · hyperlipidaemia · jaundice · nephritis acute interstitial · pancreatitis · haemorrhagic · skin reactions · vision disorders

#### BREAST FEEDING

No information available.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Diurexan** (Meda Pharmaceuticals Ltd)
  - Xipamide 20 mg Diurexan 20mg tablets | 140 tablet £13.46 DT £19.46

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Peripheral vascular disease can be either occlusive (e.g. intermittent claudication) in which occlusion of the peripheral arteries is caused by atherosclerosis, or vasospastic (e.g. Raynaud’s syndrome). Peripheral arterial occlusive disease is associated with an increased risk of cardiovascular events; this risk is reduced by measures such as Smoking cessation p. 497, effective control of blood pressure, regulating blood lipids, optimising glycemic control in diabetes, taking aspirin p. 121 in a dose of 75 mg daily, and possibly weight reduction in obesity. Exercise training can improve symptoms of intermittent claudication; revascularisation procedures may be appropriate.

Nifidiprofuryl oxalate p. 233 can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking nifidiprofuryl oxalate should be assessed for improvement after 3–6 months. Cilostazol below is licensed for use in intermittent claudication to improve walking distance in patients without peripheral tissue necrosis who do not have pain at rest; use is restricted to second-line treatment where lifestyle modifications and other appropriate interventions have failed to improve symptoms. Cilostazol should be initiated by those experienced in the management of intermittent claudication. Patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance. Inositol nicotinate p. 233 and pentoxifylline p. 234 are not established as being effective for the treatment of intermittent claudication.

Intravenous iloprost p. 184 [unlicensed] is a treatment option for critical limb ischaemia in patients unsuitable for surgery. Management of Raynaud’s syndrome includes avoidance of exposure to cold and Smoking cessation p. 497. More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud’s syndrome. Nifedipine p. 162 is useful for reducing the frequency and severity of vasospastic attacks. Alternatively, nifidiprofuryl oxalate may produce symptomatic improvement; inositol nicotinate (a nicotinic acid derivative) may also be considered. Pentoxifylline, prazosin p. 784, and moxisylyte p. 233 are not established as being effective for the treatment of Raynaud’s syndrome. Vasodilator therapy is not established as being effective for chilblains.

Advanced Pharmacy Services
Patients with peripheral vascular disease may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

**Cilostazol**

- **INDICATIONS AND DOSE**
  - Intermittent claudication in patients without rest pain and no peripheral tissue necrosis
  - **BY MOUTH**
    - Adult: 100 mg twice daily, to be taken 30 minutes before food, cilostazol should be initiated by those experienced in the management of intermittent claudication; patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance
  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Manufacturer advises reduce dose to 50 mg twice daily with concurrent use of potent inhibitors of CYP3A4, potent inhibitors of CYP2C19, omeprazole and erythromycin.

- **CONTRA-INDICATIONS**
  - Active peptic ulcer - congestive heart failure - coronary intervention in previous 6 months - haemorrhagic stroke in previous 6 months - history of severe tachyarrhythmia - myocardial infarction in previous 6 months - poorly controlled hypertension - predisposition to bleeding - proliferative diabetic retinopathy - prolongation of QT interval - severe atrial flutter - unstable angina

- **CAUTIONS**
  - Atrial fibrillation - atrial or ventricular ectopy - diabetes mellitus (higher risk of intracranial bleeding) - mild to moderate atrial flutter - stable coronary disease - surgery

- **INTERACTIONS** → Appendix 1: cilostazol

- **SIDE-EFFECTS**
  - Common or very common
    - Appetite decreased - arthralgias - diarrhoea - dizziness - gastrointestinal discomfort - gastrointestinal disorders - headache - increased risk of infection - nausea - oedema - palpitations - skin reactions - vomiting
  - Uncommon
    - Anaemia - anxiety - congestive heart failure - cough - dyspnoea - haemorrhage - hyperglycaemia - hypotension - sleep disorders - syncope
  - Rare or very rare
    - Renal impairment - thrombocytosis
  - Frequency not known
    - Agranulocytosis - bone marrow disorders - conjunctivitis - fever - granulocytopenia - hepatic disorders - hot flush - hypertension - intracranial haemorrhage - leukopenia - paresis - severe cutaneous adverse reactions (SCARs) - thrombocytopenia - tinnitus - urinary frequency increased

- **PREGNANCY**
  - Avoid—toxicity in animal studies.

- **BREAST FEEDING**
  - Present in milk in animal studies—manufacturer advises avoid.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in moderate-to-severe impairment—no information available.

- **RENAL IMPAIRMENT**
  - Avoid if eGFR less than 25 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE**
  - Blood disorders—Patients should be advised to report any unexplained bleeding, bruising, sore throat, or fever.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Cilostazol, nifidiprofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
    - Cilostazol is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment...
should have the option to continue until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta223

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - **Cilostazol (non-proprietary)**
      - Cilostazol 50 mg Cilostazol 50mg tablets | 56 tablet [PO] £40.05
        - DT = £80.05
      - Cilostazol 100 mg Cilostazol 100mg tablets | 56 tablet [PO] £33.37
        - DT = £66.74
    - **Pletal (Otsuka Pharmaceuticals (U.K.) Ltd)**
      - Pletal 50 mg Pletal 50mg tablets | 56 tablet [PO] £35.31 DT = £70.62
      - Pletal 100 mg Pletal 100mg tablets | 56 tablet [PO] £33.37 DT = £66.74

  - **CAUTIONARY AND ADVISORY LABELS**
    - **Lipid modifying drugs**
      - **Inositol nicotinate**
        - **INDICATIONS AND DOSE**
          - **Peripheral vascular disease**
            - **BY MOUTH**
              - Adult: 3 g daily in 2–3 divided doses; maximum 4 g per day
        - **CONTRA-INDICATIONS**
          - Acute phase of a cerebrovascular accident, recent myocardial infarction
        - **CAUTIONS**
          - Cerebrovascular insufficiency, unstable angina
        - **SIDE-EFFECTS**
          - Uncommon: Dizziness, flushing, headache, nausea, oedema, paraesthesia, postural hypotension, rash, syncope, vomiting
          - Frequency not known: Myalgia
        - **PREGNANCY**
          - No information available—manufacturer advises avoid unless potential benefit outweighs risk.
        - **NATIONAL FUNDING/ACCESS DECISIONS**
          - **NICE decisions**
            - Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223
            - Inositol nicotinate is **not** recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving treatment should have the option to continue until they and their clinician consider it appropriate to stop.
          - **LESS SUITABLE FOR PRESCRIBING**
            - Less suitable for prescribing.
        - **MEDICINAL FORMS**
          - There can be variation in the licensing of different medicines containing the same drug.
          - Forms available from special-order manufacturers include: oral suspension
            - **Capsule**
              - Solgar No-Flush Niacin (Solgar Vitamin and Herb) Inositol nicotinate 500 mg Solgar No-Flush Niacin 500mg capsules | 50 capsule

  - **PERIPHERAL VASODILATORS**
    - **Moxisylyte**
      - **(Thymoxamine)**
        - **INDICATIONS AND DOSE**
          - **Primary Raynaud’s syndrome (short-term treatment)**
            - **BY MOUTH**
              - Adult: Initially 40 mg 4 times a day, increased if necessary to 80 mg 4 times a day, increase dose if poor initial response, discontinue after 2 weeks if no response
        - **CONTRA-INDICATIONS**
          - Active liver disease
        - **CAUTIONS**
          - Diabetes mellitus
        - **INTERACTIONS**
          - **SIDE-EFFECTS**
            - Rare or very rare: Hepatic disorders, rash
            - Frequency not known: Diarrhoea, flushing, headache, nausea, vertigo
        - **PREGNANCY**
          - Manufacturer advises avoid.
        - **LESS SUITABLE FOR PRESCRIBING**
          - Less suitable for prescribing.
        - **MEDICINAL FORMS**
          - There can be variation in the licensing of different medicines containing the same drug.
          - Tablet
            - **Opilon (Kyowa Kirin Ltd)**
              - Moxisylyte (as Moxisylyte hydrochloride) 40 mg Opilon 40mg tablets | 112 tablet [PO] £90.22 DT = £90.22

  - **Naftidrofuryl oxalate**
    - **INDICATIONS AND DOSE**
      - **Peripheral vascular disease**
        - **BY MOUTH**
          - Adult: 100–200 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months
      - **Cerebral vascular disease**
        - **BY MOUTH**
          - Adult: 100 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months
        - **SIDE-EFFECTS**
          - Uncommon: Diarrhoea, epigastric pain, nausea, rash, vomiting
          - Rare or very rare: Liver injury, oxalate nephrolithiasis
          - Frequency not known: Oesophagitis

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Sodium tetradeyl sulfate

**INDICATIONS AND DOSE**
Sclerotherapy of reticular veins and spider veins in legs and varicose veins

- **BY INTRAVENOUS INJECTION**
- Adult: Test dose recommended before each treatment (consult product literature)

**CONTRA-INDICATIONS**
Acute infection · asthma · blood disorders · deep vein thrombosis · high risk of thromboembolism · hyperthyroidism · inability to walk · neoplasms · occlusive arterial disease · phlebitis · pulmonary embolism · recent acute superficial thrombophlebitis · recent surgery · respiratory disease · significant valvular incompetence in deep veins · skin disease · symptomatic patent foramen ovale (if administered as foam) · uncontrolled diabetes mellitus · varicose veins caused by tumours (unless tumour removed)

**CAUTIONS**
Arterial disease · asymptomatic patent foramen ovale (use smaller volumes and avoid Valsalva manoeuvre immediately after administration) · extravasation may cause necrosis of tissues · history of migraine (use smaller volumes) · resuscitation facilities must be available · venous insufficiency with lymphoedema (pain and inflammation may worsen)

**SIDE-EFFECTS**
- Common or very common Embolism and thrombosis · pain · paraesthesia
- Uncommon Skin reactions · telangiectasia
- Rare or very rare Arterial spasm · asthma · erythema · cerebrovascular insufficiency · chest pressure · circulatory collapse · confusion · cough · diarrhea · dry mouth · dyspnoea · fever · headaches · hot flush · hypersensitivity · local exfoliation · nausea · nerve damage · palpitations · presyncope · soft tissue necrosis · tongue swelling · vasculitis · vision disorders · vomiting

**PREGNANCY**
Avoid unless benefits outweigh risks—no information available.

**BREAST FEEDING**
Use with caution—no information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Modified-release tablet**
Cautory and Advisory Labels 21, 25
Trental (Sanofi)
Pentoxifylline 400 mg Trental 400 modified-release tablets | 90 tablet | £19.39 DT + £19.39

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**Pentoxifylline**

(Oxpentifylline)

**INDICATIONS AND DOSE**
Peripheral vascular disease · Venous leg ulcer (adjunct)

- **BY MOUTH**
- Adult: 400 mg 2–3 times a day

**UNLICENSED USE**
Use of pentoxifylline as adjunct therapy for venous leg ulcers is an unlicensed indication.

**CONTRA-INDICATIONS**
Acute myocardial infarction · cerebral haemorrhage · severe retinal haemorrhage · severe cardiac arrhythmias

**CAUTIONS**
Avoid in Acute porphyrias p. 1058 · coronary artery disease · diabetes (may lower blood glucose) · hypotension

**INTERACTIONS**
Appendix 1: pentoxifylline

**SIDE-EFFECTS**
Agitation · angina pectoris · angioedema · arrhythmias · bronchospasm · cholesterol · constipation · diarrhoea · dizziness · gastrointestinal discomfort · gastrointestinal disorder · haemorrhage · headache · hot flush · hypersalivation · hypotension · leucopenia · meningeal aseptic · nausea · neutropenia · skin reactions · sleep disorder · thrombocytopenia · vomiting

**PREGNANCY**
Manufacturer advises avoid—no information available.

**BREAST FEEDING**
Present in milk—manufacturer advises use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment.

**Dose adjustments**
Manufacturer advises consider dose reduction in severe impairment.

**RENAL IMPAIRMENT**
Dose adjustments
Reduce dose by 30–50% if eGFR less than 30 mL/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA232

Pentoxifylline is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA223
Chapter 3
Respiratory system

Respiratory system, drug delivery

Inhalation
This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced.

Inhaler devices
These include pressurised metered-dose inhalers, breath-actuated inhalers, and dry powder inhalers. Many patients can be taught to use a pressurised metered-dose inhaler effectively but some patients, particularly the elderly and children, find them difficult to use. Spacer devices can help such patients because they remove the need to co-ordinate actuation with inhalation. Dry powder inhalers may be useful in adults and children over 5 years who are unwilling or unable to use a pressurised metered-dose inhaler. Alternatively, breath-actuated inhalers are suitable for adults and older children provided they can use the device effectively.

Pressurised metered-dose inhalers are an effective and convenient method of drug administration in mild to moderate asthma.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation. Coughing may also occur.

The patient should be instructed carefully on the use of the inhaler and it is important to check that the inhaler continues to be used correctly because inadequate inhalation technique may be mistaken for a lack of response to the drug.

MHRA/CHM advice: Pressurised metered dose inhalers (pMDI): risk of airway obstruction from aspiration of loose objects (July 2018)
The MHRA have received reports of patients who have inhaled objects into the back of the throat—some cases objects were aspirated, causing airway obstruction. Patients should be reminded to remove the mouthpiece cover fully, shake the device and check that both the outside and inside of the mouthpiece are clear and undamaged before inhaling a dose, and to store the inhaler with the mouthpiece cover on.

Spacer devices
Spacer devices remove the need for coordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring high doses of inhaled corticosteroids, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (Volumatic®) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.

Use and care of spacer devices
Patients should inhale from the spacer device as soon as possible after actuation because the drug aerosol is very short-lived; single-dose actuation is recommended. Tidal breathing is as effective as single breaths. The device should be cleaned once a month by washing in mild detergent and then allowed to dry in air without rinsing; the mouthpiece should be wiped clean of detergent before use. Some manufacturers recommend more frequent cleaning, but this should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

Respiratory drug delivery, nebulisers
Solutions for nebulisation are available for use in severe acute asthma. They are administered over 5–10 minutes from a nebuliser usually driven by oxygen in hospital. Patients with a severe attack of asthma should preferably have oxygen during nebulisation since beta, agonists can increase arterial hypoxaemia.

A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are to deliver:
- a beta, agonist or ipratropium bromide p. 246 to a patient with an acute exacerbation of asthma or of chronic obstructive pulmonary disease;
- a beta, agonist, corticosteroid, or ipratropium bromide on a regular basis to a patient with severe asthma or reversible airways obstruction when the patient is unable to use other inhalational devices;
- an antibiotic (such as colistimethate sodium p. 556) or a mucolytic to a patient with cystic fibrosis;
- Budesonide p. 260 or adrenaline/epinephrine p. 222 to a child with severe croup;
- Pentamidine isethionate p. 602 for the prophylaxis and treatment of pneumocystis pneumonia.

The use of nebulisers in chronic persistent asthma and chronic obstructive pulmonary disease should be considered only:
- after a review of the diagnosis;
- after review of therapy (see also Chronic Obstructive Pulmonary Disease) and the patient’s ability to use handheld devices;
Respiratory system

- after increased doses of inhaled therapy from hand-held inhalers (with a spacer if necessary) have been tried for 2 weeks;
- if the patient remains breathless, despite correctly using optimal therapy.

Before prescribing a nebuliser, a home trial should preferably be undertaken to monitor response for up to 2 weeks on standard treatment and up to 2 weeks on nebulised treatment. If prescribed, patients must:
- have clear instructions from a doctor, specialist nurse, physiotherapist, or pharmacist on the use of the nebuliser (including maintenance and cleaning) and on peak-flow monitoring;
- be instructed not to treat acute attacks at home without also seeking help;
- have regular follow-up by a doctor, specialist nurse or physiotherapist after about 1 month and annually thereafter.

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30%, it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on the droplet size, pattern of breath inhalation, and condition of solution is deposited in the airways or alveoli depends on the mouthpiece and tubing. The extent to which the nebulised treatment. If prescribed, patients must:

Jet nebulisers
Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum gas flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

For patients at risk of hypercapnia, such as those with chronic obstructive pulmonary disease, oxygen can be dangerous and the nebuliser should be driven by air. If oxygen is required, it should be given simultaneously by nasal cannula.

Tubing
The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

Ultrasonic nebulisers
Ultrasonic nebulisers produce an aerosol by ultrasonic vibration of the drug solution and therefore do not require a gas flow; they are not suitable for the nebulisation of some drugs, such as dornase alfa p. 293 and nebulised suspensions.

Nebuliser diluent
Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline). In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff).

Oral
The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta2agonists, corticosteroids, theophylline p. 274, and leukotriene receptor antagonists.

Parenteral
Drugs such as beta, agonists, corticosteroids, and aminophylline p. 272 can be given by injection in acute severe asthma when administration by nebulisation is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

Peak flow meters
When used in addition to symptom-based monitoring, peak flow monitoring has not been proven to improve asthma control in either adults or children, however measurement of peak flow may be of benefit in adult patients who are ‘poor perceivers’ and hence slow to detect deterioration in their asthma, and for those with more severe asthma.

When peak flow meters are used, patients must be given clear guidelines as to the action they should take if their peak flow falls below a certain level. Patients can be encouraged to adjust some of their own treatment (within specified limits) according to changes in peak flow rate.

Peak flow charts should be issued to patients where appropriate, and are available to purchase from:

NHS Hospitals can order supplies from www.nhsforms.co.uk/ or by emailing nhsforms@mmm.com.

In Scotland, peak flow charts can be obtained by emailing stockorders.dppas@apsgroup.co.uk.

NICE decisions
Inhaler devices for children under 5 years with chronic asthma (August 2000) NICE TA10
When selecting inhaler devices for children under 5 years with chronic asthma, a child’s needs and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child’s condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered.

NICE TA10
Inhaler devices for children 5–15 years with chronic asthma (March 2002) NICE TA38
When selecting inhaler devices for children between 5–15 years with chronic asthma, a child’s needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- for other inhaled drugs, particularly bronchodilators, a wider range of devices should be considered;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

www.nice.org.uk/T10

www.nice.org.uk/T38
Airways disease, obstructive

1 Airways disease, obstructive

Asthma, chronic

Description of condition
Asthma is a common chronic inflammatory condition of the airways, associated with airway hyperresponsiveness and variable airflow obstruction. The most frequent symptoms of asthma are cough, wheeze, chest tightness, and breathlessness. Asthma symptoms vary over time and in intensity and can gradually or suddenly worsen, provoking an acute asthma attack that, if severe, may require hospitalisation.

Aims of treatment
The aim of treatment is to achieve control of asthma. Complete control of asthma is defined as no daytime symptoms, no night-time awakening due to asthma, no asthma attacks, no need for rescue medication, no limitations on activity including exercise, normal lung function (in practical terms forced expiratory volume in 1 second (FEV1) and/or peak expiratory flow (PEF) > 80% predicted or best), and minimal side-effects from treatment. In clinical practice, patients may choose to balance the aims of asthma management against the potential side-effects or inconvenience of taking medication necessary to achieve perfect control.

Lifestyle changes
Weight loss in overweight patients may lead to an improvement in asthma symptoms. Parents with asthma should be advised about the danger of smoking, to themselves and to their children with asthma, and be offered appropriate support to stop smoking. For further information, see Smoking cessation p. 457.

Breathing exercise programmes (including physiotherapist-taught methods) can be offered as an adjunct to drug treatment to improve quality of life and reduce symptoms.

Management
A stepwise approach aims to stop symptoms quickly and to improve peak flow. Treatment should be started at the level most appropriate to initial severity of asthma. The aim is to achieve early control and to maintain it by stepping up treatment as necessary and decreasing treatment when control is good. Before initiating a new drug or adjusting treatment consider whether diagnosis is correct, check adherence and inhaler technique, and eliminate trigger factors for acute attacks.

A self-management programme comprising of a written personalised action plan and education should be offered to all patients with asthma (and/or their family or carers).

Recommendations on the management of chronic asthma from the National Institute for Health and Care Excellence (NICE)—Asthma: diagnosis, monitoring and chronic asthma management guidelines (NG80, November 2017), and British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN)—British guideline on the management of asthma (SIGN 153, September 2016) differ significantly. Recommendations in BNF publications are based on NICE guidelines, and differences with BTS/SIGN (2016) have been highlighted.

Adult NICE (2017) treatment recommendations for adults apply to patients aged 17 years and over. BTS/SIGN (2016) treatment recommendations for adults apply to patients over 12 years.

Intermittent reliever therapy
Start an inhaled short-acting beta, agonist (such as salbutamol p. 252 or terbutaline sulfate p. 255), to be used as required, in all patients with asthma. For those with infrequent short-lived wheeze, occasional use of reliever therapy may be the only treatment required. Patients using more than one short-acting beta, agonist inhaler device a month should have their asthma urgently assessed and action taken to improve poorly controlled asthma.

Regular preventer (maintenance) therapy
NICE (2017) define inhaled corticosteroid doses for adults as low, moderate, or high. BTS/SIGN (2016) instead define inhaled corticosteroid doses for adults as low, medium or high (refer to individual guidelines for inhaled corticosteroid dosing information).

A low dose of inhaled corticosteroid should be started as maintenance therapy in patients who present with any one of the following features: using an inhaled short-acting beta, agonist three times a week or more, symptomatic three times a week or more, or waking at night due to asthma symptoms at least once a week. BTS/SIGN (2016) also recommend initiation in patients who have had an asthma attack in the last 2 years, and starting inhaled corticosteroids at a dose appropriate to the severity of asthma.

BTS/SIGN (2016) recommend that inhaled corticosteroids (except ciclesonide p. 262) should be initially taken twice daily, however, the same total daily dose, taken once a day, can be considered in patients with milder disease if good or complete control of asthma is established. The dose of inhaled corticosteroid should be adjusted over time to the lowest effective dose at which control of asthma is maintained.

BTS/SIGN (2016) recommend the prescribing of inhalers by brand.

Initial add-on therapy
If asthma is uncontrolled on a low dose of inhaled corticosteroid as maintenance therapy, a leukotriene receptor antagonist (such as montelukast p. 269) should be offered in addition to the inhaled corticosteroid, and the response to treatment reviewed in 4 to 8 weeks.

BTS/SIGN (2016) instead recommend a long-acting beta, agonist (LABA—such as salmeterol p. 252 or formoterol fumarate p. 250) as initial add-on therapy to inhaled corticosteroids if asthma is uncontrolled.

Additional add-on therapy
If asthma is uncontrolled on a low dose of inhaled corticosteroid and a leukotriene receptor antagonist as maintenance therapy, a LABA in combination with the inhaled corticosteroid should be offered with or without continued leukotriene receptor antagonist treatment, depending on the response achieved from the leukotriene receptor antagonist.

If asthma remains uncontrolled, offer to change the inhaled corticosteroid and LABA maintenance therapy to a MART regimen (Maintenance And Reliever Therapy—a combination of an inhaled corticosteroid and a fast-acting LABA such as formoterol in a single inhaler), with a low dose of inhaled corticosteroid as maintenance. See beclometasone with formoterol p. 259 and budesonide with formoterol p. 261.

If asthma remains uncontrolled on a MART regimen with a low dose of inhaled corticosteroid as maintenance with or without a leukotriene antagonist, consider increasing to a moderate dose of inhaled corticosteroid (either continuing a MART regimen or changing to a fixed-dose regimen of an inhaled corticosteroid and a LABA, with a short-acting beta, agonist as reliever therapy).
If asthma is still uncontrolled in patients on a moderate dose of inhaled corticosteroid as maintenance with a LABA (either as MART or a fixed-dose regimen), with or without a leukotriene receptor antagonist, consider the following options:

- increasing the inhaled corticosteroid dose to a high-dose as maintenance (this should only be offered as part of a fixed-dose regimen, with a short-acting beta, agonist used as a reliever therapy), or
- a trial of an additional drug, for example, a long-acting muscarinic receptor antagonist (such as tiotropium p. 247) or modified-release theophylline p. 274, or
- seek advice from an asthma specialist.

BTS/SIGN (2016) instead recommend that if the patient is gaining some benefit from addition of a LABA but control remains inadequate, that the LABA be continued and the dose of inhaled corticosteroid be increased to a medium-dose, if not already on this dose. If increasing the dose of inhaled corticosteroid is ineffective, consider continuing on a low dose of inhaled corticosteroid and a LABA and try adding a leukotriene receptor antagonist, or a long-acting muscarinic receptor antagonist, or modified-release theophylline p. 274.

If there is no response to the LABA, discontinue it and increase the dose of the inhaled corticosteroid to a medium-dose if not already on this dose. If increasing the dose of inhaled corticosteroid is ineffective, consider continuing on a low dose of inhaled corticosteroid and try adding a leukotriene receptor antagonist or a long-acting muscarinic receptor antagonist.

**High-dose inhaled corticosteroids and further add-on treatment**

BTS/SIGN (2016) recommend that if control remains inadequate on a combination of short-acting beta, agonist as required, a medium dose of inhaled corticosteroid, plus an additional drug, usually a LABA, to consider the following interventions:

- increase the inhaled corticosteroid to a high-dose—with high doses of inhaled corticosteroid via a pressurised metered dose inhaler (pMDI), a spacer should be used, or
- add a leukotriene receptor antagonist, or
- add modified-release theophylline p. 274, or
- add tiotropium p. 247.

If a trial of a further add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose) and refer to specialist care.

**Continuous or frequent use of oral corticosteroids**

BTS/SIGN (2016) recommend adding a regular oral corticosteroid (prednisolone p. 678) at the lowest dose to provide adequate control (under specialist care) in patients with very severe asthma uncontrolled on high-dose inhaled corticosteroids, and who have also tried (or are still receiving) a LABA, a leukotriene receptor antagonist, or modified-release theophylline p. 274.

**Monoclonal antibodies and immunosuppressants**

BTS/SIGN (2016) recommend, that under specialist initiation, immunosuppressants such as methotrexate p. 913 [unlicensed], and monoclonal antibodies such as omalizumab p. 267 (for severe persistent allergic asthma), and mepolizumab p. 267 and reslizumab p. 268 (in adults for severe eosinophilic asthma), may be considered in patients with severe asthma to achieve control and reduce the use of oral corticosteroids. See mepolizumab p. 267, omalizumab p. 267, reslizumab p. 268 National funding/access decisions.

**Child over 5 years**

For children under 5 years, NICE (2017) treatment recommendations for children apply to children aged 5–16 years and adult treatment recommendations apply to those aged 17 years and over. Whereas, for children over 5 years, BTS/SIGN (2016) treatment recommendations for children apply to children aged 5–12 years and adult treatment recommendations apply to those aged over 12 years.

**Intermittent reliever therapy**

BTS/SIGN (2016) instead define inhaled corticosteroids for children (5–12 years) as very low, low, or medium, and for children over 12 years as low, medium or high (refer to individual guidelines for inhaled corticosteroid dosing information).

A paediatric low dose of inhaled corticosteroid should be started as maintenance therapy in children who present with any one of the following features: using an inhaled short-acting beta, agonist three times a week or more, symptomatic three times a week or more, or waking at night due to asthma symptoms at least once a week.

BTS/SIGN (2016) instead recommend starting a very low dose (child 5–12 years) or a low dose (child over 12 years) of inhaled corticosteroid in children presenting with any one of the following features: using an inhaled short-acting beta, agonist three times a week or more, symptomatic three times a week or more, or waking at night due to asthma symptoms at least once a week, and starting inhaled corticosteroids at a dose appropriate to the severity of asthma.

BTS/SIGN (2016) recommend that inhaled corticosteroids (except ciclesonide p. 262) should be initially taken twice daily, however, the same total daily dose, taken once a day, can be considered in patients with milder disease if good or complete control of asthma is established. The dose of inhaled corticosteroid should be adjusted over time, to the lowest effective dose at which control of asthma is maintained.

BTS/SIGN (2016) recommend the prescribing of inhalers by brand.

**Initial add-on therapy**

If asthma is uncontrolled on a paediatric low dose of inhaled corticosteroid as maintenance therapy, consider a leukotriene receptor antagonist (such as montelukast p. 269) in addition to the inhaled corticosteroid, and review the response to treatment in 4 to 8 weeks.

BTS/SIGN (2016) instead recommend a long-acting beta, agonist (LABA—such as salmeterol p. 252 or formoterol fumarate p. 250) in children over 12 years, or a LABA or a leukotriene receptor antagonist in children 5–12 years, as initial add-on therapy to inhaled corticosteroids if asthma is uncontrolled.

**Additional add-on therapy**

If asthma is uncontrolled on a paediatric low dose of inhaled corticosteroid and a leukotriene receptor antagonist as maintenance therapy, consider discontinuation of the leukotriene receptor antagonist and initiation of a LABA in combination with the inhaled corticosteroid.

If asthma remains uncontrolled on a paediatric low dose of inhaled corticosteroid and a LABA as maintenance therapy, consider changing to a MART regimen (Maintenance And
Reliever Therapy—a combination of an inhaled corticosteroid and fast-acting LABA such as formoterol in a single inhaler) with a paediatric low dose of inhaled corticosteroid as maintenance. See budesonide with formoterol p. 261 [not licensed in all age groups].

If asthma remains uncontrolled on a MART regimen with a paediatric low dose of inhaled corticosteroid as maintenance, consider increasing to a paediatric moderate dose of inhaled corticosteroid (either continuing a MART regimen or changing to a fixed-dose regimen of an inhaled corticosteroid and a LABA, with a short-acting beta2-agonist as reliever therapy).

If asthma is still uncontrolled on a paediatric moderate dose of inhaled corticosteroid as maintenance with a LABA (either as MART or a fixed-dose regimen), consider seeking advice from an asthma specialist and the following options:

- increasing the inhaled corticosteroid dose to a paediatric high dose as maintenance (this should only be offered as part of a fixed-dose regimen, with a short-acting beta2-agonist as reliever therapy), or
- a trial of an additional drug, such as modified-release theophylline p. 274.

BTS/SIGN (2016) instead recommend that if the child is gaining some benefit from addition of a LABA but control remains inadequate, continue the LABA and increase the dose of the inhaled corticosteroid to a low-dose (child 5–12 years) or medium-dose (child over 12 years), if not already on this dose. If increasing the dose of inhaled corticosteroid is ineffective, consider continuing a very low dose (child 5–12 years) or low dose (child over 12 years) of inhaled corticosteroid and a LABA and try adding a leukotriene receptor antagonist, or modified-release theophylline p. 274, or long-acting muscarinic receptor antagonist (in children over 12 years).

If there is no response to the LABA, discontinue it and increase the dose of inhaled corticosteroid to a low-dose (child 5–12 years) or medium-dose (child over 12 years), if not already on this dose. If increasing the dose of inhaled corticosteroid is ineffective, consider continuing on a very low dose (child 5–12 years) or low dose (child over 12 years) of inhaled corticosteroid and try adding a leukotriene receptor antagonist or long-acting muscarinic receptor antagonist (in children over 12 years).

High-dose inhaled corticosteroids and further add-on treatment

BTS/SIGN (2016) recommend that if control remains inadequate on a combination of a short-acting beta2-agonist as required, a low dose (child 5–12 years) or medium dose (child over 12 years) of inhaled corticosteroid, plus an additional drug, usually a LABA, to consider the following interventions:

- increase the inhaled corticosteroid to a medium-dose (child 5–12 years) or high-dose (child over 12 years)—with high doses of inhaled corticosteroid via a pressurised metered dose inhaler (pMDI), a spacer should be used, or
- add a leukotriene receptor antagonist, or
- add modified-release theophylline p. 274, or
- add tiotropium p. 247 (in children over 12 years).

If a trial of a further add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose) and refer to specialist care.

Continuous or frequent use of oral corticosteroids

BTS/SIGN (2016) recommend adding a regular oral corticosteroid (prednisolone p. 678) at the lowest dose to provide adequate control (under specialist care) in children with very severe asthma uncontrolled on a medium dose (child 5–12 years) or high dose (child over 12 years) of inhaled corticosteroid, and who have also tried (or are still receiving) a LABA, a leukotriene receptor antagonist, or modified-release theophylline p. 274.

Monoclonal antibodies and immunosuppressants

BTS/SIGN (2016) recommend, that under specialist initiation, immunosuppressants such as methotrexate p. 913 [unlicensed], and monoclonal antibodies such as omalizumab p. 267 (child over 6 years for severe persistent allergic asthma) can be considered in children with severe asthma to achieve control and reduce the use of oral corticosteroids. See omalizumab p. 267 National funding/access decisions.

Child under 5 years

Intermittent reliever therapy

BTS/SIGN (2016) recommend that a short-acting beta2-agonist (such as salbutamol p. 252) as reliever therapy should be offered to children under 5 years with suspected asthma. A short-acting beta2-agonist should be used for symptom relief alongside maintenance treatment.

Children using more than one short-acting beta2-agonist inhaler device a month should have their asthma urgently assessed and action taken to improve poorly controlled asthma.

Regular preventer (maintenance) therapy

NICE (2017) define inhaled corticosteroid doses for children under 5 years as paediatric low or moderate. BTS/SIGN (2016) instead define inhaled corticosteroid doses for children under 5 years as very low (refer to individual guidelines for inhaled corticosteroid dosing information).

Consider an 8-week trial of a paediatric moderate dose of inhaled corticosteroid in children presenting with any of the following features: asthma-related symptoms three times a week or more, experiencing night-time awakening at least once a week, or suspected asthma that is uncontrolled with a short-acting beta2-agonist alone.

BTS/SIGN (2016) recommend the prescribing of inhalers by brand.

After 8 weeks, stop inhaled corticosteroid treatment and continue to monitor the child’s symptoms:

- if symptoms did not resolve during the trial period, review whether an alternative diagnosis is likely;
- if symptoms resolved then reoccurred within 4 weeks of stopping inhaled corticosteroid treatment, restart the inhaled corticosteroid at a paediatric low-dose as first-line maintenance therapy;
- if symptoms resolved but reoccurred beyond 4 weeks after stopping inhaled corticosteroid treatment, repeat the 8-week trial of a paediatric moderate dose of inhaled corticosteroid.

BTS/SIGN (2016) instead recommend starting a very low dose of inhaled corticosteroid as initial regular preventer therapy in children presenting with any one of the following features: using an inhaled short-acting beta2-agonist three times a week or more, symptomatic three times a week or more, or waking at night due to asthma symptoms at least once a week. In children unable to take an inhaled corticosteroid, a leukotriene receptor antagonist (such as montelukast p. 269) may be used as an alternative.

Initial add-on therapy

If suspected asthma is uncontrolled in children under 5 years on a paediatric low dose of inhaled corticosteroid as maintenance therapy, consider a leukotriene receptor antagonist (such as montelukast p. 269) in addition to the inhaled corticosteroid.

If suspected asthma is uncontrolled in children under 5 years on a paediatric low dose of inhaled corticosteroid and a leukotriene receptor antagonist as maintenance therapy, stop the leukotriene receptor antagonist and refer the child to an asthma specialist.

Decreasing treatment

Consider decreasing maintenance therapy when a patient’s asthma has been controlled with their current
maintenance therapy for at least three months. When deciding which drug to decrease first and at what rate, the severity of asthma, the side-effects of treatment, duration on current dose, the beneficial effect achieved, and the patient’s preference, should be considered. Patients should be regularly reviewed when decreasing treatment.

Patients should be maintained at the lowest possible dose of inhaled corticosteroid. Reductions should be considered every three months, decreasing the dose by approximately 25–50% each time. Reduce the dose slowly as patients deteriorate at different rates. Only consider stopping inhaled corticosteroid treatment completely for people who are using a paediatric or adult low dose inhaled corticosteroid alone as maintenance therapy and are symptom-free.

Exercise-induced asthma

For most patients, exercise-induced asthma is an illustration of poorly controlled asthma and regular treatment including inhaled corticosteroids should therefore be reviewed. If exercise is a specific problem in patients already taking inhaled corticosteroids who are otherwise well controlled, consider adding either a leukotriene receptor antagonist, a long-acting beta agonist, an oral beta agonist, sodium cromoglicate p. 270 or nedocromil sodium p. 270, or theophylline p. 274. An inhaled short-acting beta agonist, agonists used immediately before exercise is the drug of choice.

Pregnancy

Women with asthma should be closely monitored during pregnancy. It is particularly important that asthma be well controlled during pregnancy; when this is achieved there is little or no increased risk of adverse maternal or fetal complications.

Women should be counselled about the importance and safety of taking their asthma medication during pregnancy to maintain good control. Women who smoke should be advised about the dangers to themselves and to their baby and be offered appropriate support to stop smoking. For further information, see Smoking cessation p. 497.

Short-acting beta agonists, LABAs, oral and inhaled corticosteroids, sodium cromoglicate p. 270 and nedocromil sodium p. 270, and oral and intravenous theophylline p. 274 (with appropriate monitoring) can be used as normal during pregnancy. There is limited information on use of a leukotriene receptor antagonist during pregnancy, however, where indicated to achieve adequate control, they should not be withheld.

Advanced Pharmacy Services

Patients with asthma may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Useful Resources


www.getintopharma.com
have not had a good initial response to inhaled bronchodilator therapy [unlicensed use]. In an acute asthma attack, intravenous aminophylline p. 272 is not likely to produce any additional bronchodilation compared to standard therapy with inhaled bronchodilators and corticosteroids. However, in some patients with near-fatal or life-threatening acute asthma with a poor response to initial therapy, intravenous aminophylline may provide some benefit. Magnesium sulfate by intravenous infusion or aminophylline should only be used after consultation with, or on the recommendation of, senior medical staff.

**Child over 2 years**

**Levels of severity**

The nature of treatment required for the management of acute asthma depends on the level of severity, described as follows:

- **Mild acute asthma**
  - Able to talk in sentences
  - Arterial oxygen saturation (SpO₂) ≥ 92%
  - Peak flow > 50% best or predicted
  - Heart rate ≤ 140/minute in children aged 2–5 years; heart rate ≤ 125/minute in children over 5 years
  - Respiratory rate ≤ 40/minute in children aged 2–5 years; respiratory rate ≤ 30/minute in children over 5 years

- **Severe acute asthma**
  - Can’t complete sentences in one breath or too breathless to talk or feed
  - SpO₂ < 92%
  - Peak flow 33–50% best or predicted
  - Heart rate > 140/minute in children aged 2–5 years; heart rate > 125/minute in children over 5 years
  - Respiratory rate > 40/minute in children aged 2–5 years; respiratory rate > 30/minute in children over 5 years

- **Life-threatening acute asthma**
  - Any one of the following in a child with severe asthma:
    - SpO₂ < 92%
    - Peak flow < 33% best or predicted
    - Silent chest
    - Cyanosis
    - Poor respiratory effort
    - Hypotension
    - Exhaustion
    - Confusion

**Management**

Following initial assessment, supplementary high flow oxygen should be given to all children with life-threatening acute asthma or SpO₂ < 94% to achieve normal saturations of 94–98%.

First-line treatment for acute asthma is an inhaled short-acting beta₂ agonist (salbutamol or terbutaline sulfate) given as soon as possible, ideally via a metered-dose inhaler and spacer device in mild to moderate acute asthma. Children with severe or life-threatening acute asthma should be transferred to hospital urgently.

In all cases of acute asthma, children should be prescribed an adequate once daily dose of oral prednisolone. Treatment for up to 3 days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. Intravenous hydrocortisone should be reserved for severely affected children who are unable to retain oral medication.

Nebulised ipratropium bromide can be combined with beta₂ agonist treatment for children with severe or life-threatening acute asthma or in those with a poor initial response to beta₂ agonist therapy to provide greater bronchodilation. Consider adding magnesium sulfate to nebulised salbutamol and ipratropium bromide in the first hour in children with a short duration of acute severe asthma symptoms presenting with an oxygen saturation less than 92%.

Children with continuing severe asthma despite frequent nebulised beta₂ agonists and ipratropium bromide plus oral corticosteroids, and those with life-threatening features, need urgent review by a specialist with a view to transfer to a high dependency unit or paediatric intensive care unit (PICU) to receive second-line intravenous therapies.

In a severe asthma attack where the child has not responded to initial inhaled therapy, early addition of a single bolus dose of intravenous salbutamol may be an option. Continuous intravenous infusion of salbutamol, administered under specialist supervision with continuous ECG and electrolyte monitoring, should be considered in children with unreliable inhalation or severe refractory asthma. Aminophylline may be considered in children with severe or life-threatening acute asthma unresponsive to maximal doses of bronchodilators and corticosteroids. Aminophylline is not recommended in children with mild to moderate acute asthma. Intravenous magnesium sulfate p. 1051 has been used for acute asthma [unlicensed use] although its place in management is not yet established.

**Child under 2 years**

- **Inhaled short-acting beta₂ agonists** are the initial treatment of choice for acute asthma in children under 2 years. For mild to moderate acute asthma attacks, a metered-dose inhaler with a spacer and mask is the optimal drug delivery device.

**Follow up in all cases**

- **Episodes of acute asthma** may be a failure of preventative therapy. Review is required to prevent further episodes. A careful history should be taken to establish the reason for the asthma attack. Inhaler technique should be checked and regular treatment should be reviewed. Patients should be given a written asthma action plan aimed at preventing relapse, optimising treatment, and preventing delay in seeking assistance in future attacks. It is essential that the patient’s GP practice is informed within 24 hours of discharge from the emergency department or hospital following an asthma attack. Patients who have had a near-fatal asthma attack should be kept under specialist supervision indefinitely. A respiratory specialist should follow up all patients admitted with a severe asthma attack for at least one year after the admission.

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**Bronchodilators**

**Adrenoceptor agonists (sympathomimetics)**

Selective beta₂ agonists produce bronchodilation. A short-acting beta₂ agonist (such as salbutamol p. 252 and terbutaline sulfate p. 255) is used for immediate relief of asthma symptoms while some long-acting beta₂ agonists are added to an inhaled corticosteroid in patients requiring prophylactic treatment.

Adrenaline/epinephrine p. 222 (which has both alpha- and beta-adrenoceptor agonist properties) is used in the emergency management of acute allergic and anaphylactic reactions, in angioedema, in cardiopulmonary resuscitation, and in the management of severe croup.

**Long-acting beta₂ agonists**

Formoterol fumarate p. 250 and salmeterol p. 252 are longer-acting beta₂ agonists which are administered by inhalation. They should be used for asthma only in patients who regularly use an inhaled corticosteroid.
Combination inhalers that contain a long-acting β₂ agonist and a corticosteroid ensure that long-acting β₂ agonists are not used without concomitant corticosteroids. Indacaterol p. 251 and olodaterol p. 251 are long-acting β₂ agonists licensed for chronic obstructive pulmonary disease in adults; they are not indicated for the relief of acute bronchospasm.

Vilanterol is a long-acting β₂ agonist, agonist available only in a combination inhaler with fluticasone furoate or/and with umeclidinium p. 249.

**Oral**

Oral preparations of β₂ agonists may be used by patients who cannot manage the inhaled route. They are sometimes used for children and the elderly, but inhaled β₂ agonists are more effective and have fewer side-effects. The longer-acting oral preparations, including bamberterol hydrochloride p. 250, may be of value in nocturnal asthma but they have a limited role and inhaled long-acting β₂ agonists are usually preferred.

**Parenteral**

Salmeterol or terbutaline sulfate can be given intravenously for severe or life-threatening acute asthma; patients should be carefully monitored and the dose adjusted according to response and heart rate. The regular use of β₂ agonists by the subcutaneous route is not recommended since the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started. In adults, β₂ agonists may also be given by intramuscular injection.

**Children**

A pressurised metered-dose inhaler should be used with a spacer device in children under 5 years. A β₂ agonist may also be given by mouth but administration by inhalation is preferred; a long-acting inhaled β₂ agonist may be used where appropriate. In severe attacks nebulisation using a selective β₂ agonist or ipratropium bromide p. 246 is advisable.

**Antimuscarinic bronchodilators**

Ipratropium bromide can provide short-term relief in chronic asthma, but short-acting β₂ agonists act more quickly and are preferred. Ipratropium bromide by nebulisation can be added to other standard treatment in life-threatening asthma or if acute asthma fails to improve with standard therapy. The aerosol inhalation of ipratropium bromide can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Its maximal effect occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Acicline bromide p. 245, glycopyrronium bromide p. 246, tiotropium p. 247, and umeclidinium p. 249 are licensed for the maintenance treatment of adults with chronic obstructive pulmonary disease. They are not suitable for the relief of acute bronchospasm.

**Theophylline**

Theophylline p. 274 is a xanthine used as a bronchodilator in asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. Theophylline may have an additive effect when used in conjunction with small doses of β₂ agonists; the combination may increase the risk of side-effects, including hypokalaemia.

Theophylline is given by injection as aminophylline p. 272, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe acute asthma.

**Compound bronchodilator preparations**

In general, patients are best treated with single-ingredient preparations, such as a selective β₂ agonist or ipratropium bromide, so that the dose of each drug can be adjusted. However, a combination product may be appropriate for patients stabilised on individual components in the same proportion.

**Chronic obstructive pulmonary disease**

**Management**

Smoking cessation p. 497 reduces the progressive decline in lung function in chronic obstructive pulmonary disease (COPD, chronic bronchitis, or emphysema). Infection can complicate chronic obstructive pulmonary disease and may be prevented by vaccination (pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1316 and influenza vaccine p. 1322).

A trial of a high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate or severe airflow obstruction in the absence of doubt. Symptoms of chronic obstructive pulmonary disease may be alleviated by an inhaled short-acting β₂ agonist or a short-acting antimuscarinic bronchodilator used as required.

When the airflow obstruction is more severe, regular inhaled therapy should be used. It is important to check compliance and inhaler technique before initiating a new drug.

If the Forced Expiratory Volume in 1 second (FEV₁), is 50% of predicted or more, either a long-acting antimuscarinic bronchodilator or a long-acting β₂ agonist should be used. Short-acting antimuscarinic bronchodilators should be discontinued when a long-acting antimuscarinic bronchodilator is started. A long-acting β₂ agonist with a corticosteroid in a combination inhaler can be used for patients who remain symptomatic despite regular treatment with a long-acting β₂ agonist.

If FEV₁ is less than 50% of predicted, either a long-acting antimuscarinic bronchodilator or a long-acting β₂ agonist, with a corticosteroid in a combination inhaler should be used.

In any patient who remains breathless or continues to have exacerbations, triple therapy with a long-acting β₂ agonist and a corticosteroid in a combination inhaler plus a long-acting antimuscarinic bronchodilator should be used. If an inhaled corticosteroid is not appropriate, a long-acting antimuscarinic bronchodilator can be used with a long-acting β₂ agonist, (see Use of inhaled therapies in chronic obstructive pulmonary disease algorithm, below).

If symptoms persist or if the patient is unable to use an inhaler, oral modified-release aminophylline p. 272 or theophylline p. 274 can be used.

Indacaterol p. 251 is a long-acting β₂ agonist licensed for the maintenance treatment of chronic obstructive pulmonary disease.

In patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations, rolflumilast p. 271 is licensed as an adjunct to existing bronchodilator treatment.

A mucolytic drug may be considered for a patient with a chronic productive cough.

Long-term oxygen therapy prolongs survival in patients with severe chronic obstructive pulmonary disease and hypoxaemia.

During an exacerbation of chronic obstructive pulmonary disease, bronchodilator therapy can be administered through a nebuliser if necessary and oxygen given if appropriate.
Aminophylline can be given intravenously if response to nebulised bronchodilators is poor. A short course of oral corticosteroid, such as prednisolone for 7–14 days, should be given if increased breathlessness interferes with daily activities. Antibacterial treatment is required if sputum becomes more purulent than usual, or if there are other signs of infection. Patients who have had an episode of hypercapnic respiratory failure should be given a 24% or 28% Venturi mask and an oxygen alert card endorsed with the oxygen saturations required during previous exacerbations. Patients and their carers should be instructed to show the card to emergency healthcare providers in the event of an exacerbation.

Oxygen alert card based on British Thoracic Society guideline for emergency oxygen use in adult patients (October 2008)

Oxygen alert card

Name:

I am at risk of type II respiratory failure with a raised CO₂ level.

Please use my ____% Venturi mask to achieve an oxygen saturation of ____% to ____% during exacerbations.

Use compressed air to drive nebulisers (with nasal oxygen at 2 litres/minute). If compressed air not available, limit oxygen-driven nebulisers to 6 minutes.

Use compressed air to drive nebulisers (with nasal oxygen at 2 litres/minute). If compressed air not available, limit oxygen-driven nebulisers to 6 minutes.

Oxygen alert card is available at www.brit-thoracic.org.uk.

Advanced Pharmacy Services

Patients with chronic obstructive pulmonary disease may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Oxygen

Overview

Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; the administration of an inappropriate concentration of oxygen can have serious or even fatal consequences. Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near-normal oxygen saturation; in most acutely ill patients with a normal or low arterial carbon dioxide (P₂CO₂), oxygen saturation should be 94–98% oxygen saturation. However, in some clinical situations such as cardiac arrest and carbon monoxide poisoning it is more appropriate to aim for the highest possible oxygen saturation until the patient is stable. A lower target of 88–92% oxygen saturation is indicated for patients at risk of hypercapnic respiratory failure. High concentration oxygen therapy is safe in uncomplicated cases of conditions such as pneumonia, pulmonary thromboembolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions low arterial oxygen (P₅O₂) is usually associated with low or normal arterial carbon dioxide (P₂CO₂), and therefore there is little risk of hypoventilation and carbon dioxide retention.

In acute severe asthma, the arterial carbon dioxide (P₂CO₂) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide (P₂CO₂) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients at risk of hypercapnic respiratory failure, which is more likely in those with:

- chronic obstructive pulmonary disease;
- advanced cystic fibrosis;
- severe non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target oxygen saturation of 88–92%. The aim is to provide the patient with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis. Patients may carry an oxygen alert card.

Domiciliary oxygen

Oxygen should only be prescribed for use in the home after careful evaluation in hospital by respiratory experts. Patients should be advised of the risks of continuing to smoke when receiving oxygen therapy, including the risk of fire. Smoking cessation therapy p. 497 should be recommended before home oxygen prescription.

Air travel

Some patients with arterial hypoxaemia require supplementary oxygen for air travel. The patient’s requirement should be discussed with the airline before travel.

Long-term oxygen therapy

Long-term administration of oxygen (usually at least 15 hours daily) prolongs survival in some patients with chronic obstructive pulmonary disease. Assessment for long-term oxygen therapy requires measurement of arterial blood gas tensions. Measurements should be taken on 2 occasions at least 3 weeks apart to demonstrate clinical stability, and not sooner than 4 weeks after an acute exacerbation of the disease. Long-term oxygen therapy should be considered for patients with:

- chronic obstructive pulmonary disease with P₂O₂<7.3 kPa when breathing air during a period of clinical stability;
- chronic obstructive pulmonary disease with P₂O₂ 7.3–8 kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, peripheral oedema, or evidence of pulmonary hypertension;
- severe chronic asthma with P₂O₂<7.3 kPa or persistent disabling breathlessness;
- interstitial lung disease with P₂O₂<8 kPa and in patients with P₂O₂>8 kPa with disabling dyspnoea;
- cystic fibrosis when P₂O₂<7.3 kPa or if P₂O₂ 7.3–8 kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, pulmonary hypertension, or peripheral oedema;
- pulmonary hypertension, without parenchymal lung involvement when P₂O₂<8 kPa;
- neuromuscular or skeletal disorders, after specialist assessment;
- obstructive sleep apnoea despite continuous positive airways pressure therapy, after specialist assessment;

In acute severe asthma, the arterial carbon dioxide (P₂CO₂) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide (P₂CO₂) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.
Use of inhaled therapies in chronic obstructive pulmonary disease

Breathlessness and exercise limitation

<table>
<thead>
<tr>
<th>FEV₁ ≥ 50%</th>
<th>FEV₁ &lt; 50%</th>
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<tbody>
<tr>
<td>Long-acting β₂ agonist</td>
<td>Long-acting β₂ agonist plus inhaled corticosteroid</td>
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<td>Long-acting muscarinic antagonist (may continue at all stages) in a combination inhaler</td>
<td>Long-acting β₂ agonist plus inhaled corticosteroid (may continue at all stages) in a combination inhaler</td>
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<tr>
<td>Discontinue short-acting muscarinic antagonist or long-acting muscarinic antagonist four times a day</td>
<td>Consider long-acting β₂ agonist plus long-acting muscarinic antagonist if inhaled corticosteroid declined or not tolerated</td>
</tr>
</tbody>
</table>

Exacerbations or persistent breathlessness

<table>
<thead>
<tr>
<th>Persistent exacerbations or breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting β₂ agonist plus inhaled corticosteroid in a combination inhaler</td>
</tr>
<tr>
<td>Consider long-acting β₂ agonist plus long-acting muscarinic antagonist if inhaled corticosteroid declined or not tolerated</td>
</tr>
</tbody>
</table>

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for patients on long-term oxygen therapy who need to be away from home on a regular basis. Patients who are not on long-term oxygen therapy can be considered for ambulatory oxygen therapy if there is evidence of exercise-induced oxygen desaturation and of improvement in blood oxygen saturation and exercise capacity with oxygen. Ambulatory oxygen therapy is not recommended for patients with heart failure or those who smoke.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as oxygen cylinders. Oxygen flow can be adjusted as the cylinders are equipped with an oxygen flow meter with ‘medium’ (2 litres/minute) and ‘high’ (4 litres/minute) settings. Oxygen delivered from a cylinder should be passed through a humidifier if used for long periods.

Oxygen concentrators are more economical for patients who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis. A concentrator is recommended for a patient who

- pulmonary malignancy or other terminal disease with disabling dyspnoea;
- heart failure with daytime PaO₂ < 7.3 kPa when breathing air or with nocturnal hypoaxaemia;
- paediatric respiratory disease, after specialist assessment.

Increased respiratory depression is seldom a problem in patients with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occur.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness not relieved by other treatment in patients with severe chronic obstructive pulmonary disease, interstitial lung disease, heart failure, and in palliative care. It is important, however, that the patient does not rely on oxygen instead of obtaining medical help or taking more specific treatment. Short-burst oxygen therapy can be used to improve exercise capacity and recovery; it should only be continued if there is proven improvement in breathlessness or exercise tolerance.

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requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a ‘Y’ connection.

A nasal cannula is usually preferred for long-term oxygen therapy from an oxygen concentrator. It can, however, produce dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the patient to talk, eat, and drink, but the concentration of oxygen is not controlled; this may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the patient is underventilating.

Arrangements for supplying oxygen
The following oxygen services may be ordered in England and Wales:
- emergency oxygen;
- short-burst (intermittent) oxygen therapy;
- long-term oxygen therapy;
- ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The clinician will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the patient or carers consent, to pass on the patient’s details to the supplier, the fire brigade, and other relevant organisations. The supplier will contact the patient to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the patient or carer to use the equipment.

The clinician should send the HOOF to the supplier who will continue to provide the service until a revised HOOF is received, or until notified that the patient no longer requires the home oxygen service.

- East of England, North East: BOC Medical: Tel: 0800 136 603 Fax: 0800 169 9989
- South West: Air Liquide: Tel: 0808 202 2229 Fax: 0191 497 4340
- London, East Midlands, North West: Air Liquide: Tel: 0800 823 773 Fax: 0800 781 4610
- Yorkshire and Humberside, West Midlands, Wales: Air Products: Tel: 0800 373 580 Fax: 0800 264 709
- South East Coast, South Central: Dolby Vivosol: Tel: 0843 814 402 Fax: 0800 781 4610

In Scotland refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. Prescribers should complete a Scottish Home Oxygen Order Form (SHOOF) and email it to Health Facilities Scotland. Health Facilities Scotland will then liaise with their consultant to arrange the supply of oxygen. Further information can be obtained at: www.dolbyvivosol.com/our-services/healthcare-professionals/home-oxygen-services-sco.aspx.

In Northern Ireland oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. Prescriptions for oxygen cylinders and accessories can be dispensed by pharmacists contracted to provide domiciliary oxygen services.

Croup
Management
Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. dexamethasone p. 675) by mouth may be of benefit.

More severe croup (or mild croup that might cause complications) calls for hospital admission; a single dose of a corticosteroid (e.g. dexamethasone or prednisolone p. 678 by mouth) should be administered before transfer to hospital. In hospital, dexamethasone (by mouth or by injection) or budesonide p. 260 (by nebulisation) will often reduce symptoms; the dose may need to be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline/epinephrine p. 222 solution 1 in 1000 (1 mg/mL) should be given with close clinical monitoring; the effects of nebulised adrenaline/epinephrine last 2–3 hours and the child needs to be monitored carefully for recurrence of the obstruction.

Antimuscarinics
Antimuscarinics (inhaled)

**Indications and dose**

Maintenance treatment of chronic obstructive pulmonary disease
- **By inhalation of powder**
  - Adult: 375 micrograms twice daily
- **Dose equivalence and conversion**
  - Each 375 microgram inhalation of aclidinium bromide delivers 322 micrograms of aclidinium.

**CAUTIONS**

- Arrhythmia (when newly diagnosed within last 12 months)
- Arrhythmia (when newly diagnosed within last 6 months)
- Arrhythmia (when newly diagnosed within last 3 months)
- Heart failure (hospitalisation with moderate or severe heart failure within last 12 months)
- Myocardial infarction within last 6 months
- Unstable angina
- Hypersensitivity
- Diarrhoea - nasopharyngitis
- Angioedema
- Rare or very rare
- Breastfeeding
- Patients or carers should be given advice on appropriate inhaler technique.

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**

- Eklira (AstraZeneca UK Ltd) 🔗
  - Aclidinium bromide 375 microgram per 1 dose Eklira
  - 322 micrograms/dose Genair
  - 80 dose pack £32.50 27 = £32.50

[www.getintopharma.com](http://www.getintopharma.com)
Acidimium bromide with formoterol

19-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, acidimium bromide p. 245, formoterol fumarate p. 250.

**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**INDICATIONS AND DOSE**

- Maintenance treatment of chronic obstructive pulmonary disease
  - By Inhalation of Powder

**CAUTIONS**

- Convulsive disorders · phaeochromocytoma

**INTERACTIONS**

-> Appendix 1: acidimium · beta, agonists

**PATIENT AND CARER ADVICE**

- Patients or carers should be given advice on appropriate inhaler technique.

**INHALATION POWDER**

- **Duakir** (AstraZeneca UK Ltd) ▼
  - Formoterol fumarate dihydrate 11.8 microgram per 1 dose, Acidimium bromide 396 microgram per 1 dose Duakir 340micrograms/dose / 12micrograms/dose Genuair | 60 dose [POM] £32.50 DT = £32.50

Glycopyrronium bromide (Glycopyrrolate)

13-Sep-2017

**INDICATIONS AND DOSE**

- Maintenance treatment of chronic obstructive pulmonary disease
  - By Inhalation of Powder
  - Adult: 1 capsule once daily

**DOSE EQUIVALENCE AND CONVERSION**

- Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium).

**CAUTIONS**

- Arrhythmia (excluding chronic stable atrial fibrillation) · history of myocardial infarction · history of QT-interval prolongation · left ventricular failure · unstable ischaemic heart disease

**SIDE-EFFECTS**

- Common or very common · Increased risk of infection · insomnia · pain

- Uncommon · Asthenia · cystitis · dental caries · dyspepsia · epistaxis · hyperglycaemia · hypersensitivity · numbness · respiratory disorders · throat irritation

**PREGNANCY**

- Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

- Manufacturer advises use only if potential benefit outweighs risk.

**RENAL IMPAIRMENT**

- Manufacturer advises use only if potential benefit outweighs risk if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

- Patients or carers should be given advice on appropriate inhaler technique.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**INHALATION POWDER**

- **Seebri Breezhaler** (Novartis Pharmaceuticals UK Ltd)
  - Glycopyrronium bromide 54 microgram per 1 dose, Indacaterol (as Indacaterol maleate) 85 microgram per 1 dose Seebri Breezhaler 85microgram/43microgram inhalation powder capsules with device | 10 capsule [POM] £10.83 DT = £10.83 | 30 capsule [POM] £32.50 DT = £32.50

Glycopyrronium with indacaterol

17-Feb-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, glycopyrronium bromide above, indacaterol p. 251.

**INDICATIONS AND DOSE**

- Maintenance treatment of chronic obstructive pulmonary disease
  - By Inhalation of Powder
  - Adult: 1 inhalation daily

**CAUTIONS**

- Convulsive disorders

**INTERACTIONS**

-> Appendix 1: beta, agonists · glycopyrronium

**PATIENT AND CARER ADVICE**

- Patients or carers should be given advice on appropriate inhaler technique and reminded that the capsules are not for oral administration.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**INHALATION POWDER**

- **Ultibro Breezhaler** (Novartis Pharmaceuticals UK Ltd) ▼
  - Glycopyrronium bromide 54 microgram per 1 dose, Indacaterol (as Indacaterol maleate) 85 microgram per 1 dose Ultibro Breezhaler 85microgram/43microgram inhalation powder capsules with device | 10 capsule [POM] £10.83 DT = £10.83 | 30 capsule [POM] £32.50 DT = £32.50

Ipratropium bromide

25-Jul-2018

**INDICATIONS AND DOSE**

- Reversible airways obstruction
  - By Inhalation of Aerosol

- Child 1 month-5 years: 20 micrograms 3 times a day
- Child 6-11 years: 20–40 micrograms 3 times a day
- Child 12-17 years: 20–40 micrograms 3–4 times a day

- Reversible airways obstruction, particularly in chronic obstructive pulmonary disease
  - By Inhalation of Aerosol

- Adult: 20–40 micrograms 3–4 times a day

**INHALATION SOLUTION**

- By Inhalation of Nebulised Solution

- Child 1 month-5 years: 125–250 micrograms as required; maximum 1 mg per day
- Child 6-11 years: 250 micrograms as required; maximum 1 mg per day
- Child 12-17 years: 500 micrograms as required, doses higher than max. can be given under medical supervision; maximum 2 mg per day
- Adult: 500 micrograms as required, doses higher than max. can be given under medical supervision; maximum 2 mg per day

www.getintopharma.com
### Airways disease, obstructive 247

#### Atrovent

Atrovent 250 micrograms/1ml nebuliser liquid UDVs | 20 unit dose [P33] £14.14 DT + £4.90

### Pressurised inhalation

- **Atrovent** (Boehringer Ingelheim Ltd)
  - Ipratropium bromide 20 microgram per 1 dose
  - Ipratropium bromide 20 micrograms/dose inhaler CFC free | 200 dose [P32] £5.56 DT + £5.56

- **Inhalvent** (Alissia Healthcare Research Ltd)
  - Ipratropium bromide 20 micrograms/dose inhaler | 200 dose [P33] £5.56 DT + £5.56

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#### Ipratropium with salbutamol

**The properties listed below are those particular to the combination only. For the properties of the components please consider, ipratropium bromide p. 246, salbutamol p. 252.**

### Indications and dose

**Bronchospasm in chronic obstructive pulmonary disease**

- **By inhalation of nebulised solution**
- **Adult:** 0.5/2.5 mg 3–4 times a day

### Interactions

- **Appendix 1:** beta, agonists - ipratropium

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#### Nebuliser liquid

- **Combivent** (Boehringer Ingelheim Ltd)
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulphate) 1 mg per 1 ml
  - Combivent nebuliser liquid 2.5ml UDVs | 60 unit dose [P32] £24.10 DT + £24.10

- **Ipramol** (Teva UK Ltd)
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulphate) 1 mg per 1 ml
  - Ipramol nebuliser solution 2.5ml Steri-Neb unit dose vials | 60 unit dose [P33] £23.83 DT + £24.10

### Tiotropium

**Maintenance treatment of chronic obstructive pulmonary disease**

- **By inhalation of powder**
- **Adult:** 1 capsule once daily

### Dose equivalence and conversion

- For Spiriva® inhalation powder, 1 capsule contains a metered dose of 18 micrograms tiotropium; for Braltau® inhalation powder, 1 capsule contains a metered dose of 13 micrograms tiotropium.
- The delivered dose of Spiriva® and Braltau® inhalation powder products are the same (10 micrograms); no dose adjustment is necessary when switching between brands.

**Spiriva Respimat®**

**Maintenance treatment of chronic obstructive pulmonary disease:** Severe asthma [add-on to inhaled corticosteroid (at least 500 micrograms budesonide daily or equivalent) and at least 1 controller in patients who have suffered one or more severe exacerbations in the last year]

- **By inhalation of aerosol**
- **Adult:** 5 micrograms once daily (continued)

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[www.getintopharma.com](http://www.getintopharma.com)
Severe asthma [add-on to inhaled corticosteroid (over 400 micrograms budesonide daily or equivalent) and 1 controller, or inhaled corticosteroid (200–400 micrograms budesonide daily or equivalent) and 2 controllers, in patients who have suffered one or more severe exacerbations in the last year]

- By inhalation of aerosol
- Child 6–11 years: 5 micrograms once daily
- Severe asthma [add-on to inhaled corticosteroid (over 800 micrograms budesonide daily or equivalent) and 1 controller, or inhaled corticosteroid (400–800 micrograms budesonide daily or equivalent) and 2 controllers, in patients who have suffered one or more severe exacerbations in the last year]

- By inhalation of aerosol
- Child 12–17 years: 5 micrograms once daily

Dose equivalence and conversion
- For Spiriva Respimat®: 2 puffs is equivalent to 5 micrograms tiotropium.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
SMC No. 1028/15
- In adults The Scottish Medicines Consortium has advised (August 2015) that tiotropium (Spiriva Respimat®) is accepted for use within NHS Scotland as add-on maintenance bronchodilator treatment in adults with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 micrograms budesonide/day or equivalent) and long-acting β₂-agonists and who experienced one or more severe exacerbations in the previous year.
SMC No. 411/07
- In adults The Scottish Medicines Consortium has advised (December 2017) that tiotropium (Spiriva Respimat®) is accepted for use within NHS Scotland as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease.
SMC No. SMC2118
- The Scottish Medicines Consortium has advised (January 2019) that tiotropium (Spiriva Respimat®) is accepted for use within NHS Scotland as add-on maintenance bronchodilator treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the preceding year.

All Wales Medicines Strategy Group (AWMSG) decisions
AWMSG No. 1882
The All Wales Medicines Strategy Group has advised (December 2018) that tiotropium (Spiriva Respimat®) is recommended as an option for use within NHS Wales as add-on maintenance bronchodilator treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the preceding year.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder
- Braltus®
  - Tiotropium (as tiotropium bromide) 10 microgram Braltus 10 microgram inhalation powder capsules with Zonda inhaler | 30 capsule £25.80 DT = £25.80
  - Spiriva®

Pressurised inhalation
- Spiriva Respimat (Boehringer Ingelheim Ltd)
  - Tiotropium (as tiotropium bromide) 2.5 microgram per 1 dose Spiriva Respimat 2.5 micrograms/dose solution for inhalation cartridge with device | 60 dose £23.00 DT = £23.00

Tiotropium with olodaterol
15-Feb-2016
The properties listed below are those particular to the combination only. For the properties of the components please consider, tiotropium p. 247, olodaterol p. 251.

INDICATIONS AND DOSE
Maintenance treatment of chronic obstructive pulmonary disease
- By inhalation of aerosol
- Adult: 2 puffs once daily

INTERACTIONS
- Appendix 1: β₂-agonists · tiotropium

PATIENT AND CARER ADVISE
Patients or carers should be given advice on appropriate inhaler technique.
Umeclidinium

- **INDICATIONS AND DOSE**
  Maintenance treatment of chronic obstructive pulmonary disease
  - **BY INHALATION OF POWDER**
    - Adult: 55 micrograms once daily

- **DOSE EQUIVALENCE AND CONVERSION**
  Each 65 microgram inhalation of umclidinium bromide delivers 55 micrograms of umclidinium.

- **CAUTIONS**
  Cardiac disorders (particularly cardiac rhythm disorders)

- **INTERACTIONS** → Appendix 1: umclidinium

- **SIDE-EFFECTS**
  - Uncommon
  - Rare or very rare
  - Combined use or excess dosage

- **PREGNANCY**
  Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING**
  Manufacturer advises avoid — no information available.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in severe impairment (no information available).

- **PATIENT AND CARER ADVICE**
  Patient or carers should be given advice on appropriate inhaler technique.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

1. **Inhalation powder**
   - Umeclidinium with vilanterol (non-proprietary)
     - Vilanterol (as Vilanterol trifenatate) 22 microgram per 1 dose,
     - Umeclidinium bromide 65 microgram per 1 dose
   - Anoro Ellipta (GlaxoSmithKline UK Ltd)
     - Vilanterol (as Vilanterol trifenatate) 22 microgram per 1 dose,
     - Umeclidinium bromide 65 microgram per 1 dose

**BETA_2-ADRENOCEPTOR AGONISTS, SELECTIVE**

**Beta_2- adrenoceptor agonists, selective**

- **CONTRA-INDICATIONS**
  Severe pre-eclampsia

- **CAUTIONS**
  Arrhythmias - cardiovascular disease - diabetes
  (risk of hyperglycaemia and ketoadiposis, especially with intravenous use) - hypertension - hyperthyroidism - hypokalaemia - susceptibility to QT-interval prolongation

- **MONITORING REQUIREMENTS**
  In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).

- **PATIENT AND CARER ADVICE**
  Patient or carers should be given advice on appropriate inhaler technique.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**
- Umeclidinium with vilanterol (non-proprietary)
  - Vilanterol (as Vilanterol trifenatate) 22 microgram per 1 dose,
  - Umeclidinium bromide 65 microgram per 1 dose
- Anoro Ellipta (GlaxoSmithKline UK Ltd)
  - Vilanterol (as Vilanterol trifenatate) 22 microgram per 1 dose,
  - Umeclidinium bromide 65 microgram per 1 dose

**Umeclidinium with vilanterol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, umclidinium above.

- **INDICATIONS AND DOSE**
  Maintenance treatment of chronic obstructive pulmonary disease
  - **BY INHALATION OF POWDER**
    - Adult: 1 inhalation once daily

- **CONTRA-INDICATIONS**
  Severe pre-eclampsia

- **CAUTIONS**
  Arrhythmias - cardiovascular disease - diabetes
  (risk of hyperglycaemia and ketoadiposis, especially with intravenous use) - hypertension - hyperthyroidism - hypokalaemia - susceptibility to QT-interval prolongation

- **MONITORING REQUIREMENTS**
  In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).

- **PATIENT AND CARER ADVICE**
  Patient or carers should be advised to seek medical advice when the prescribed dose of beta_2 agonist fails to provide the usual degree of symptomatic relief.
Airways disease, obstructive

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BETA2-ADRENOCEPTOR AGONISTS, SELECTIVE ▶ LONG-ACTING

Bambuterol hydrochloride

05-Jun-2018

DRUG ACTION Bambuterol is a pro-drug of terbutaline.

INDICATIONS AND DOSE

Asthma (patients who have previously tolerated beta2-agonists) | Other conditions associated with reversible airways obstruction (patients who have previously tolerated beta2-agonists)

- BY MOUTH
  - Adult: 20 mg once daily, dose to be taken at bedtime

Asthma (patients who have not previously tolerated beta2-agonists) | Other conditions associated with reversible airways obstruction (patients who have not previously tolerated beta2-agonists)

- BY MOUTH
  - Adult: Initially 10 mg once daily for 1–2 weeks, then increased if necessary to 20 mg once daily, dose to be taken at bedtime

INTERACTIONS ▶ Appendix 1: beta2 agonists

SIDE-EFFECTS

- Common or very common: Anxiety, behaviour abnormal, muscle cramps, sleep disorder
- Frequency not known: Akathisia, angioedema, bronchospasm, circulatory collapse, hypersensitivity, hypotension, skin reactions

PREGNANCY

Manufacturer advises avoid—no information available.

BREAST FEEDING

Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises avoid in severe impairment or cirrhosis (risk of unpredictable conversion to terbutaline; direct terbutaline use preferred).

RENAL IMPAIRMENT

Dose adjustments Reduce initial dose by half if eGFR less than 50 mL/minute/1.73 m².

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- **Bambec** (AstraZeneca UK Ltd)
  - Bambuterol hydrochloride 10 mg Bambec 10mg tablets | 30 tablet [PDF] £5.99 DT + £3.99

Formoterol fumarate
(Eformoterol fumarate)

INDICATIONS AND DOSE

Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy | Nighttime asthma in patients requiring long-term regular bronchodilator therapy | Prophylaxis of exercise-induced bronchospasm in patients requiring long-term regular bronchodilator therapy | Chronic asthma in patients who regularly use an inhaled corticosteroid

- BY INHALATION OF POWDER
- Child 6–11 years: 12 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
  - Child 12–17 years: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
- Adult: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

- BY INHALATION OF AEROSOL
- Child 12–17 years: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily, a daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose
- Adult: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- BY INHALATION OF POWDER
- Adult: 12 micrograms twice daily
- Adult: 12 micrograms twice daily (max. per dose 24 micrograms), for symptom relief additional doses may be taken to maximum daily dose; maximum 48 micrograms per day

PHARMACOKINETICS

At recommended inhaled doses, the duration of action of formoterol is about 12 hours.

OXIS ®

CHRONIC ASTHMA

- BY INHALATION OF POWDER
- Child 6–17 years: 6–12 micrograms 1–2 times a day (max. per dose 12 micrograms), occasionally doses up to the maximum daily may be needed, reassess treatment if additional doses required on more than 2 days a week; maximum 48 micrograms per day
- Adult: 6–12 micrograms 1–2 times a day, increased if necessary up to 24 micrograms twice daily (max. per dose 36 micrograms), occasionally doses up to the maximum daily may be needed, reassess treatment if additional doses required on more than 2 days a week; maximum 72 micrograms per day

RELIEF OF BRONCHOSPASM

- BY INHALATION OF POWDER
- Child 6–17 years: 6–12 micrograms
- Adult: 6–12 micrograms

PROPHYLAXIS OF EXERCISE-INDUCED BRONCHOSPASM

- BY INHALATION OF POWDER
- Child 6–17 years: 6–12 micrograms, dose to be taken before exercise
- Adult: 12 micrograms, dose to be taken before exercise

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- BY INHALATION OF POWDER
- Adult: 12 micrograms 1–2 times a day (max. per dose 24 micrograms), for symptom relief additional doses up to maximum daily dose can be taken; maximum 48 micrograms per day

IMPORTANT SAFETY INFORMATION

CHM ADVICE

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta2 agonist (formoterol) should:
Indacaterol

Indications and Dose

Maintenance treatment of chronic obstructive pulmonary disease

By inhalation of powder

Adult: 150 micrograms once daily, then increased to 300 micrograms once daily.

Caution

Convulsive disorders

Interactions

Appendix 1: beta, agonists

Side-effects

Common or very common
- Chest pain
- Cough
- Increased risk of infection
- Muscle complaints
- Oropharyngeal pain
- Peripheral oedema
- Rhinorrhoea
- Throat irritation

Common
- Diabetes mellitus
- Hypersensitivity
- Musculoskeletal pain
- Paraesthesia
- Skin reactions

Pregnancy

Manufacturer advises use only if potential benefit outweighs risk.

Breast feeding

Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment

Use with caution in severe impairment—no information available.

Patient and carer advice

Patients or carers should be given advice on how to administer indacaterol inhalation powder.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder

- Easyhaler (formoterol) (Orion Pharma (UK) Ltd)
  - Formoterol fumarate dihydrate 12 microgram per 1 dose
  - 246.00
  - Formoterol fumarate dihydrate 24 microgram per 1 dose
  - 492.00

- Foradil (Novartis Pharmaceuticals UK Ltd)
  - Formoterol fumarate dihydrate 12 microgram per 1 dose
  - 246.00

- Oxis Turbohaler (AstraZeneca UK Ltd)
  - Formoterol fumarate dihydrate 6 microgram per 1 dose
  - 120 capsule (POD) £23.75 DT = £23.75
  - Formoterol fumarate dihydrate 12 microgram per 1 dose
  - 60 capsule (POD) £28.06 DT = £28.06

- Atimos Modulite (Chiesi Ltd)
  - Formoterol fumarate dihydrate 12 microgram per 1 dose
  - 100 dose (POD) £30.06 DT = £30.06

Combination available: Glycopyrronium with indacaterol, p. 246

Olodaterol

Indications and Dose

Maintenance treatment of chronic obstructive pulmonary disease

By inhalation

Adult: 5 micrograms once daily

Dose equivalence and conversion

2 puffs is equivalent to 5 micrograms.

Caution

Aneurysm - convulsive disorders

Interactions

Appendix 1: beta, agonists

Side-effects

Common or very common
- Nasopharyngitis
- Rash
- Increased risk of infection

Rare or very rare
- Angina pectoris
- Arthralgia
- Hypotension
- Insomnia
- Malaise
- Metabolic acidosis
- Muscle spasms
- Nervousness

Pregnancy

Manufacturer advises avoid—no information available.

Breast feeding

Manufacturer advises avoid—present in milk in animal studies.
252 Airways disease, obstructive

Respiratory system

In children

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- Salmeterol (as Salmeterol hydrochloride) 2.5 microgram per 1 dose
- Salmeterol (as Salmeterol hydrochloride) 50 microgram per 1 dose

Combinations available: Tiotropium with olodaterol, p. 249

**INDICATIONS AND DOSE**

Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy

- Child 12-17 years: 50 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 100 micrograms twice daily
- Adult: 50 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 100 micrograms twice daily

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

- Adult: 50 micrograms twice daily

**PHARMACOKINETICS**

- At recommended inhaled doses, the duration of action of salmeterol is about 12 hours.

**UNLICENSED USE**

- In children Neovent® not licensed for use in children under 12 years.

**IMPORTANT SAFETY INFORMATION**

**CHM ADVICE**

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta₂ agonist (salmeterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

**MHRA/CHM ADVICE: PRESSURISED Metered Dose Inhalers (PMDIs) RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)**

See Respiratory system, drug delivery p. 235.

**INTERACTIONS**

→ Appendix 1: beta₂ agonists

**SIDE-EFFECTS**

- Common or very common Muscle cramps
- Uncommon Nervousness, skin reactions
- Rare or very rare Arthralgia, bronchospasm, chest pain, insomnia, oedema, ophthalmic irritation

**PREGNANCY**

Inhaled drugs for asthma can be taken as normal during pregnancy.

**BREAST FEEDING**

Inhaled drugs for asthma can be taken as normal during breast-feeding.

**PATIENT AND CARER ADVICE**

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma www.medicinesforchildren.org.uk/salmeterol-inhaler-asthma

**INDICATIONS AND DOSE**

Inhaled short-acting beta₂ agonists are not recommended for use in children over 12 years.

**INDICATIONS AND DOSE**

**INTERACTIONS**

→ Appendix 1: beta₂ agonists

**SIDE-EFFECTS**

- Common or very common Muscle cramps
- Uncommon Nervousness, skin reactions
- Rare or very rare Arthralgia, bronchospasm, chest pain, insomnia, oedema, ophthalmic irritation

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**PATIENT AND CARER ADVICE**

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Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma www.medicinesforchildren.org.uk/salmeterol-inhaler-asthma

**IMPORTANCE SAFETY INFORMATION**

**CHM ADVICE**

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- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

**MHRA/CHM ADVICE: PRESSURISED Metered Dose Inhalers (PMDIs) RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)**

See Respiratory system, drug delivery p. 235.

**INTERACTIONS**

→ Appendix 1: beta₂ agonists

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Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma www.medicinesforchildren.org.uk/salmeterol-inhaler-asthma

**IMPORTANCE SAFETY INFORMATION**

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- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

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See Respiratory system, drug delivery p. 235.

**INTERACTIONS**

→ Appendix 1: beta₂ agonists

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- Rare or very rare Arthralgia, bronchospasm, chest pain, insomnia, oedema, ophthalmic irritation

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Inhaled drugs for asthma can be taken as normal during breast-feeding.

**PATIENT AND CARER ADVICE**

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma www.medicinesforchildren.org.uk/salmeterol-inhaler-asthma

**IMPORTANCE SAFETY INFORMATION**

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To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta₂ agonist (salmeterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

**MHRA/CHM ADVICE: PRESSURISED Metered Dose Inhalers (PMDIs) RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)**

See Respiratory system, drug delivery p. 235.

**INTERACTIONS**

→ Appendix 1: beta₂ agonists

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Inhaled drugs for asthma can be taken as normal during breast-feeding.

**PATIENT AND CARER ADVICE**

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist.

Medicines for Children leaflet: Salmeterol inhaler for asthma www.medicinesforchildren.org.uk/salmeterol-inhaler-asthma
Airways disease, obstructive 253

Bronchospasm

Prophylaxis of allergen- or exercise-induced bronchospasm

BY INHALATION OF AEROSOL

Adult: 200 micrograms

Acute asthma

BY INHALATION OF AEROSOL

Child: 2–10 puffs, each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer, each puff is equivalent to 100 micrograms

Child: 2–10 years: 2.5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

Child 12–17 years: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

Moderate, severe, or life-threatening acute asthma

BY INHALATION OF NEBULISED SOLUTION

Child 1–2 years: 2.5 mg, repeated up to 4 times daily or more frequently in severe cases

Child 3–6 years: 5 mg, repeated every 4 hours

Child 7–11 years: 10 micrograms/kg (max. per dose 200 micrograms)

Child 12–17 years: 5 mg, repeated up to 4 times a day

Moderate and severe acute asthma

BY INHALATION OF AEROSOL

Child: 2–10 puffs, each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer, each puff is equivalent to 100 micrograms

Noveliser

Child 2–10 years: 200 micrograms daily for persistent symptoms

Child 11–12 years: 400 micrograms, up to 3 times daily for persistent symptoms

Child 13–17 years: 800 micrograms daily for persistent symptoms

Exacerbation of reversible airways obstruction (including nocturnal asthma) / Prophylaxis of allergen- or exercise-induced bronchospasm

BY INHALATION OF AEROSOL

Child: 100–200 micrograms, up to 4 times a day for persistent symptoms

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child: 3–11 years: 4 mg twice daily

Child 12–17 years: 8 mg twice daily

Child 12–17 years: 8 mg twice daily

Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist supervision in hospital)

BY INTRAVENOUS INFUSION

Adult: Initially 10 micrograms/minute, rate increased gradually according to response at 10-minute intervals until contractions diminish then increase rate slowly until contractions cease (maximum rate 45 micrograms/minute), maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours, maximum duration 48 hours

PHARMACOKINETICS

At recommended inhaled doses, the duration of action of salbutamol is about 3 to 5 hours.

EASYHALER® SALBUTAMOL

Acute bronchospasm

BY INHALATION OF POWDER

Child: Initially 100–200 micrograms, increased if necessary to 400 micrograms; maximum 800 micrograms per day

Prophylaxis of allergen- or exercise-induced bronchospasm

BY INHALATION OF POWDER

Adult: 200 micrograms

SALBULIN NOVOLIZER®

Acute bronchospasm

BY INHALATION OF POWDER

Adult: Initially 100–200 micrograms, up to 800 micrograms daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm

BY INHALATION OF POWDER

Adult: 200 micrograms

VENTOLIN ACCUHALER®

Acute bronchospasm

BY INHALATION OF POWDER

Adult: Initially 200 micrograms, up to 4 times daily for persistent symptoms

Prophylaxis of allergen- or exercise-induced bronchospasm

BY INHALATION OF POWDER

Adult: 200 micrograms

UNLICENSED USE

With oral use in children Syrup and tablets not licensed for use in children under 2 years

With intravenous use in children Injection and solution for intravenous infusion not licensed for use in children under 12 years. Administration of undiluted salbutamol injection through a central venous catheter is not licensed.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: PRESSURISED METERED DOSE INHALERS (PMDI): RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)

See Respiratory system, drug delivery p. 235.

CONTRA-INDICATIONS

When used for uncomplicated premature labour under specialist supervision Abruptio placenta · antepartum haemorrhage · cord compression · eclampsia · history of cardiac disease · intra-uterine fetal death · intra-uterine infection · placenta praevia · pulmonary hypertension · severe pre-eclampsia · significant risk factors for myocardial ischaemia · threatened miscarriage

CAUTIONS

GENERAL CAUTIONS High doses of beta₂ agonists can be dangerous in some children
Respiratory system

When used by inhalation

▶ With intravenous use in adults
▶ With intravenous use in children

BREAST FEEDING
▶ With parenteral use
▶ Frequency not known
▶ With parenteral use
▶ Frequency not known
▶ Rare or very rare

SIDE-EFFECTS
INTERACTIONS

With intravenous use

- glucose and lactate concentrations, and the patient normal during breast-feeding.

- cardiovascular disease (should be assessed by a

- Airways disease, obstructive

- bronchodilator by

- continuous intravenous infusion, dilute to a concentration of 200 micrograms/mL with glucose 5% or sodium chloride 0.9%. For premature labour by continuous intravenous infusion, dilute with glucose 5% to a concentration of 200 micrograms/mL for use in a syringe pump or for other infusion methods (preferably via controlled infusion device), dilute to a concentration of 20 micrograms/mL; close attention to patient’s fluid and electrolyte status essential.

- When used by inhalation For inhalation by aerosol or dry powder, advise patients and carers not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible. For inhalation by nebuliser, the dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution.

- Medicines for Children leaflet: Salbutamol inhaler for asthma and wheeze www.medicinesforchildren.org.uk/salbutamol-inhaler-asthma-and-wheeze

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Salbutamol (Non-proprietary)
  - Salbutamol (as Salbutamol sulfate) 2 mg Salbutamol 2mg tablets ▼ 28 tablet [P] £11.21 DT = £10.52
  - Salbutamol (as Salbutamol sulfate) 4 mg Salbutamol 4mg tablets ▼ 28 tablet [P] £113.85 DT = £107.00

Inhalation powder
▶ Easyhaler (salbutamol) (Orion Pharma (UK) Ltd)
  - Salbutamol 100 microgram per 1 dose Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler ▼ 200 dose [P] £3.31 DT = £3.31
  - Salbutamol 200 microgram per 1 dose Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler ▼ 200 dose [P] £6.63 DT = £6.63
▶ Salbutam Novolizer (Meda Pharmaceuticals Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Salbutam Novolizer 100micrograms/dose inhalation powder ▼ 200 dose [P] £4.95
  - Salbutam Novolizer 100micrograms/dose inhalation powder refill ▼ 200 dose [P] £2.75
▶ Ventolin Accuhaler (GlaxoSmithKline UK Ltd)
  - Salbutamol 200 microgram per 1 dose Ventolin 200micrograms/dose Accuhaler ▼ 60 dose [P] £3.60 DT = £3.60

Solution for injection
▶ Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 500 microgram per 1 ml Ventolin 500micrograms/1ml solution for injection ampoules ▼ 5 ampoule [P] £1.91

Solution for infusion
▶ Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Ventolin 5mg/5ml solution for infusion ampoules ▼ 10 ampoule [P] £24.81

Oral solution
▶ Salbutamol (Non-proprietary)
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml Salbutamol 2mg/5ml oral solution sugar free sugar-free ▼ 150 ml [P] N DT = £1.15
▶ Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml Ventolin 2mg/5ml syrup sugar-free ▼ 150 ml [P] £1.15 DT = £1.15

Pressurised inhalation
▶ Airomir (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Airomir 100micrograms/dose inhaler ▼ 200 dose [P] £1.97 DT = £1.50
▶ Airomir Autohaler (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Airomir 100micrograms/dose Autohaler ▼ 200 dose [P] £6.62 DT = £6.30
▶ Salamol (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Salamol 100micrograms/dose inhaler CFC free ▼ 200 dose [P] £1.46 DT = £1.50
▶ Salamol Easi-Breathe (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Salamol 100micrograms/dose Easi-Breathe inhaler ▼ 200 dose [P] £6.30 DT = £6.30
▶ Ventolin Evoorhaler (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Ventolin 100micrograms/dose Evoorhaler ▼ 200 dose [P] £1.50 DT = £1.50

Nebuliser liquid
▶ Salbutamol (Non-proprietary)
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials ▼ 20 unit dose [P] £2.48 DT = £2.17
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials ▼ 20 unit dose [P] £3.91 DT = £3.91
▶ Salamol Steri-Neb (Teva UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml Salamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials ▼ 20 unit dose [P] £3.82 DT = £3.91
Terbutaline sulfate

- **INDICATIONS AND DOSE**
  - **Asthma** | Other conditions associated with reversible airways obstruction
  - **BY INHALATION OF POWDER**
    - Adult: Initially 2.5 mg 3 times a day 1 to 2 weeks, then increased to up to 5 mg 3 times a day, by use of inhalation preferred over by mouth
  - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - Adult: 250–500 micrograms up to 4 times a day, reserve intravenous beta2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
  - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - Child: 90–300 micrograms/hour for 8–10 hours, to be administered as a solution containing 3–5 micrograms/mL, high doses require close monitoring, reserve intravenous beta2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
  - **BY INHALATION OF POWDER**
    - Adult: 500 micrograms up to 4 times a day, for persistent symptoms
  - **BY INHALATION OF NEBULISED SOLUTION**
    - Adult: 5–10 mg 2–4 times a day, additional doses may be necessary in severe acute asthma

- **Acute asthma**
  - **BY SUBCUTANEOUS INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
    - Child 2–14 years: 10 micrograms/kg up to 4 times a day (max. per dose 300 micrograms), reserve intravenous beta2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
  - **Child 15–17 years**: 250–500 micrograms up to 4 times a day, reserve intravenous beta2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
  - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - Child: Loading dose 2–4 micrograms/kg, then 1–10 micrograms/kg/hour, dose to be adjusted according to response and heart rate, close monitoring is required for doses above 10 micrograms/kg/hour, reserve intravenous beta2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

- **Moderate, severe, or life-threatening acute asthma**
  - **BY INHALATION OF NEBULISED SOLUTION**
    - Child 1 month–4 years: 5 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available
    - Child 5–11 years: 5–10 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available
    - Child 12–17 years: 10 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available
    - Adult: 10 mg, repeat every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

- **EXACERBATION OF REVERSIBLE AIRWAYS OBSTRUCTION (INCLUDING NOCTURAL ASTHMA)**
  - **BY INHALATION OF POWDER**
    - Child 5–17 years: 500 micrograms up to 4 times a day, for occasional use only
  - **BY MOUTH**
    - Child 1 month–6 years: 75 micrograms/kg 3 times a day (max. per dose 2.5 mg), administration by mouth is not recommended
    - Child 7–14 years: 2.5 mg 2–3 times a day, administration by mouth is not recommended
    - Child 15–17 years: Initially 2.5 mg 3 times a day, then increased if necessary to 5 mg 3 times a day, administration by mouth is not recommended

- **Uncomplicated premature labour (between 22 and 37 weeks of gestation) (Specialist supervision in hospital)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 5 micrograms/minute for 20 minutes, then increased in steps of 2.5 micrograms/minute every 20 minutes until contractions have ceased (more than 10 micrograms/minute should seldom be given—20 micrograms/minute should not be exceeded), continue for 1 hour, then reduced in steps of 2.5 micrograms/minute every 20 minutes to lowest dose that maintains suppression (maximum total duration 48 hours)

- **PHARMACOKINETICS**
  - At recommended inhaled doses, the duration of action of terbutaline is about 3 to 5 hours.
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection.

**Solution for injection**

- **Bricanyl** (AstraZeneca UK Ltd)
  - Terbutaline sulfate 500 microgram per 1 ml
  - Terbutaline sulfate 2.5mg/5ml solution for injection ampoules | 10 ampoule ($P$, £20) + £20.09
  - Bricanyl 500micrograms/1ml solution for injection ampoules | 5 ampoule ($P$, £6.48) + £6.48

**Inhalation powder**

- **Bricanyl Turbohaler** (AstraZeneca UK Ltd)
  - Terbutaline sulfate 500 microgram per 1 dose
  - Bricanyl 500micrograms/dose Turbohaler | 120 dose ($P$, £8.30) + £8.30

**Nebuliser liquid**

- **Terbutaline sulfate (Non-proprietary)**
  - Terbutaline sulfate 2.5 mg per 1 ml
  - Terbutaline 5mg/2ml nebuliser liquid unit dose vials | 20 unit dose ($P$, £4.04) + £4.04

- **Bricanyl Respules** (AstraZeneca UK Ltd)
  - Terbutaline sulfate 2.5 mg per 1 ml
  - Bricanyl 5mg/2ml Respules | 20 unit dose ($P$, £11.64) + £4.04

**Tablet**

- **Bricanyl** (AstraZeneca UK Ltd)
  - Terbutaline sulfate 5 mg
  - Bricanyl 5mg tablets | 100 tablet ($P$, £14.73) + £14.73

**DIRECTIONS FOR ADMINISTRATION**

- **With intravenous use in children** For *continuous intravenous infusion*, dilute to a concentration of 5 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; if fluid-restricted, dilute to a concentration of 100 micrograms/mL.

- **When used by inhalation** For *nebulisation*, dilute nebuliser solution with sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; terbutaline and ipratropium bromide solutions are compatible and may be mixed for nebulisation.

- **With intravenous use in adults** For *bronchodilation* by *continuous intravenous infusion*, dilute 1.5–2.5 mg with 500 mL glucose 5% or sodium chloride 0.9% and give over 8–10 hours. For premature labour by *continuous intravenous infusion*, dilute in glucose 5% and give via controlled infusion device preferably a syringe pump; if syringe pump available dilute to a concentration of 100 micrograms/mL; if syringe pump not available dilute to a concentration of 10 micrograms/mL; close attention to patient’s fluid and electrolyte status essential.

**PATIENT AND CARER ADVICE**

- When used by inhalation For *inhalation by dry powder*, advise patients and carers not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled terbutaline fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible. For *inhalation by nebuliser*, the dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution.

**CORTICOSTEROIDS**

**Airways disease, use of corticosteroids**

**Asthma, use of corticosteroids**

**Inhaled corticosteroids**

Corticosteroids are effective in asthma; they reduce airway inflammation (and hence reduce oedema and secretion of mucus into the airway).

An inhaled corticosteroid is used regularly for prophylaxis of asthma. *Regular use* of inhaled corticosteroids reduces the risk of exacerbation of asthma.

Current and previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary. Corticosteroid inhalers must be used regularly for maximum benefit. Beclomethasone dipropionate p. 257, budesonide p. 260, fluticasone p. 262, and mometasone furoate p. 265 appear to be equally effective.

In adults using an inhaled corticosteroid and a long-acting beta₂ agonist for the prophylaxis of asthma, but who are poorly controlled, ‘Symbicort®’ or ‘Duod Resp Spirax®’ (both containing budesonide with formoterol p. 261) or ‘Fostair®’ beclomethasone with formoterol p. 259 can be used as relievers (instead of a short-acting beta, agonist), in addition to their regular use for the prophylaxis of asthma.

**Oral corticosteroids**

Systemic corticosteroid therapy may be necessary during episodes of stress, such as severe infection, or when airway obstruction or mucus prevent drug access to smaller airways.

An acute attack of asthma should be treated with a short course of an oral corticosteroid starting with a high dose. Patients whose asthma has deteriorated rapidly usually respond quickly to corticosteroids. The dose can usually be stopped abruptly; tapering is not needed provided that the patient receives an inhaled corticosteroid in an adequate dose (apart from those on maintenance oral corticosteroid treatment or where oral corticosteroids are required for 3 or more weeks). In patients who have needed several courses of oral corticosteroids and in whom the possibility of a period on maintenance corticosteroids is being considered, it may be useful to taper the corticosteroid dose gradually to identify a threshold dose for asthma control. This should only be done after other standard options for controlling asthma have been tried.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Regular peak-flow measurements help to optimise the dose.

**Parenteral corticosteroids**

Hydrocortisone injection p. 676 has a role in the emergency treatment of acute severe asthma.

**Chronic obstructive pulmonary disease, use of corticosteroids**

**Inhaled corticosteroids**

In *chronic obstructive pulmonary disease* inhaled corticosteroid therapy may reduce exacerbations when given in combination with an inhaled long-acting beta, agonist.

**Oral corticosteroids**

During an acute exacerbation of chronic obstructive pulmonary disease, prednisolone p. 676 should be given; treatment can be stopped abruptly. Prolonged treatment with oral prednisolone is of no benefit and maintenance treatment is not normally recommended.

**Monitoring Requirements**

- In adults Uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient’s fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).
Corticosteroids (inhaled)

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes. The MHRA recommends that patients should be advised to report any blurred vision or other visual disturbances with corticosteroid treatment given by any route; consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems.

**SIDE-EFFECTS**

- **Common or very common** Headache, oral candidiasis, pneumonia (in patients with COPD) (in adults), taste altered, voice alteration
- **Uncommon** Anxiety, bronchospasm paradoxical, cataract, vision blurred
- **Rare or very rare** Adrenal suppression, behaviour abnormal, glaucoma, growth retardation (in children), sleep disorder

**SIDE-EFFECTS, FURTHER INFORMATION**

Systemic absorption may follow inhaled administration particularly if high doses are used or if treatment is prolonged. Therefore also consider the side-effects of systemic corticosteroids.

- **Candidiasis** The risk of oral candidiasis can be reduced by using a spacer device with the corticosteroid inhaler; rinsing the mouth with water after inhalation of a dose may also be helpful. An anti-fungal oral suspension or oral gel can be used to treat oral candidiasis without discontinuing corticosteroid therapy.
- **Paradoxical bronchospasm** The potential for paradoxical bronchospasm (calling for discontinuation and alternative therapy) should be borne in mind. Mild bronchospasm may be prevented by inhalation of a short-acting beta2 agonist beforehand (or by transfer from an aerosol inhalation to a dry powder inhalation).

- **PREGNANCY** Inhaled drugs for asthma can be taken as normal during pregnancy.
- **BREAST FEEDING** Inhaled corticosteroids for asthma can be taken as normal during breast-feeding.

**MONITORING REQUIREMENTS**

- In children The height and weight of children receiving prolonged treatment with inhaled corticosteroids should be monitored annually; if growth is slowed, referral to a paediatrician should be considered.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE decisions**
  - Inhaled corticosteroids for the treatment of chronic asthma in children under 12 years (November 2007) NICE TAs
  - In children For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual child (taking into consideration NICE TAs 38 and 10), within its marketing authorisation, is recommended. For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting beta2 agonist is considered appropriate, the following apply:
    - the use of a combination inhaler within its marketing authorisation is recommended as an option;
    - the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence;
  - if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual child is recommended.
  - [www.nice.org.uk/TA131](http://www.nice.org.uk/TA131)
- Inhaled corticosteroids for the treatment of chronic asthma in adults and children over 12 years (March 2008) NICE TA138
  - For adults and children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual (taking into consideration NICE TAs 38 and 10), within its marketing authorisation is recommended.
  - For adults and children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting beta2 agonist is considered appropriate, the following apply:
    - the use of a combination inhaler within its marketing authorisation is recommended as an option;
    - the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence;
    - if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual is recommended.
  - [www.nice.org.uk/TA138](http://www.nice.org.uk/TA138)

**Beclometasone dipropionate** (Beclomethasone dipropionate)

**INDICATIONS AND DOSE**

- **Prophylaxis of asthma**
  - **BY INHALATION OF POWDER**
    - Child 5–11 years: 100–200 micrograms twice daily, dose to be adjusted as necessary
    - Child 12–17 years: 200–400 micrograms twice daily; increased if necessary up to 800 micrograms twice daily, dose to be adjusted as necessary
    - Adult: 200–400 micrograms twice daily; increased if necessary up to 800 micrograms twice daily, dose to be adjusted as necessary

**DOSE EQUIVALENTS AND CONVERSIONS**

- Dose adjustments may be required for some inhaler devices, see under individual preparations.

**CLENIL MODULITE ®**

- **Prophylaxis of asthma**
  - **BY INHALATION OF AEROSOL**
    - Child 2–11 years: 100–200 micrograms twice daily
    - Child 12–17 years: 200–400 micrograms twice daily, adjusted according to response; increased if necessary up to 1 mg twice daily
    - Adult: 200–400 micrograms twice daily, adjusted according to response; increased if necessary up to 1 mg twice daily

**KELHALE ®**

- **Prophylaxis of asthma**
  - **BY INHALATION OF AEROSOL**
    - Adult: 50–200 micrograms twice daily; increased if necessary up to 400 micrograms twice daily

**POTENCY**

- Kelhale ® has extra-fine particles and is more potent than traditional beclomethasone dipropionate CFC-containing inhalers.
QVAR \textsuperscript{®} PREPARATIONS

Prophylaxis of asthma
- BY INHALATION OF AEROSOL
  - Child: 100 micrograms twice daily; increased if necessary up to 400 micrograms twice daily
  - Adult: 200 micrograms twice daily; increased if necessary up to 400 micrograms twice daily

POTENCY
- Qvar\textsuperscript{®} has extra fine particles, is more potent than traditional beclometasone dipropionate CFC-containing inhalers and is approximately twice as potent as Clenil Modulite\textsuperscript{®}.

SOPROBEC \textsuperscript{®}

Prophylaxis of asthma
- BY INHALATION OF AEROSOL
  - Child: 100 micrograms twice daily; increased if necessary up to 400 micrograms daily in 2–4 divided doses
  - Adult: 200 micrograms twice daily, adjusted according to response; increased if necessary up to 2 mg daily in 2–4 divided doses

**UNLICENSED USE** Easyhaler\textsuperscript{®} Beclometasone Dipropionate is not licensed for use in children under 18 years. Clenil Modulite\textsuperscript{®} - 200 and - 250 are not licensed for use in children under 12 years.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (JULY 2008)
Beclometasone dipropionate CFC-free pressurised metered-dose inhalers (Qvar\textsuperscript{®} and Clenil Modulite\textsuperscript{®}) are not interchangeable and should be prescribed by brand name; Qvar\textsuperscript{®} has extra fine particles, is more potent than traditional beclometasone dipropionate CFC-containing inhalers, and is approximately twice as potent as Clenil Modulite\textsuperscript{®}.

MHRA/CHM ADVICE: PRESSURISED Metered Dose Inhalers (PMDI): RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)
See Respiratory system, drug delivery p. 235.

**INTERACTIONS** \rightarrow Appendix 1: corticosteroids

**SIDE-EFFECTS**
- Common or very common Throat irritation
- Rare or very rare Wheezing

**PRESCRIBING AND DISPENSING INFORMATION**
The MHRA has advised (July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name.

SOPROBEC \textsuperscript{®} Soprobec\textsuperscript{®} is not interchangeable with other CFC-free beclometasone dipropionate inhalers.

KELHALE \textsuperscript{®} Manufacturer advises when switching a patient with well-controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of Kelhale\textsuperscript{®} should be prescribed for 200–250 micrograms of budesonide or 100 micrograms of fluticasone propionate; the dose of Kelhale\textsuperscript{®} should be adjusted according to response, up to a maximum of 800 micrograms daily. Manufacturer advises when switching a patient with poorly-controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of Qvar\textsuperscript{®} should be prescribed for 200–250 micrograms of beclometasone dipropionate or budesonide and for 100 micrograms of fluticasone propionate. When switching a patient with poorly controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of Qvar\textsuperscript{®} should be prescribed for 100 micrograms of beclometasone dipropionate, budesonide, or fluticasone propionate; the dose of Qvar\textsuperscript{®} should be adjusted according to response.

CLENIL MODULITE \textsuperscript{®} Clenil Modulite\textsuperscript{®} is not interchangeable with other CFC-free beclometasone propionate inhalers.

**PATIENT AND CARER ADVICE** Steroid card should be issued with high doses of inhaled beclometasone dipropionate.

Medicines for Children leaflet: Beclometasone inhaler for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/beclometasone-inhaler-asthma-prevention-prophylaxis-0

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary
Clenil Modulite\textsuperscript{®} 50 micrograms metered inhalation may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment Inhalation powder

CAUTIONARY AND ADVISORY LABELS 8, 10
- Easyhaler (beclometasone) (Onion Pharma (UK) Ltd) Beclometasone dipropionate 200 microgram per 1 dose Easyhaler Beclometasone 200 micrograms/dose dry powder inhaler | 200 dose \textsuperscript{®} £14.93 DT = £14.93

Pressurised inhalation

CAUTIONARY AND ADVISORY LABELS 8, 10
- Clenil Modulite (Chiesi Ltd) Beclometasone dipropionate 50 microgram per 1 dose Clenil Modulate 50 micrograms/dose inhaler | 200 dose \textsuperscript{®} £3.70 DT = £3.70

- Beclometasone dipropionate 100 microgram per 1 dose Clenil Modulate 100 micrograms/dose inhaler | 200 dose \textsuperscript{®} £7.42 DT = £7.42

- Beclometasone dipropionate 200 microgram per 1 dose Clenil Modulate 200 micrograms/dose inhaler | 200 dose \textsuperscript{®} £16.17 DT = £16.17

- Beclometasone dipropionate 250 microgram per 1 dose Clenil Modulate 250 micrograms/dose inhaler | 200 dose \textsuperscript{®} £16.29 DT = £16.29

- Kelhale (Cipla EU Ltd) Beclometasone dipropionate 50 microgram per 1 dose Kelhale 50 micrograms/dose inhaler | 200 dose \textsuperscript{®} £5.20 DT = £5.20

- Beclometasone dipropionate 100 microgram per 1 dose Kelhale 100 micrograms/dose inhaler | 200 dose \textsuperscript{®} £7.42 DT = £7.42

- Qvar (Teva UK Ltd) Beclometasone dipropionate 50 microgram per 1 dose Qvar 50 micrograms/dose inhaler | 200 dose \textsuperscript{®} £17.21 DT = £17.21

- Beclometasone dipropionate 100 microgram per 1 dose Qvar 100 micrograms/dose inhaler | 200 dose \textsuperscript{®} £17.21 DT = £17.21

- Qvar Easi-Breathe (Teva UK Ltd) Beclometasone dipropionate 50 microgram per 1 dose Qvar 50 micrograms/dose inhaler | 200 dose \textsuperscript{®} £7.87 DT = £7.87

- Beclometasone dipropionate 100 microgram per 1 dose Qvar 100 micrograms/dose inhaler | 200 dose \textsuperscript{®} £17.21 DT = £17.21

- Beclometasone dipropionate 50 microgram per 1 dose Qvar 50 micrograms/dose/inhaler | 200 dose \textsuperscript{®} £7.42 DT = £7.42

- Beclometasone dipropionate 100 microgram per 1 dose Qvar 100 micrograms/dose/inhaler | 200 dose \textsuperscript{®} £17.21 DT = £17.21

- Soprobec (Glenmark Pharmaceuticals Europe Ltd) Beclometasone dipropionate 50 microgram per 1 dose Soprobec 50 micrograms/dose inhaler | 200 dose \textsuperscript{®} £7.28 DT = £7.28

- Beclometasone dipropionate 100 microgram per 1 dose Soprobec 100 micrograms/dose/inhaler | 200 dose \textsuperscript{®} £5.57 DT = £5.57

- Beclometasone dipropionate 200 microgram per 1 dose Soprobec 200 micrograms/dose inhaler | 200 dose \textsuperscript{®} £12.13 DT = £12.13

- Beclometasone dipropionate 250 microgram per 1 dose Soprobec 250 micrograms/dose inhaler | 200 dose \textsuperscript{®} £11.22 DT = £11.22

www.getintopharma.com
Beclometasone with formoterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, beclometasone dipropionate p. 257, formoterol fumarate p. 250.

**INDICATIONS AND DOSE**

**FOSTAIR® NEXTThaler® 100/6**

**Asthma maintenance therapy**
- By inhalation of powder
- Adult: 1–2 inhalations twice daily; maximum 4 inhalations per day

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- By inhalation of powder
- Adult: 2 inhalations twice daily

**DOSE EQUIVALENCE AND CONVERSION**
- For inhalation of powder, when switching patients from other beclometasone dipropionate formulations with non-extra-fine particle size distribution to Fostair NEXTThaler®, the dose should be adjusted according to response.
- 1 inhalation is equivalent to 100 micrograms beclometasone dipropionate and 6 micrograms formoterol fumarate.

**FOSTAIR® NEXTThaler® 200/6**

**Asthma maintenance therapy**
- By inhalation of powder
- Adult: 2 inhalations twice daily; maximum 4 inhalations per day

**DOSE EQUIVALENCE AND CONVERSION**
- For inhalation of powder, when switching patients from other beclometasone dipropionate formulations with non-extra-fine particle size distribution to Fostair NEXTThaler®, the dose should be adjusted according to response.
- 1 inhalation is equivalent to 200 micrograms beclometasone dipropionate and 6 micrograms formoterol fumarate.

**FOSTAIR® 100/6**

**Asthma maintenance therapy**
- By inhalation of aerosol
- Adult: 1–2 inhalations twice daily; maximum 4 inhalations per day

**Asthma, maintenance and reliever therapy**
- By inhalation of aerosol
- Adult: Maintenance 1 inhalation twice daily; 1 inhalation as required, for relief of symptoms; maximum 8 inhalations per day

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted**
- By inhalation of aerosol
- Adult: 2 inhalations twice daily

**DOSE EQUIVALENCE AND CONVERSION**
- For inhalation of aerosol, when switching patients from other beclometasone dipropionate and formoterol fumarate inhalers, dose should be adjusted according to response—100 micrograms of beclometasone dipropionate extrane in Fostair® is equivalent to 250 micrograms of beclometasone dipropionate in a non-extrane formulation.
- 1 inhalation is equivalent to 100 micrograms beclometasone dipropionate and 6 micrograms formoterol fumarate.

**INDICATIONS AND DOSE**

**Moderate-to-severe chronic obstructive pulmonary disease**
- By inhalation of aerosol
- Adult: 2 inhalations twice daily

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (JULY 2008)**

Fostair® contains extra-fine particles of beclometasone dipropionate and is more potent than traditional beclometasone dipropionate CFC-free inhalers. The dose of beclometasone dipropionate in Fostair® should be lower than non-extra-fine formulations of beclometasone dipropionate and will need to be adjusted to the individual needs of the patient.

**INTERACTIONS**
- Appendix 1: beta-agonists: corticosteroids

**PATIENT AND CARER ADVICE**
Patients or carers should be given advice on how to administer beclometasone with formoterol aerosol for inhalation. With high doses, a steroid card should be supplied.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**

| **FOSTAIR® NEXTThaler (Chiesi Ltd)** |
| Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose Fostair NEXTThaler 100 micrograms/dose dry powder inhaler | 120 dose £29.32 DT + £29.32 |
| Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 200 microgram per 1 dose Fostair NEXTThaler 200 micrograms/dose dry powder inhaler | 120 dose £29.32 DT + £29.32 |

**Pressurised inhalation**

| **FOSTAIR® (Chiesi Ltd)** |
| Formoterol fumarate dihydrate 6 microgram, Beclometasone dipropionate 200 microgram Fostair 200 micrograms/dose dry powder inhaler | 120 dose £29.32 DT + £29.32 |
| Formoterol fumarate dihydrate 6 microgram per 1 dose, Beclometasone dipropionate 100 microgram per 1 dose Fostair 100 micrograms/dose dry powder inhaler | 120 dose £29.32 DT + £29.32 |

**Beclometasone with formoterol and glycopyrronium**

The properties listed below are those particular to the combination only. For the properties of the components please consider, beclometasone dipropionate p. 257, formoterol fumarate p. 250, glycopyrronium bromide p. 246.

**INDICATIONS AND DOSE**

**Moderate-to-severe chronic obstructive pulmonary disease**
- By inhalation of aerosol
- Adult: 2 inhalations twice daily
Respiratory system

INTERACTIONS → Appendix 1: beta, agonists · corticosteroids · glycopyrronium

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (October 2017) that beclometasone with formoterol and glycopyrronium (Trimbow®) is accepted for restricted use within NHS Scotland for the maintenance treatment of adults with severe chronic obstructive pulmonary disease.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation

CAUTIONARY AND ADVISORY LABELS 8, 10

Trimbow (Chiesi Ltd)
Formoterol fumarate dihydrate 5 microgram per 1 dose, Glycopyrronium (as Glycopyrronium bromide) 9 microgram per 1 dose, Beclometasone dipropionate 87 microgram per 1 dose Trimbow 8micrograms/dose / 8micrograms/dose / 8micrograms/dose inhaler | 120 dose (PVP) £44.50

Budesonide

21-Dec-2017

DRUG ACTION Budesonide is a glucocorticoid, which exerts significant local anti-inflammatory effects.

INDICATIONS AND DOSE

Prophylaxis of mild to moderate asthma (in patients stabilised on twice daily dose)

BY INHALATION OF POWDER

Child 6-11 years: 200–400 micrograms once daily, dose to be given in the evening

Child 12-17 years: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

Prophylaxis of asthma

BY INHALATION OF POWDER

Child 6-11 years: 100–400 micrograms twice daily, dose to be as necessary

Child 12-17 years: 100–800 micrograms twice daily, dose to be as necessary

Adult: 100–800 micrograms twice daily, dose to be as necessary

BY INHALATION OF NEBULISED SUSPENSION

Child 6 months-11 years: 125–500 micrograms twice daily, adjusted according to response; maximum 2 mg per day

Child 12-17 years: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day

Adult: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day

POTENCY

Dose adjustments may be required for some inhaler devices, see under individual preparations.

BUDELIN NOVOLIZER ®

Prophylaxis of asthma

BY INHALATION OF POWDER

Adult: 200–800 micrograms twice daily, dose is adjusted as necessary

Alternative in mild to moderate asthma, for patients previously stabilised on a twice daily dose

BY INHALATION OF POWDER

Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), to be taken in the evening

PULMICORT ® RESPULES

Prophylaxis of asthma

BY INHALATION OF NEBULISED SUSPENSION

Child 3 months-11 years: Initially 0.5–1 mg twice daily, reduced to 0.25–0.5 micrograms twice daily

Child 12-17 years: Initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily

Adult: Initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily

PULMICORT ® TURBOHALER

Prophylaxis of asthma

BY INHALATION OF POWDER

Adult: 100–800 micrograms twice daily, dose to be as necessary

Alternative in mild to moderate asthma, for patients previously stabilised on a twice daily dose

BY INHALATION OF POWDER

Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), to be taken in the evening

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder

CAUTIONARY AND ADVISORY LABELS 8, 10

Budelin Novizer (Meda Pharmaceuticals Ltd)
Budesonide 200 microgram per 1 dose Budelin Novizer 200micrograms/dose inhalation powder | 100 dose (PVP) £14.86 DT + £14.86
Budelin Novizer 200micrograms/dose inhalation powder refill | 100 dose (PVP) £9.59 DT + £9.59

Easyhaler (budesonide) (Orion Pharma (UK) Ltd)
Budesonide 100 microgram per 1 dose Easyhaler Budesonide 100micrograms/dose dry powder inhaler | 200 dose (PVP) £8.86 DT + £14.25

Budesonide 200 microgram per 1 dose Easyhaler Budesonide 200micrograms/dose dry powder inhaler | 200 dose (PVP) £11.71

Budesonide 400 microgram per 1 dose Easyhaler Budesonide 400micrograms/dose dry powder inhaler | 100 dose (PVP) £11.71

Pulmicort Turbohaler (AstraZeneca UK Ltd)
Budesonide 100 microgram per 1 dose Pulmicort 100 Turbohaler | 200 dose (PVP) £14.25 DT + £14.25

Budesonide 200 microgram per 1 dose Pulmicort 200 Turbohaler | 100 dose (PVP) £14.25 DT + £14.25

Budesonide 400 microgram per 1 dose Pulmicort 400 Turbohaler | 50 dose (PVP) £14.25 DT + £14.25

Nebuliser liquid

CAUTIONARY AND ADVISORY LABELS 8, 10

Budesonide (Non-proprietary)
Budesonide 250 microgram per 1 ml Budesonide 500micrograms/2ml nebuliser liquid unit dose vials | 20 unit dose (PVP) £25.51 DT + £25.43
Budesonide 500 microgram per 1 ml Budesonide 1mg/2ml nebuliser liquid unit dose vials | 20 unit dose (PVP) £37.69 DT + £37.68

www.getintopharma.com
**Budesonide with formoterol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, budesonide p. 260, formoterol fumarate p. 250.

- **INDICATIONS AND DOSE**

**Budesonide 250 microgram per 1 ml** Pulmicort 0.5mg Resuples | 20 unit dose £6.54 | £31.70 DT + £25.43
**Budesonide 500 microgram per 1 ml** Pulmicort 1mg Resuples | 20 unit dose £9.30 | £48.00 DT + £37.68

**Asthma, maintenance therapy**

- **BY INHALATION OF POWDER**
- **Adult:** 1–2 inhalations twice daily

**Asthma, maintenance and reliever therapy**

- **BY INHALATION OF POWDER**
- **Adult:** Maintenance 2 inhalations daily in 1–2 divided doses, increased if necessary to 2 inhalations twice daily.
- **Child 6–17 years:** Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- **Adult:** Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**FOBUMIX® 80/4.5 EASYHALER**

**Asthma, maintenance therapy**

- **BY INHALATION OF POWDER**
- **Adult:** 1–2–4 inhalations twice daily, increased if necessary up to 4 inhalations twice daily
- **Child 6–17 years:** Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- **Adult:** Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**SYMBICORT 100/6 TURBOHALER®**

**Asthma, maintenance therapy**

- **BY INHALATION OF POWDER**
- **Child 6–17 years:** Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- **Adult:** Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**SYMBICORT 200/6 TURBOHALER®**

**Asthma, maintenance therapy**

- **BY INHALATION OF POWDER**
- **Child 6–17 years:** Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- **Adult:** Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 70% of predicted (post-bronchodilator)**

- **BY INHALATION OF POWDER**
- **Adult:** 1 inhalation twice daily

**FOBUMIX® 320/9 EASYHALER**

**Asthma, maintenance therapy**

- **BY INHALATION OF POWDER**
- **Adult:** 1–2–4 inhalations twice daily, increased if necessary up to 4 inhalations twice daily
- **Child 6–17 years:** Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- **Adult:** Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 70% of predicted (post-bronchodilator)**

- **BY INHALATION OF POWDER**
- **Adult:** 2 puffs twice daily

**Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 70% of predicted (post-bronchodilator)**

- **BY INHALATION OF POWDER**
- **Adult:** 2 puffs twice daily
Ciclesonide

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Child 12–17 years: 160 micrograms once daily; reduced to 80 micrograms once daily, if control maintained; increased if necessary up to 320 micrograms twice daily, in severe asthma
  - Adult: 160 micrograms once daily; reduced to 80 micrograms once daily, if control maintained; increased if necessary up to 320 micrograms twice daily, in severe asthma

**SIDE-EFFECTS**

- Cushing’s syndrome

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe impairment (risk of increased exposure, no information available).

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer ciclesonide aerosol inhaler.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Fluticasone**

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**

- **BY INHALATION OF POWDER**
  - Child 5–15 years: Initially 50–100 micrograms twice daily (max. per dose 200 micrograms twice daily), dose to be adjusted as necessary
Fluticasone with formoterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 262, formoterol fumarate p. 250.

- **INDICATIONS AND DOSE**
  - **FLUTIFORM® 125**
  - Prophylaxis of asthma
    - **BY INHALATION OF AEROSOL**
    - Child 12–17 years: 2 puffs twice daily
    - Adult: 2 puffs twice daily
  - **FLUTIFORM® 250**
  - Prophylaxis of asthma
    - **BY INHALATION OF AEROSOL**
    - Child 12–17 years: 2 puffs twice daily
    - Adult: 2 puffs twice daily

- **INTERACTIONS** → Appendix 1: beta, agonists - corticosteroids

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer fluticasone with formoterol aerosol inhalation.
  - With high doses, a steroid card should be provided.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Pressurised inhalation**
    - **CAUTIONARY AND ADVISORY LABELS 8, 10** (high doses)
      - Flutiform (Napp Pharmaceuticals Ltd)
      - Formoterol fumarate dihydrate 5 microgram per 1 dose, Fluticasone propionate 50 microgram per 1 dose Flutiform 50micrograms/dose / 5micrograms/dose inhaler | 120 dose PKS £14.40 DT = £14.40
      - Formoterol fumarate dihydrate 5 microgram per 1 dose, Fluticasone propionate 125 microgram per 1 dose Flutiform 125micrograms/dose / 5micrograms/dose inhaler | 120 dose PKS £28.00 DT = £28.00
      - Formoterol fumarate dihydrate 10 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Flutiform 250micrograms/dose / 10micrograms/dose inhaler | 120 dose PKS £45.56 DT = £45.56

Fluticasone with salmeterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 262, salmeterol p. 252.

- **INDICATIONS AND DOSE**
  - **AIRFLUSAL FORSPIRO®**
    - Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 60% of predicted
    - Prophylaxis of asthma
      - **BY INHALATION OF POWDER**
      - Adult: 1 inhalation twice daily
  - **AIRFLUSAL® 125**
  - Prophylaxis of moderate-to-severe asthma
    - **BY INHALATION OF AEROSOL**
    - Adult: 2 inhalations twice daily
  - **AIRFLUSAL® 250**
  - Prophylaxis of moderate-to-severe asthma
    - **BY INHALATION OF AEROSOL**
    - Adult: 2 inhalations twice daily
264 Airways disease, obstructive

Respiratory system

Fluticasone with umeclidinium and vilanterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 262, umeclidinium p. 249.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Inhalation powder**
    - **CAUTIONARY AND ADVISORY LABELS** 8, 10 (excluding Seretide 100 Accuhaler®)
      - AirFluSal Forspiro (Sandoz Ltd)
        - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 125 microgram per 1 dose AirFluSal Forspiro 50micrograms/dose / 250micrograms/dose dry powder inhaler | 60 dose (PO) £29.97 DT + £32.74
      - Seretide Accuhaler (GliazoSmithKline UK Ltd)
        - Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 100 microgram per 1 dose Seretide 100 Accuhaler | 60 dose (PO) £18.00 DT + £18.00
      - Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Seretide 250 Accuhaler | 60 dose (PO) £35.00 DT + £35.00
      - Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose, Fluticasone propionate 500 microgram per 1 dose Seretide 500 Accuhaler | 60 dose (PO) £32.74 DT + £32.74

- **Pressurised inhalation**
  - **CAUTIONARY AND ADVISORY LABELS** 8, 10 (excluding Seretide 50 Evohaler®)
    - AirFluSal (Sandoz Ltd)
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 125 microgram per 1 dose AirFluSal 25micrograms/dose / 125micrograms/dose inhaler | 120 dose (PO) £18.50 DT + £23.45
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose AirFluSal 25micrograms/dose / 250micrograms/dose inhaler | 120 dose (PO) £24.95 DT + £29.32
    - Serello (Cipla EU Ltd)
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 125 microgram per 1 dose Serello 25micrograms/dose / 125micrograms/dose inhaler | 120 dose (PO) £14.99 DT + £19.45
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Serello 25micrograms/dose / 250micrograms/dose inhaler | 120 dose (PO) £19.99 DT + £29.32
    - Seretide Evohaler (GliazoSmithKline UK Ltd)
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 50 microgram per 1 dose Seretide 50 Evohaler | 120 dose (PO) £18.00 DT + £18.00
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 125 microgram per 1 dose Seretide 125 Evohaler | 120 dose (PO) £23.45 DT + £23.45
      - Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose, Fluticasone propionate 250 microgram per 1 dose Seretide 250 Evohaler | 120 dose (PO) £29.32 DT + £29.32

- **Fluticasone with umeclidinium and vilanterol**

- **INDICATIONS AND DOSE**
  - **Maintenance of moderate-to-severe chronic obstructive pulmonary disease**
    - **BY INHALATION OF POWDER**
      - Adult: 1 inhalation once daily, dose should be taken at the same time each day

- **CAUTIONS**
  - Convulsive disorders • pulmonary tuberculosis • thyrotoxicosis
  - **INTERACTIONS** Appendix 1: beta·agonists · corticosteroids · umeclidinium
Fluticasone with vilanterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 262.

- **SIDE-EFFECTS**
  - Common or very common Back pain · increased risk of infection
  - Uncommon Oropharyngeal pain

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on appropriate inhaler technique.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - In adults The Scottish Medicines Consortium has advised (March 2014) that fluticasone furoate/vilanterol (Relvar Ellipta®) is accepted for restricted use within NHS Scotland in patients with severe chronic obstructive pulmonary disease with a forced expiratory volume in one second (FEV1) less than 50% of the predicted normal value.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Inhalation powder**
    - Trelegy Ellipta® (GlaxoSmithKline UK Ltd)
      - Vilanterol (as Vilanterol trifenate) 22 microgram per 1 dose, Umeclidinium bromide 65 microgram per 1 dose, Fluticasone furoate 92 microgram per 1 dose. Trelegy Ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler | 30 dose | £44.50
    - Relvar Ellipta® (GlaxoSmithKline UK Ltd)
      - Vilanterol 22 microgram per 1 dose, Fluticasone furoate 92 microgram per 1 dose. Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler | 30 dose | £22.00

- **INTERACTIONS** → Appendix 1: corticosteroids

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain · arthralgia · back pain · bone fracture · cough · dysphonia · fever · increased risk of infection · muscle spasms · oropharyngeal pain
  - Uncommon Vision blurred
  - Rare or very rare Angiodema · anxiety

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution. Dose adjustments Manufacturer advises maximum dose of 92 microgram/22 microgram once daily in moderate to severe impairment.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer fluticasone with vilanterol powder for inhalation. A steroid card should be provided.
**ENZYME INHIBITORS**

**Human alpha₁-proteinase inhibitor**

**17-Aug-2017**

- **DRUG ACTION** Human alpha₁-proteinase inhibitor is a normal plasma constituent; it inhibits neutrophil elastase (an enzyme released in response to inflammation) in the lungs.

- **INDICATIONS AND DOSE**
  - Progression of emphysema in patients with severe alpha₁-proteinase inhibitor deficiency, despite optimal treatment with other standard therapies (specialist use only)
    - BY INTRAVENOUS INFUSION
      - Adult: 60 mg/kg once weekly

- **CONTRA-INDICATIONS**
  - IgA deficiency with confirmed antibodies against IgA—increased risk of severe hypersensitivity reactions

- **CAUTIONS**
  - Consider vaccination against hepatitis A and hepatitis B - hypersensitivity reactions - IgA deficiency (without known antibodies to IgA)—increased risk of hypersensitivity reactions
  - Hypersensitivity reactions. Hypersensitivity reactions may occur, even in patients who have previously tolerated treatment. Manufacturer advises close monitoring, including vital signs, during the first infusions. If a reaction occurs, manufacturer advises to decrease the rate of infusion or discontinue treatment; if symptoms improve promptly after stopping, the infusion may be resumed at a slower infusion rate.

- **SIDE-EFFECTS**
  - **Common or very common** Dizziness - headache - nausea
  - **Uncommon** Asthenia - confusion - flushing - hypersensitivity - hypotension - sensation abnormal - skin reactions - syncope - tachycardia - throat oedema
  - **Rare or very rare** Chest pain - chills - fever - hyperhidrosis
  - **Frequency not known** Eye swelling - facial swelling - lip swelling - lymph node pain

- **PREGNANCY** Manufacturer advises caution—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **PRESCRIBING AND DISPENSING INFORMATION** Manufacturer advises to record the brand name and batch number after each administration (in case of transmission of infective agents).

- **PATIENT AND CARER ADVICE** Manufacturer advises patients receiving treatment at home should receive appropriate training regarding self-administration, and be informed of the signs of hypersensitivity reactions.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
    - The Scottish Medicines Consortium has advised (August 2016) that human alpha₁-proteinase inhibitor (Respreeza®) is not recommended for use within NHS Scotland for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha₁-proteinase inhibitor deficiency. The manufacturer did not present a sufficiently robust clinical or economic analysis.

  - All Wales Medicines Strategy Group (AWMSG) decisions
    - The All Wales Medicines Strategy Group has advised (March 2017) that human alpha₁-proteinase inhibitor (Respreeza®) is not recommended for use within NHS Wales for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha₁-proteinase inhibitor deficiency. The case for clinical and cost-effectiveness has not been proven.

- **MATERIAL FORMS**
  - **Powder and solvent for solution for infusion**
    - **ELECTROLYTES:** May contain Sodium
      - *Respreeza* (CSL Behring UK Ltd)

- **DRUGS FOR RESPIRATORY DISEASES**

  - **MONOCLONAL ANTIBODIES**

  - **Benralizumab**
    - **DRUG ACTION** Benralizumab is a humanised monoclonal antibody that interferes with interleukin-5 receptor binding, thereby reducing the survival of eosinophils and basophils.

    - **INDICATIONS AND DOSE**
      - **Severe eosinophilic asthma** (specialist use only)
        - **BY SUBCUTANEOUS INJECTION**
          - **Adult:** Initially 30 mg every 4 weeks for the first 3 doses, then maintenance 30 mg every 8 weeks, to be administered into the thigh, abdomen or upper arm

    - **SIDE-EFFECTS**
      - **Common or very common** Fever - headache - hypersensitivity (may be delayed) - pharyngitis
      - **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—limited data available.

    - **CAUTIONS**
      - Pre-existing helminth infection

    - **PHARMACOKINETICS**
      - The half-life of benralizumab is approx. 15 days.

    - **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises to take the syringe out of the refrigerator at least 30 minutes before administration, and to avoid injecting into areas of the skin that are tender, bruised, erythematous, or hardened—consult product literature for further information.

    - **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8°C) and protect from light.

    - **PATIENT AND CARER ADVICE** Manufacturer advises patients and their carers should be instructed to seek medical advice if their asthma remains uncontrolled or if symptoms worsen after initiation of treatment.

    - **NATIONAL FUNDING/ACCESS DECISIONS**
      - **NICE decisions**
        - **Benralizumab for treating severe eosinophilic asthma (March 2019)** NICE T565
          - Benralizumab (Fasenra®), as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if:
            - the patient has agreed to and followed the optimised standard treatment plan, and
the blood eosinophil count has been recorded as
300 cells per microlitre or more and the patient has had 4
or more exacerbations needing systemic corticosteroids
in the previous 12 months, or has had continuous oral
corticosteroids of at least the equivalent of prednisolone
5 mg per day over the previous 6 months (that is, the
patient is eligible for mepolizumab), or
the blood eosinophil count has been recorded as
400 cells per microlitre or more with 3 or more
exacerbations needing systemic corticosteroids in the
past 12 months (that is, the patient is eligible for reslizumab).
Benralizumab is recommended only if the manufacturer
provides it according to the commercial arrangement.
At 12 months stop benralizumab if the asthma has not
responded adequately or continue benralizumab if the
asthma has responded adequately and assess response
each year.
Benralizumab is not recommended if neither
mepolizumab nor reslizumab are recommended (see NICE
technology appraisal guidances 431 and 479).
Patients whose treatment was started within the NHS
before this guidance was published should have the option
to continue treatment, without change to their funding
arrangements, until they and their NHS clinician consider
it appropriate to stop.
www.nice.org.uk/guidance/ta565

**MEDICINAL FORMS** There can be variation in the licensing of
different medicines containing the same drug.

**Solution for injection**
- Fasenra (AstraZeneca UK Ltd) ▼
- Benralizumab 30 mg per 1 ml Fasenra 30mg/1ml solution for
  injection pre-filled syringes | 1 pre-filled disposable injection
  (PoS) £1,955.00 (Hospital only)

**Mepolizumab** 08-May-2019

**DRUG ACTION** Mepolizumab is a humanised anti-
interleukin-5 (anti-IL-5) monoclonal antibody; it reduces
the production and survival of eosinophils

**INDICATIONS AND DOSE**

Add on treatment for severe refractory eosinophilic
asthma (under expert supervision)
- BY SUBCUTANEOUS INJECTION
  - Adults: 100 mg every 4 weeks

**CAUTIONS** Helminth infection

**CAUTIONS, FURTHER INFORMATION**

- Helminth infections. Manufacturer advises pre-existing
  helminth infections should be treated before initiation of
  therapy, if patients become infected during treatment and
  do not respond to anti-helmintic treatment, consider
  treatment interruption.

**SIDE-EFFECTS**

- Common or very common Abdominal pain upper -
  administration related reaction - back pain - eczema - fever
  - headache - hypersensitivity - increased risk of infection
  - nasal congestion

**PREGNANCY** Manufacturer advises avoid unless potential
benefit outweighs risk—limited data available.

**BREAST FEEDING** Manufacturer advises avoid—present in
milk in animal studies.

**PATIENT AND CARER ADVICE**

Asthma Patients and their carers should be advised to seek
medical advice if their asthma remains uncontrolled or
worsens after initiation of treatment.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Mepolizumab for treating severe refractory eosinophilic
  asthma (January 2017) NICE TA431

  Mepolizumab (Nucala®), as an add-on to optimised
  standard therapy, is recommended as an option for
treating severe refractory eosinophilic asthma in adults,
only if:

  - the blood eosinophil count is 300 cells/microlitre or
  more in the previous 12 months, and

  - the person has agreed to and followed the optimised
  standard treatment plan and has had 4 or more asthma
  exacerbations requiring systemic corticosteroids in the
  previous 12 months or had continuous oral
corticosteroids of at least the equivalent of prednisolone
  5 mg per day over the previous 6 months, and

  - the manufacturer provides mepolizumab with the
  discount agreed in the patient access scheme.

At 12 months of treatment:

- stop mepolizumab if the asthma has not responded
  adequately, or

- continue treatment if the asthma has responded
  adequately and assess response each year.

Patients whose treatment was started within the NHS
before this guidance was published should have the option
to continue treatment, without change to their funding
arrangements, until they and their NHS clinician consider
it appropriate to stop.
www.nice.org.uk/guidance/ta431

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1149/16

The Scottish Medicines Consortium has advised (June 2016)
that mepolizumab (Nucala®) is accepted for restricted use
within NHS Scotland as an add-on treatment for severe
refractory eosinophilic asthma in adults who have
eosinophils of at least 150 cells/microlitre (0.15 × 10^9/L) at
initiation of treatment and have had at least four asthma
exacerbations in the preceding year or are receiving
maintenance treatment with oral corticosteroids. This
advice is contingent upon the continuing availability of
the patient access scheme in NHS Scotland or a list price
that is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of
different medicines containing the same drug.

**Powder for solution for injection**

EXCIPIENTS: May contain Polysorbates
- Nucala (GlaxoSmithKline UK Ltd) ▼
- Mepolizumab 100 mg Nucala 100mg powder for solution for
  injection vials | 1 vial (PoS) £840.00 (Hospital only)

**Omalizumab**

**INDICATIONS AND DOSE**

Prophylaxis of severe persistent allergic asthma
- BY SUBCUTANEOUS INJECTION
  - Adult: Dose according to immunoglobulin E
    concentration and body-weight (consult product
    literature)

Add-on therapy for chronic spontaneous urticaria in
patients who have had an inadequate response to H1
antihistamine treatment
- BY SUBCUTANEOUS INJECTION
  - Adult: 300 mg every 4 weeks

**CAUTIONS** Autoimmune disease - susceptibility to
helminth infection—discontinue if infection does not
respond to anthelmintic

**SIDE-EFFECTS**

- Common or very common Headache - skin reactions

www.getintopharma.com
Uncommon Cough • diarrhoea • dizziness • drowsiness • dyspnea • fatigue • flushing • increased risk of infection • influenza like illness • limb swelling • nausea • paraesthesia • photosensitivity reaction • postural hypotension • respiratory disorders • syncope • weight increased

Rare or very rare Angioedema • hypersensitivity • systemic lupus erythematosus (SLE)

Frequency not known Alopecia • eosinophilic granulomatosis with polyangiitis • immune thrombocytopenic purpura • joint disorders • lymphadenopathy • myalgia

SIDE-EFFECTS, FURTHER INFORMATION

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy.

Hypersensitivity reactions Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

PREGNANCY Manufacturer advises avoid unless essential—crosses the placenta.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises caution (no information available).

RENAL IMPAIRMENT Manufacturer advises caution—no information available.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Omalizumab for severe persistent allergic asthma (April 2013) NICE TA278 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in patients aged 6 years and over:

• who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and

• only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta, agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

Patients currently receiving omalizumab whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA278

Omalizumab for previously treated chronic spontaneous urticaria (June 2015) NICE TA339 Omalizumab is an option as add-on therapy for the treatment of severe chronic spontaneous urticaria in patients 12 years and over, only if:

• the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more,

• the patient’s condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists,

• omalizumab is stopped at or before the fourth dose if the condition has not responded,

• omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded and is restarted only if the condition relapses,

• omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy,

• the manufacturer provides omalizumab with the discount agreed in the patient access scheme.

Patients currently receiving omalizumab whose disease does not meet the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA339

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2014) that omalizumab (Xolair®) is accepted for restricted use within NHS Scotland for the treatment of chronic spontaneous urticaria in patients aged 12 years and over, who have had an inadequate response to combination therapy with H1-antihistamines, leukotriene receptor antagonists and H1-antihistamines, used according to current treatment guidelines.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Xolair® (Novartis Pharmaceuticals UK Ltd)

Omalizumab 150 mg per 1 ml Xolair 150mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £256.15

Xolair® 75mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £128.07

Resilizumab

DRUG ACTION Resilizumab is a humanised monoclonal antibody that interferes with interleukin-5 receptor binding, thereby reducing the survival and activity of eosinophils.

INDICATIONS AND DOSE

Severe eosinophilic asthma (adjunctive therapy when inadequately controlled by high-dose corticosteroids plus another standard treatment) (specialist use only)

BY INTRAVENOUS INFUSION

Adult: (consult product literature)

PHARMACOKINETICS

• The half-life of reslizumab is approx. 24 days.

CAUTIONS

Hypersensitivity reactions • pre-existing helminth infection

CAUTIONS, FURTHER INFORMATION

Helminth infection Manufacturer advises to treat pre-existing helminth infections before starting reslizumab—consider temporarily discontinuing reslizumab if patient becomes infected during therapy and does not respond to anti-helminth treatment.

Hypersensitivity reactions Serious hypersensitivity reactions, including life-threatening anaphylaxis, can occur and manufacturer advises to monitor closely during treatment and for at least 20 minutes after completion of infusion; in the event of a hypersensitivity reaction, treatment should be permanently discontinued.

SIDE-EFFECTS

Uncommon Anaphylactic reaction • myalgia

Frequency not known Secondary malignancy

PREGNANCY Manufacturer advises avoid—limited information available.

BREAST FEEDING Manufacturer advises avoid during first few days after birth—risk of transfer of antibodies to infant cannot be excluded; present in milk in animal studies.
Montelukast

- **INDICATIONS AND DOSE**
  - **Prophylaxis of asthma**
    - **BY MOUTH**
      - Child 6 months–5 years: 4 mg once daily, dose to be taken in the evening
      - Child 6–14 years: 5 mg once daily, dose to be taken in the evening
      - Adult: 10 mg once daily, dose to be taken in the evening

Symptomatic relief of seasonal allergic rhinitis in patients with asthma.

- **BY MOUTH**
  - Child 15–17 years: 10 mg once daily, dose to be taken in the evening
  - Adult: 10 mg once daily, dose to be taken in the evening

- **INTERACTIONS** → Appendix 1: montelukast
- **SIDE-EFFECTS**
  - Common or very common Diarrhoea · fever · gastrointestinal discomfort · headache · nausea · skin reactions · upper respiratory tract infection · vomiting
  - Uncommon Akathisia · anxiety · arthralgia · asthenia · behaviour abnormal · depression · dizziness · drowsiness · dry mouth · haemorrhage · irritability · malaise · muscle complaints · oedema · seizure · sensation abnormal · sleep disorders
  - Rare or very rare Angioedema · concentration impaired · disorientation · eosinophilic granulomatosis with polyangiitis · erythema nodosum · hallucination · hepatic disorders · memory loss · palpatations · pulmonary eosinophilia · suicidal tendencies · tremor
  - SIDE-EFFECTS, FURTHER INFORMATION Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) has occurred very rarely in association with the use of montelukast; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

- **PREGNANCY** Manufacturer advises avoid unless essential. There is limited evidence for the safe use of montelukast during pregnancy; however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.

- **BREAST FEEDING** Manufacturer advises avoid unless essential.

- **DIRECTIONS FOR ADMINISTRATION** Granules may be swallowed or mixed with cold, soft food (not liquid) and taken immediately.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of chewable tablet formulations may include cherry.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer montelukast granules. Medicines for Children leaflet: Montelukast for asthma
  
  www.medicinesforchildren.org.uk/montelukast-asthma

- **NATIONAL FUNDING/ACCESS DECISIONS**

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**LEUKOTRIENE RECEPTOR ANTAGONISTS**

Leukotriene receptor antagonists

**Overview**

The leukotriene receptor antagonist montelukast below blocks the effects of cysteinyl leukotrienes in the airways.

Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid, but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis, but they are less effective in those with severe asthma who are also receiving high doses of other drugs.
corticosteroid use and who are not capable of using inhaled corticosteroids; **Singulair**® granules should be initiated by a specialist in paediatric asthma.

**SINGULAIR® CHEWABLE TABLETS**

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (June 2007) that **SINGULAIR®** chewable tablets are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; **Singulair**® chewable tablets should be initiated by a specialist in paediatric asthma.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Granules

- **Montelukast (Non-proprietary)**
  - Montelukast (as Montelukast sodium) 4 mg, Montelukast 4mg granules sachets sugar free sugar-free | 28 sachet (PMD) £4.91–£19.99 DT = £5.25
- **Singulair** (Merck Sharp & Dohme Ltd)
  - Montelukast (as Montelukast sodium) 4 mg, Singulair Paediatric 4mg granules sachets sugar-free | 28 sachet (PMD) £25.69 DT = £5.25

#### Tablet

- **Montelukast (Non-proprietary)**
  - Montelukast (as Montelukast sodium) 10 mg, Montelukast 10mg tablets | 28 tablet (PMD) £26.97 DT = £1.17
  - **Singulair** (Merck Sharp & Dohme Ltd)
    - Montelukast (as Montelukast sodium) 10 mg, Singulair 10mg tablets | 28 tablet (PMD) £26.97 DT = £1.17

#### Chewable tablet

**CAUTIONARY AND ADVISORY LABELS**

- **EXCIPIENTS:** May contain Aspartame
  - **Montelukast (Non-proprietary)**
    - Montelukast (as Montelukast sodium) 4 mg, Montelukast 4mg chewable tablets sugar free sugar-free | 28 tablet (PMD) £25.69 DT = £1.14
    - Montelukast (as Montelukast sodium) 5 mg, Montelukast 5mg chewable tablets sugar free sugar-free | 28 tablet (PMD) £25.69 DT = £1.26
  - **Singulair** (Merck Sharp & Dohme Ltd)
    - Montelukast (as Montelukast sodium) 4 mg, Singulair Paediatric 4mg chewable tablets sugar-free | 28 tablet (PMD) £25.69 DT = £1.14
    - Montelukast (as Montelukast sodium) 5 mg, Singulair Paediatric 5mg chewable tablets sugar-free | 28 tablet (PMD) £25.69 DT = £1.26

### MAST-CELL STABILISERS

**Cromoglicate and related therapy**

**Overview**

The mode of action of sodium cromoglicate below and nedocromil sodium below is not completely understood. They may be of value in asthma with an allergic basis, but, in practice, it is difficult to predict who will benefit; they could probably be given for 4 to 6 weeks to assess response. Dose frequency is adjusted according to response but is usually 3 to 4 times a day initially; this may subsequently be reduced.

In general, prophylaxis with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalations. There is evidence of efficacy of nedocromil sodium in children aged 5–12 years. Sodium cromoglicate and nedocromil sodium are of no value in the treatment of acute attacks of asthma.

Sodium cromoglicate can prevent exercise-induced asthma. However, exercise-induced asthma may reflect poor overall control and the patient should be reassessed.

Sodium cromoglicate and nedocromil sodium may also have a role in allergic conjunctivitis; sodium cromoglicate is used also in allergic rhinitis and allergy-related diarrhoea.

### Nedocromil sodium

#### INDICATIONS AND DOSE

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Child 5–17 years: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily
  - Adult: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily

**DOSE EQUIVALENCE AND CONVERSION**

- 2 puffs = 4 mg.

#### UNLICENSED USE

- In children Not licensed for use in children under 6 years.

### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE: PRESSURISED METERED DOSE INHALERS (PMDI): RISK OF AIRWAY OBSTRUCTION FROM ASPIRATION OF LOOSE OBJECTS (JULY 2018)**

See Respiratory system, drug delivery p. 235.

**SIDE-EFFECTS**

- **Common or very common** Bronchospasm · cough · gastrointestinal discomfort · headache · nausea · taste altered · vomiting
- **Frequency not known** Pharyngitis · throat irritation

**SIDE-EFFECTS, FURTHER INFORMATION**

If paradoxical bronchospasm occurs, a fast-acting inhaled bronchodilator such as salbutamol or terbutaline should be used to control symptoms; treatment with nedocromil should be discontinued.

**PREGNANCY**

Inhaled drugs can be taken as normal during pregnancy.

**BREAST FEEDING**

Inhaled drugs can be taken as normal during breast-feeding.

**TREATMENT CESSATION**

Withdrawal should be done gradually over a period of one week—symptoms of asthma may recur.

**PREScribing AND DISPensing INFORMATION**

Flavours of inhalers may include mint.

**PATIENT AND CARER ADVICE**

Regular use is necessary. Patient counselling is advised for Nedocromil aerosol for inhalation (administration).

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

**CAUTIONARY AND ADVISORY LABELS**

- **Nedocromil sodium 2 mg per 1 dose**
  - Tilade 2mg/dose inhaler CFC free | 112 Dose (PMD) £39.94 DT = £39.94

### Sodium cromoglicate

(Sodium cromoglicate)

#### INDICATIONS AND DOSE

**Prophylaxis of asthma**

- **BY INHALATION OF AEROSOL**
  - Child 5–17 years: Initially 10 mg 4 times a day, additional dose may also be taken before exercise, increased if necessary to 10 mg 6–8 times a day; maintenance 5 mg 4 times a day, 5 mg is equivalent to 1 puff
  - Adult: Initially 10 mg 4 times a day, additional dose may also be taken before exercise, increased if necessary to 10 mg 6–8 times a day; maintenance 5 mg 4 times a day, 5 mg is equivalent to 1 puff

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**www.getintopharma.com**
Airways disease, obstructive 271

PHOSPHODIESTERASE TYPE-4 INHIBITORS

Roflumilast 08-Feb-2019

- **DRUG ACTION** Roflumilast is a phosphodiesterase type-4 inhibitor with anti-inflammatory properties.

- **INDICATIONS AND DOSE** Adjunct to bronchodilators for the maintenance treatment of patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations.
  - **BY MOUTH**
    - Adult: Initially 250 micrograms once daily for 28 days, then maintenance 500 micrograms once daily

- **CONTRA-INDICATIONS** Cancer (except basal cell carcinoma) · concomitant treatment with immunosuppressive drugs (except short-term systemic corticosteroids) · history of depression associated with suicidal ideation or behaviour · moderate to severe cardiac failure · severe acute infectious disease · severe immunological disease

- **CAUTIONS** History of psychiatric illness (discontinue if new or worsening psychiatric symptoms occur) · latent infection (such as tuberculosis, viral hepatitis, herpes infection)

- **INTERACTIONS** → Appendix 1: roflumilast

- **SIDE-EFFECTS**
  - Common or very common Appetite decreased · diarrhea · gastrointestinal discomfort · headache · insomnia · nausea · weight decreased
  - Uncommon Anxiety · asthenia · back pain · dizziness · gastrointestinal disorders · malaise · muscle complaints · muscle weakness · palpitations · skin reactions · tremor · vertigo · vomiting
  - Rare or very rare Angioedema · constipation · depression · gynaecomastia · haematochezia · respiratory tract infection · suicidal tendencies · taste altered

- **CONCEPTION AND CONTRACEPTION** Women of child-bearing age should use effective contraception.

- **PREGNANCY** Manufacturer advises avoid—tocolytic in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

- **MONITORING REQUIREMENTS** Monitor body-weight.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and carers should be instructed to report changes in behaviour or mood and any suicidal ideation.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

  - **Capsule**
    - **CAUTIONARY AND ADVISORY LABELS** 22
    - **Nalcrom** (Sanofi)
    - Sodium cromoglicate 100 mg. Nalcrom 100mg capsules | 100 capsule (POM) £41.14 DT = £41.14

  - **Pressurised inhalation**
    - **CAUTIONARY AND ADVISORY LABELS** 8
    - **Intal** (Sanofi)
    - Sodium cromoglicate 5 mg per 1 dose Intal 5mg/dose inhaler CFC free | 112 dose (POM) £18.33 DT = £18.33

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE decisions**
    - Roflumilast for treating chronic obstructive pulmonary disease (July 2017) NICE TA461 Roflumilast (Daxas®), as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in patients with chronic bronchitis, only if:
      - the disease is severe, defined as a forced expiratory volume in one second (FEV₁) after a bronchodilator of less than 50% of predicted normal, and
      - the person has had two or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.

    Treatment with roflumilast should be started by a specialist in respiratory medicine.

www.getintopharma.com
Patients currently receiving roflumilast whose disease does not meet the above criteria should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta461

Scottish Medicines Consortium (SMC) decisions
SMC No. 635/10
The Scottish Medicines Consortium has advised (September 2017) that roflumilast (Daxas®) is not recommended for use within NHS Scotland for maintenance treatment of severe chronic obstructive pulmonary disease (forced expiratory volume in one second [FEV₁] after a bronchodilator of less than 50% predicted) associated with chronic bronchitis in adults with a history of frequent exacerbations as add on to bronchodilator treatment as there was insufficient evidence submitted and the economic case was not demonstrated.

**M EDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Daxas (AstraZeneca UK Ltd) ▼
- Roflumilast 250 microgram Daxas 250 microgram tablets | 28 tablet [PSD] £35.20
- Roflumilast 500 microgram Daxas 500 microgram tablets | 30 tablet [PSD] £37.71 DT = £37.71

**SIDE-EFFECTS**
- Frequency not known
  - With intravenous use Acute angle closure glaucoma · angina pectoris · appetite decreased · cardiac arrest · dizziness · hypokalaemia · intracranial haemorrhage · psychotic disorder · pulmonary oedema
  - With oral use Arrhythmias · circulation impaired · dry mouth · enuresis · hypertension · sedation

**PREGNANCY**
- With oral use Manufacturer advises avoid.
- With intravenous use Increased fetal heart rate reported with parenteral ephedrine.

**BREAST FEEDING**
Present in milk; manufacturer advises avoid—irritability and disturbed sleep reported.

**RENA L IMPAIRMENT**
Use with caution.

**LESS SUITABLE FOR PRESCR IETING**
- With oral use Ephedrine tablets are less suitable and less safe for use as a bronchodilator than the selective beta₂ agonists.

**EXCEPTIONS TO LEGAL CATEGORY**

**M EDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection.

**Tablet**
- Ephedrine hydrochloride (Non-proprietary)
  - Ephedrine hydrochloride 15 mg Ephedrine hydrochloride 15 mg tablets | 28 tablet [PSD] £56.98 DT = £58.33
  - Ephedrine hydrochloride 30 mg Ephedrine hydrochloride 30 mg tablets | 28 tablet [PSD] £94.49 DT = £88.37

**Solution for injection**
- Ephedrine hydrochloride (Non-proprietary)
  - Ephedrine hydrochloride 3 mg per 1 ml Ephedrine 30 mg/10 ml solution for injection ampoules | 10 ampoule [PSD] £1.93.02
  - Ephedrine 30 mg/10 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection [PSD] £7.59–£9.50 | 12 pre-filled disposable injection [PSD] £11.90
  - Ephedrine hydrochloride 30 mg per 1 ml Ephedrine 30 mg/1 ml solution for injection ampoules | 10 ampoule [PSD] £52.50–£60.28 DT = £60.28

**X ANTHINES**

**Aminophylline**

**INDICATIONS AND DOSE**
Severe acute asthma in patients not previously treated with theophylline
- By slow intravenous injection
  - Child: 5 mg/kg (max. per dose 500 mg), to be followed by intravenous infusion
  - Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

Severe acute asthma
- By intravenous infusion
  - Child 1 month–11 years: 1 mg/kg/hour, adjusted according to plasma-theophylline concentration
  - Child 12–17 years: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
  - Adult: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
  - Elderly: 300 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

www.getintopharma.com
Severe acute exacerbation of chronic obstructive pulmonary disease in patients not previously treated with theophylline

- **BY SLOW INTRAVENOUS INJECTION**
- Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

Severe acute exacerbation of chronic obstructive pulmonary disease

- **BY INTRAVENOUS INFUSION**
- Adult: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
- Elderly: 300 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

Chronic asthma

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Child (body-weight 40 kg and above): Initially 225 mg twice daily for 1 week, then increased if necessary to 450 mg twice daily, adjusted according to plasma-theophylline concentration

Reversible airway obstruction

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult (body-weight 40 kg and above): Initially 225 mg twice daily for 1 week, then increased if necessary to 450 mg twice daily, adjusted according to plasma-theophylline concentration

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Dose adjustment may be necessary if smoking started or stopped during treatment.

DOSES AT EXTREMES OF BODY-WEIGHT

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal weight for height.

PHARMACOKINETICS

- Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water.
- Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of aminophylline are important because the toxic dose is close to the therapeutic dose.

PHYLLOCONTIN CONTINUUS® FORTE

Reversible airways obstruction

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: Initially 350 mg twice daily for 1 week, then increased if necessary to 700 mg twice daily, increase dose according to plasma-theophylline concentration

UNLICENSED USE

- In children: Aminophylline injection not licensed for use in children under 6 months.

CAUTIONS

- Arrhythmias following rapid intravenous injection - cardiac arrhythmias or other cardiac disease - elderly (increased plasma-theophylline concentration) - epilepsy - fever - hypertension - hyperthyroidism - peptic ulcer - risk of hypokalaemia

INTERACTIONS

- Appendix 1: aminophylline

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Headache - nausea - palpitations - seizure (more common when given too rapidly by intravenous injection)

SPECIFIC SIDE-EFFECTS

- With intravenous use: Abdominal pain - anxiety - arrhythmia (more common when given too rapidly by intravenous injection) - confusion - delirium - diarrhoea - dizziness - electrolyte imbalance - gastrointestinal haemorrhage - gastrooesophageal refflux disease - hyperthermia - hyperventilation - hypotension (more common when given too rapidly by intravenous injection) - insomnia - mania - metabolic disorder - pain - skin reactions - tachycardia (more common when given too rapidly by intravenous injection) - thirst - tremor - vertigo - visual impairment - vomiting

- With oral use: Arrhythmias - central nervous system stimulation - epigastric discomfort

SIDE-EFFECTS, FURTHER INFORMATION

- Potentially serious hypokalaemia may result from beta-agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

Overdose

- Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

- For specific details on the management of poisoning, see Theophylline, under Emergency treatment of poisoning p. 1359.

- **ALLERGY AND CROSS-SENSITIVITY** Allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis.

- **PREGNANCY** Neonatal irritability and apnoea have been reported. Theophylline can be taken as normal during pregnancy as it is particularly important that asthma should be well controlled during pregnancy.

- **BREASTFEEDING** Present in milk—irritability in infant reported; modified-release preparations preferable. Theophylline can be taken as normal during breast-feeding.

- **HEPATIC IMPAIRMENT** Theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of aminophylline are important because the toxic dose is close to the therapeutic dose.

- **MONITORING REQUIREMENTS**

- Aminophylline is monitored therapeutically in terms of plasma-theophylline concentrations.

- Measurement of plasma-theophylline concentration may be helpful and is essential if a loading dose of intravenous aminophylline is to be given to patients who are already taking theophylline, because serious side-effects such as convulsions and arrhythmias can occasionally precede other symptoms of toxicity.

- In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

- If aminophylline is given intravenously, a blood sample should be taken 4–6 hours after starting treatment.

- With oral use: Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).

DIRECTIONS FOR ADMINISTRATION

- With intravenous use: For intravenous injection, give very slowly over at least 20 minutes (with close monitoring).
With intravenous use in children For intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%.

With intravenous use in adults For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%.

With intramuscular use Aminophylline is too irritant for intramuscular use.

Prescribing and dispensing information Patients taking theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline.

Consider intravenous aminophylline for treatment of severe and life-threatening acute asthma only after consultation with senior medical staff.

Modified release The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral aminophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

Phyllocontin Continus® Forte Phyllocontin Continus® Forte tablets are for smokers and other patients where theophylline half-life is shorter.

Medicinal forms There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion pre-formed, modified-release, andophylline (Non-proprietary)

Aminophylline 25 mg per 1 ml Aminophylline 250mg/10ml solution for injection ampoules | 10 ampoule (BD) £8.50 DT + £8.50

Modified-release tablet Cautionary and advisory labels 25

Phyllocontin Continus® (Napp Pharmaceuticals Ltd)

Aminophylline hydrate 225 mg Phyllocontin Continus 225mg tablets | 56 tablet (£) £4.40 DT + £2.40

Aminophylline hydrate 350 mg Phyllocontin Forte Continus 350mg tablets | 56 tablet £6.22 DT + £4.22

Theophylline

indications and dose

Dose adjustment due to interactions Dose adjustment may be necessary if smoking started or stopped during treatment.

Pharmacokinetics Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of theophylline are important because the toxic dose is close to the therapeutic dose.

Nuelin SA® 175mg Tablets

Reversible airways obstruction | Severe acute asthma | Chronic asthma

By mouth using modified-release medicines

Adult: 175–350 mg every 12 hours

Chronic asthma

By mouth using modified-release medicines

Child 6–11 years: 175 mg every 12 hours

Child 12–17 years: 175–350 mg every 12 hours

Nuelin SA® 250 Tablets

Reversible airways obstruction | Severe acute asthma | Chronic asthma

By mouth using modified-release medicines

Adult: 250–500 mg every 12 hours

Chronic asthma

By mouth using modified-release medicines

Child 6–11 years: 250–500 mg every 12 hours

Child 12–17 years: 250–500 mg every 12 hours

Slo-Phyllin®

Chronic asthma

By mouth using modified-release medicines

Child: 2–5 years: 60–120 mg every 12 hours

Child 6–11 years: 125–250 mg every 12 hours

Child 12–17 years: 250–500 mg every 12 hours

Reversible airways obstruction | Severe acute asthma | Chronic asthma

By mouth using modified-release medicines

Adult: 250–500 mg every 12 hours

Uniphyllin Continus®

Chronic asthma

By mouth using modified-release medicines

Child 2–11 years: 9 mg/kg every 12 hours (max. per dose 200 mg), dose may be increased in some children with chronic asthma; increased to 10–16 mg/kg every 12 hours (max. per dose 400 mg), may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

Child 12–17 years: 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

Reversible airways obstruction | Severe acute asthma

Chronic asthma

By mouth using modified-release medicines

Adult: 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

Caution Cardiac arrhythmias or other cardiac disease, elderly (increased plasma-theophylline concentration), epilepsy, fever, hyperthyroidism, peptic ulcer - risk of hypokalaemia

Interactions Appendix 1: theophylline

Side-effects Anxiety, arthralgia, diarrhoea, dizziness, gastrointestinal discomfort, gastrooesophageal reflux disease, headache, hypouricaemia, nausea, palpitations, seizure, skin reactions, sleep disorders, tremor, urinary disorders, vomiting

Side-effects, Further information Potentially serious hypokalaemia may result from beta-agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

Overdose Theophylline in overdose can cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis,
convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

For details on the management of poisoning, see Theophylline, under Emergency treatment of poisoning p. 1359.

- **PREGNANCY** Neonatal irritability and apnoea have been reported. Theophylline can be taken as normal during pregnancy as it is particularly important that asthma should be well controlled during pregnancy.

- **BREAST FEEDING** Present in milk—irritability in infant reported; modified-release preparations preferable. Theophylline can be taken as normal during breast-feeding.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure). 

  **Dose adjustments** Manufacturer advises consider dose reduction.

- **MONITORING REQUIREMENTS**

  ▶ In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

  ▶ Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).

- **DIRECTIONS FOR ADMINISTRATION**

  **SLO-PHYLLIN®**

  ▶ In adults Swallow whole with fluid or swallow enclosed granules with soft food (e.g. yoghurt).

  ▶ In children Contents of the capsule (enteric-coated granules) may be sprinkled on to a spoonful of soft food (e.g. yoghurt) and swallowed without chewing.

- **PRESCRIBING AND DISPENSING INFORMATION**

  The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral theophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

- **PATIENT AND CARER ADVICE**

  **SLO-PHYLLIN®** Patient or carer should be given advice on how to administer theophylline modified release capsules.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Modified-release tablet**

  **CAUTIONARY AND ADVISORY LABELS 21, 25**

  ▶ Nuelin SA (Meda Pharmaceuticals Ltd)

    Theophylline 175 mg Nuelin SA 175mg tablets | 60 tablet [P] £6.38 DT = £6.38

    Theophylline 250 mg Nuelin SA 250 tablets | 60 tablet [P] £8.92 DT = £8.92

  ▶ Uniphyllin Continus (Napp Pharmaceuticals Ltd)

    Theophylline 200 mg Uniphyllin Continus 200mg tablets | 56 tablet [P] £2.96 DT = £2.96

    Theophylline 300 mg Uniphyllin Continus 300mg tablets | 56 tablet [P] £4.77 DT = £4.77

  ▶ Resp-Ease 6% (Pari Medical)

    Theophylline 400 mg Resp-Ease 400mg tablets | 56 tablet [P] £5.65 DT = £5.65

- **Modified-release capsule**

  **CAUTIONARY AND ADVISORY LABELS 25**

  ▶ SLO-PHYLLIN®(Merck Serono Ltd)

    Theophylline 60 mg SLO-Phyllin 60mg capsules | 56 capsule [P] £2.76 DT = £2.76

  ▶ Resp-Ease (Venture Healthcare Ltd)

    Theophylline 125 mg Resp-Ease 125mg capsules | 56 capsule [P] £3.48 DT = £3.48

    Theophylline 250 mg Resp-Ease 250mg capsules | 56 capsule [P] £6.34 DT = £6.34

**Respiratory system**

- **Nebuliser solutions**

  **HYPERTONIC SODIUM CHLORIDE SOLUTIONS**

  **INDICATIONS AND DOSE**

  **MUCOCLEAR® 3%**

  Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis) | Mild to moderate acute viral bronchiolitis in infants

  ▶ By Inhalation of Nebulised Solution

    ▶ Adult: 4 mL 2–4 times a day, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects

  **MUCOCLEAR® 6%**

  Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis) | By Inhalation of Nebulised Solution

  ▶ Adult: 4 mL twice daily, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects

  **NEBUSAL®**

  Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis) | By Inhalation of Nebulised Solution

  ▶ Adult: 4 mL up to twice daily, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects

  **Resp-Ease® 6%**

  Mobilise lower respiratory tract secretions and prevent drying of bronchial mucous. | By Inhalation of Nebulised Solution

  ▶ Adult: (consult product literature)

  ▶ Resp-Ease 6% inhalation solution 4 ml ampoules (Venture Healthcare Ltd)

    60 vial = NHS indicative price = £22.00 - Drug Tariff (Part IXa)

    600 ampoule = NHS indicative price = £21.00 - Drug Tariff (Part IXa)
Peak flow meters: low range

- **LOW RANGE PEAK FLOW METERS**
  - **MEDI**® **LOW RANGE**
    - Range 40–420 litres/minute.
    - Compliant to standard EN ISO 23747:2007 except for scale range.
  - **Mini-Wright peak flow meter low range** (Medicareplus International Ltd)
    - 1 device - NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50
  - **POCKETPEAK® LOW RANGE**
    - Range 30–400 litres/minute.
    - Compliant to standard EN ISO 23747:2007 except for scale range.
  - **Mini-Wright peak flow meter low range** (Clement Clarke International Ltd)
    - 1 device - NHS indicative price = £7.14 • Drug Tariff (Part IXa) price = £6.50
  - **nSpire Pocket Peak peak flow meter low range** (nSpire Health Ltd)
    - 1 device - NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £6.50

Peak flow meters: standard range

- **STANDARD RANGE PEAK FLOW METERS**
  - **AIRZONE®**
    - Range 60–720 litres/minute.
  - **AirZone peak flow meter standard range** (Clement Clarke International Ltd)
    - 1 device - NHS indicative price = £4.69 • Drug Tariff (Part IXa) price = £4.50
  - **MEDI® STANDARD RANGE**
    - Range 60–800 litres/minute.
  - **Medi peak flow meter standard range** (Medicareplus International Ltd)
    - 1 device - NHS indicative price = £4.50 • Drug Tariff (Part IXa) price = £4.50
  - **MICROPEAK®**
    - Range 60–900 litres/minute.
  - **MicroPeak peak flow meter standard range** (Micro Medical Ltd)
    - 1 device - NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50
  - **MINI-WRIGHT® STANDARD RANGE**
    - Range 60–800 litres/minute.
  - **Mini-Wright peak flow meter standard range** (Clement Clarke International Ltd)
    - 1 device - NHS indicative price = £7.08 • Drug Tariff (Part IXa) price = £7.08
  - **PIKO-1®**
    - Range 15–999 litres/minute.
  - **nSpire Piko-1 peak flow meter standard range** (nSpire Health Ltd)
    - 1 device - NHS indicative price = £9.50 • Drug Tariff (Part IXa) price = £9.50
  - **Pinnacle®**
    - Range 60–900 litres/minute.
  - **Fyne Dynamics Pinnacle peak flow meter standard range** (Fyne Dynamics Ltd)
    - 1 device - NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50
  - **POCKETPEAK® STANDARD RANGE**
    - Range 60–800 litres/minute.

nSpire Pocket Peak peak flow meter standard range (nSpire Health Ltd)
1 device • NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £6.50

**VITALOGRAPH®**
Range 50–800 litres/minute.
Vitalograph peak flow meter standard range (Vitalograph Ltd)
1 device • NHS indicative price = £4.83 • Drug Tariff (Part IXa) price = £4.50

Spacers

- **SPACERS**
  - **AZA SPACER®**
    - For use with all pressurised (aerosol) inhalers.
  - **AZA Spacer** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £4.15 • Drug Tariff (Part IXa)
  - **AZA Spacer with medium mask** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa)
  - **AZA Spacer with small mask** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa)
  - **ABLE SPACER®**
    - Small-volume device. For use with all pressurised (aerosol) inhalers.
  - **Able Spacer** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £4.39 • Drug Tariff (Part IXa)
  - **Able Spacer with medium mask** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa)
  - **Able Spacer with small mask** (Clement Clarke International Ltd)
    - 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa)
  - **AEROCHAMBER PLUS®**
    - Medium-volume device. For use with all pressurised (aerosol) inhalers.
  - **AeroChamber Plus** (Trudell Medical UK Ltd)
    - 1 device • NHS indicative price = £4.94 • Drug Tariff (Part IXa)
  - **AeroChamber Plus with adult mask** (Trudell Medical UK Ltd)
    - 1 device • NHS indicative price = £6.24 • Drug Tariff (Part IXa)
  - **AeroChamber Plus with child mask** (Trudell Medical UK Ltd)
    - 1 device • NHS indicative price = £6.24 • Drug Tariff (Part IXa)
  - **AeroChamber Plus with infant mask** (Trudell Medical UK Ltd)
    - 1 device • NHS indicative price = £6.24 • Drug Tariff (Part IXa)
  - **BABYHALER®**
    - For paediatric use with Flixotide®, and Ventolin® inhalers.

**PRESCRIBING AND DISPENSING INFORMATION**
Not available for NHS prescription.

- **Babyhaler** (GlaxoSmithKline UK Ltd)
  - 1 device • No NHS indicative price available • Drug Tariff (Part IXa)
- **HALERAID®**
  - Device to place over pressurised (aerosol) inhalers to aid when strength in hands is impaired (e.g. in arthritis). For use with Flixotide®, Serevent®, and Ventolin® inhalers.

**PRESCRIBING AND DISPENSING INFORMATION**
Not available for NHS prescription.

- **Haleraid-120** (GlaxoSmithKline UK Ltd)
  - 1 device • No NHS indicative price available • Drug Tariff (Part IXa)
  - **Optichamber®**
    - For use with all pressurised (aerosol) inhalers.
  - **Optichamber (Respironics (UK) Ltd)**
    - 1 device • NHS indicative price = £6.06 • Drug Tariff (Part IXa)
  - **Optichamber® DIAMOND**
    - For use with all pressurised (aerosol) inhalers.
  - **Optichamber Diamond (Respironics (UK) Ltd)**
    - 1 device • NHS indicative price = £7.49 • Drug Tariff (Part IXa)
Allergic conditions

2 Allergic conditions

Antihistamines, allergen immunotherapy and allergic emergencies

Antihistamines

All antihistamines are of potential value in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hayfever), and they may be of some value in vasomotor rhinitis. They reduce rhinorrhea and sneezing but are usually less effective for nasal congestion. Antihistamines are used topically in the eye, in the nose, and on the skin.

Oral antihistamines are also of some value in preventing urticaria and are used to treat urticarial rashes, pruritus, and insect bites and stings; they are also used in drug allergies. Injections of chlorphenamine maleate p. 283 or promethazine hydrochloride p. 286 are used as an adjunct to adrenaline/epinephrine p. 222 in the emergency treatment of anaphylaxis and angioedema. Antihistamines (including cinnarizine p. 438, cyclizine p. 430, and promethazine teoclate p. 438) may also have a role in nausea and vomiting. Buclizine is included as an anti-emetic in a preparation for migraine. Antihistamines may also have a role in occasional insomnia.

All older antihistamines cause sedation but amin嗪azine tartrate p. 282 and promethazine may be more sedating whereas chlorphenamine maleate and cyclizine may be less so. This sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older, ‘sedating’ antihistamines is superior to another and patients vary widely in their response.

Non-sedating antihistamines such as acrivastine p. 279, bilastine p. 279, cetirizine hydrochloride p. 279, desloratadine p. 280 (an active metabolite of loratadine p. 281), fexofenadine hydrochloride p. 280 (an active metabolite of terfenadine), levocetirizine hydrochloride p. 281 (an isomer of cetirizine hydrochloride), loratadine and mizolastine p. 282 cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

Allergen immunotherapy

Immunotherapy using allergen vaccines containing house dust mite, animal dander (cat or dog), or extracts of grass and tree pollen can reduce symptoms of asthma and allergic rhinoconjunctivitis. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in individuals with hypersensitivity to wasp and bee stings. An oral preparation of grass pollen extract (Graza®) is also licensed for disease-modifying treatment of grass pollen–induced rhinitis and conjunctivitis. Those requiring immunotherapy must be referred to a hospital specialist for accurate diagnosis, assessment, and treatment.

Omalizumab p. 267 is a monoclonal antibody that binds to immunoglobulin E (IgE). It is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high dose inhaled corticosteroid together with a long-acting beta, agonist. Omalizumab should be initiated by physicians in specialist centres experienced in the treatment of severe persistent asthma. Omalizumab is also indicated as add-on therapy for the treatment of chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment.

Anaphylaxis and allergic emergencies

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by the rapid onset of respiratory and/or circulatory problems and is usually associated with skin and mucosal changes; prompt treatment is required. Patients with pre-existing asthma, especially poorly controlled asthma, are at particular risk of life-threatening reactions. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cow’s milk protein, peanuts, sesame, shellfish, soy, and tree nuts may also precipitate anaphylaxis (see Food allergy p. 84). Medicinal products particularly associated with anaphylaxis include blood products, vaccines, hyposensitising (allergen) preparations, antibacterials, aspirin and other NSAIDs, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available for injections associated with special risk. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal

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products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens.

**Treatment of anaphylaxis**

Adrenaline/epinephrine provides physiological reversal of the immediate symptoms associated with hypersensitivity reactions such as anaphylaxis and angioedema.

First-line treatment includes:

- securing the airway, restoration of blood pressure (laying the patient flat and raising the legs, or in the recovery position if unconscious or nauseous and at risk of vomiting);
- administering adrenaline/epinephrine (by intramuscular injection in a dose of 300 micrograms may be appropriate for immediate self-administration); the dose should be repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. Patients receiving beta-blockers require special consideration;
- administering high-flow oxygen and intravenous fluids is also of primary importance;
- administering an antihistamine, such as chlorphenamine maleate, by slow intravenous injection or intramuscular injection is a useful adjunctive treatment, given after adrenaline.
- Administering an intravenous corticosteroid such as hydrocortisone p. 676 (preferably as sodium succinate) is of secondary value in the initial management of anaphylaxis because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected patients.

**Continuing respiratory deterioration** requires further treatment with bronchodilators including inhaled or intravenous salbutamol p. 252, inhaled ipratropium bromide p. 246, intravenous aminophylline p. 272, or intravenous magnesium sulfate p. 1051 [unlicensed indication] (as for acute severe asthma); in addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

When a patient is so ill that there is doubt about the adequacy of the circulation, the initial injection of adrenaline/epinephrine may need to be given as a dilute solution by the intravenous route.

Cardiopulmonary arrest may follow an anaphylactic reaction; resuscitation should be started immediately. On discharge, patients should be considered for further treatment with an oral antihistamine and an oral corticosteroid for up to 3 days to reduce the risk of further reaction. Patients should be instructed to return to hospital if symptoms recur and to contact their general practitioner if necessary.

Patients who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis. Avoidance of the allergen is the principal treatment; if appropriate, an adrenaline/epinephrine auto-injector should be given for self-administration or a replacement supplied.

**Intramuscular adrenaline (epinephrine)**

The intramuscular route is the first choice route for the administration of adrenaline/epinephrine in the management of anaphylaxis. Adrenaline/epinephrine is best given as an intramuscular injection into the anterolateral aspect of the middle third of the thigh; it has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site.

Patients with severe allergy should be instructed in the self-administration of adrenaline/epinephrine p. 222 by intramuscular injection.

Prompt injection of adrenaline/epinephrine is of paramount importance. The adrenaline/epinephrine doses recommended for the emergency treatment of anaphylaxis by appropriately trained healthcare professionals are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

**Intravenous adrenaline (epinephrine)**

Intravenous adrenaline/epinephrine should be given only by those experienced in its use, in a setting where patients can be carefully monitored.

When the patient is severely ill and there is real doubt about the adequacy of the circulation and absorption after intramuscular injection, adrenaline/epinephrine can be given by slow intravenous injection repeated according to response; if multiple doses are required, adrenaline/epinephrine should be given as a slow intravenous infusion stopping when a response has been obtained.

It is important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

The intravenous route is also used for cardiac resuscitation.

**Angioedema**

Angioedema is dangerous if laryngeal oedema is present. In this circumstance adrenaline/epinephrine injection and oxygen should be given as described under **Anaphylaxis**; antihistamines and corticosteroids should also be given. Tracheal intubation may be necessary.

**Hereditary angioedema**

The treatment of hereditary angioedema should be under specialist supervision. Unlike allergic angioedema, adrenaline/epinephrine, corticosteroids, and antihistamines should not be used for the treatment of acute attacks, including attacks involving laryngeal oedema, as they are ineffective and may delay appropriate treatment—intubation may be necessary. The administration of C1-esterase inhibitor p. 289, an endogenous complement blocker derived from human plasma, (in fresh frozen plasma or in partially purified form) can terminate acute attacks of hereditary angioedema; it can also be used for short-term prophylaxis before dental, medical or surgical procedures. Conestat alfa p. 290 and icatibant p. 290 are licensed for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency.

Tranexamic acid p. 110 and danazol p. 742 [unlicensed indication] are used for short-term and long-term prophylaxis of hereditary angioedema. Short-term prophylaxis with tranexamic acid or danazol is started several days before planned procedures (e.g. dental work) and continued for 2–5 days afterwards. Danazol should be avoided in children because of its androgenic effects.

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**Dose of intramuscular injection of adrenaline (epinephrine) for the emergency treatment of anaphylaxis by healthcare professionals**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Volume of adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month-5 years</td>
<td>150 micrograms</td>
<td>0.15 mL 1 in 1000 (1 mg/mL) adrenaline¹</td>
</tr>
<tr>
<td>Child 6-11 years</td>
<td>300 micrograms</td>
<td>0.3 mL 1 in 1000 (1 mg/mL) adrenaline</td>
</tr>
<tr>
<td>Child 12-17 years</td>
<td>500 micrograms</td>
<td>0.5 mL 1 in 1000 (1 mg/mL) adrenaline²</td>
</tr>
<tr>
<td>Adult</td>
<td>500 micrograms</td>
<td>0.5 mL 1 in 1000 (1 mg/mL) adrenaline</td>
</tr>
</tbody>
</table>

These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse and respiratory function.

1. Use suitable syringe for measuring small volume
2. 300 micrograms (0.3 mL) if child is small or prepubertal
ANTIHISTAMINES › NON-SEDATING

Acrivastine 19-May-2017  
- INDICATIONS AND DOSE  
Symptomatic relief of allergy such as hayfever, chronic idiopathic urticaria
  - BY MOUTH  
    - Child 12-17 years: 8 mg 3 times a day  
    - Adult: 8 mg 3 times a day
- CONTRA-INDICATIONS  
  Avoid in Acute porphyrias p. 1058 - elderly
- INTERACTIONS  
  → Appendix 1: antihistamines, non-sedating
- SIDE-EFFECTS  
  - Common or very common  
    Drowsiness, dry mouth
  - Frequency not known  
    Dizziness, rash
- SIDE-EFFECTS, FURTHER INFORMATION  
  Non-sedating antihistamines such as acrivastine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.
- ALLERGY AND CROSS-SENSITIVITY  
  Contra-indicated if history of hypersensitivity to triprolidine.
- PREGNANCY  
  Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- BREAST FEEDING  
  Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- PATIENT AND CARER ADVICE  
  Patients or carers should be given advice on how to administer bilastine tablets.
  - Driving and skilled tasks  
    Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
- MEDICINAL FORMS  
  There can be variation in the licensing of different medicines containing the same drug.
  - Tablet  
    CAUTIONARY AND ADVISORY LABELS  
    23  
    - Ilaxten (A. Menarini Farmaceutica Internazionale SRL)  
      Bilastine 20 mg  
      Ilaxten 20mg tablets  |  30 tablet [POM] £15.09

Bilastine 22-May-2007  
- INDICATIONS AND DOSE  
Symptomatic relief of allergic rhinoconjunctivitis and urticaria
  - BY MOUTH  
    - Child 12-17 years: 20 mg once daily  
    - Adult: 20 mg once daily
- CONTRA-INDICATIONS  
  Avoid in Acute porphyrias p. 1058
- INTERACTIONS  
  → Appendix 1: antihistamines, non-sedating
- SIDE-EFFECTS  
  - Common or very common  
    Drowsiness, headache
  - Uncommon  
    Anxiety, appetite increased, asthenia, bundle branch block, diarrhoea, dry mouth, dyspnoea, fever, gastritis, gastrointestinal discomfort, insomnia, nasal complaints, nausea, oral herpes, pre-existing condition improved, pruritus, QT interval prolongation, sinus arrhythmia, thirst, tinnitus, vertigo, weight increased
- SIDE-EFFECTS, FURTHER INFORMATION  
  Non-sedating antihistamines such as bilastine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.
- PREGNANCY  
  Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- BREAST FEEDING  
  Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- PATIENT AND CARER ADVICE  
  Patients or carers should be given advice on how to administer bilastine tablets.
  - Driving and skilled tasks  
    Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
- MEDICINAL FORMS  
  There can be variation in the licensing of different medicines containing the same drug.
  - Tablet  
    CAUTIONARY AND ADVISORY LABELS  
    23  
    - Ilaxten (A. Menarini Farmaceutica Internazionale SRL)  
      Bilastine 20 mg  
      Ilaxten 20mg tablets  |  30 tablet [POM] £15.09

Cetirizine hydrochloride  
- INDICATIONS AND DOSE  
Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopic dermatitis
  - BY MOUTH  
    - Child 2-5 years: 2.5 mg twice daily  
    - Child 6-11 years: 5 mg twice daily  
    - Child 12-17 years: 10 mg once daily  
    - Adult: 10 mg once daily
- CAUTIONS  
  Epilepsy
- INTERACTIONS  
  → Appendix 1: antihistamines, non-sedating
- SIDE-EFFECTS  
  - Uncommon  
    Agitation, asthma, diarrhoea, malaise, paraesthesia, skin reactions
  - Rare or very rare  
    Aggression, angioedema, confusion, depression, hallucination, hepatic function abnormal, insomnia, movement disorders, oculogyration, oedema, seizure, syncope, tachycardia, taste altered, thrombocytopenia, tic, tremor, urinary disorders, vision disorders, weight increased
- Frequency not known  
  Abdominal pain, appetite increased, dizziness, diarrhoea, dry mouth, headache, memory loss, nausea, pharyngitis, suicidal ideation, vertigo
- SIDE-EFFECTS, FURTHER INFORMATION  
  Non-sedating antihistamines such as cetirizine hydrochloride cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.
- PREGNANCY  
  Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- BREAST FEEDING  
  Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- PATIENT AND CARER ADVICE  
  Patients or carers should be given advice on how to administer bilastine tablets.
  - Driving and skilled tasks  
    Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
- MEDICINAL FORMS  
  There can be variation in the licensing of different medicines containing the same drug.
  - Tablet  
    CAUTIONARY AND ADVISORY LABELS  
    23  
    - Ilaxten (A. Menarini Farmaceutica Internazionale SRL)  
      Cetirizine hydrochloride 20 mg  
      Ilaxten 20mg tablets  |  30 tablet [POM] £15.09

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Respiratory system

ALLERGY AND CROSS-SENSITIVITY

▶ Rare or very rare
▶ Common or very common

INTERACTIONS

PATIENT AND CARER ADVICE

Driving and skilled tasks Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary
Cetirizine Tablets 10 mg may be prescribed.

Cetirizine Oral Solution 5 mg/5 mL may be prescribed.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Oral solution

EXCIPIENTS: May contain Propylene glycol
- Cetirizine hydrochloride (Non-proprietary)
  Cetirizine hydrochloride 1 mg per 1 ml Cetirizine 1 mg/ml oral solution sugar-free 300 mL (PO) £1.12 DT = £1.12
- Cetirizine hydrochloride 10 mg Cetirizine 10 mg tablets 30 tablet (PO) £0.85–£0.86 DT = £0.86
- Cetirizine hydrochloride 10 mg (Merck Sharp & Dohme Ltd) Cetirizine hydrochloride 10 mg Benadryl Allergy Liquid 10 mL Flavours of 200 mL (PO) £3.09 DT = £3.09

Tablet
- Cetirizine hydrochloride (Merck Sharp & Dohme Ltd) Cetirizine Tablets 10 mg 30 tablet (PO) £0.85–£0.86 DT = £0.86

Capsule
- Cetirizine hydrochloride (McNeil Products Ltd) Cetirizine Tablets 10 mg 30 tablet (PO) £0.85–£0.86 DT = £0.86

Fexofenadine hydrochloride

INDICATIONS AND DOSE

Symptomatic relief of seasonal allergic rhinitis
- BY MOUTH
  - Child 6-11 years: 30 mg twice daily
  - Child 12-17 years: 120 mg once daily
  - Adult: 120 mg once daily
Symptomatic relief of chronic idiopathic urticaria
- BY MOUTH
  - Child 6-11 years: 180 mg once daily
  - Adult: 180 mg once daily

PHARMACOKINETICS

Desloratadine is a metabolite of loratadine.

INTERACTIONS

Appendix 1: antihistamines, non-sedating

SIDE-EFFECTS

Common or very common Asthenia · dry mouth · headache
Rare or very rare Akathisia · arrhythmias · diarrhoea · dizziness · drowsiness · gastrointestinal discomfort · hallucination · hepatic disorders · insomnia · myalgia · nausea · palpitations · seizure · vomiting

Frequency not known Behaviour abnormal · photosensitivity reaction · QT interval prolongation

SIDE-EFFECTS, FURTHER INFORMATION
Non-sedating antihistamines such as fexofenadine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.

ALLERGY AND CROSS-SENSITIVITY
Contra-indicated if history of hypersensitivity to loratadine.
Levocetirizine hydrochloride

**INDICATIONS AND DOSE**

Symptomatic relief of allergy such as hay fever, urticaria

- **BY MOUTH**
  - Child 6–17 years: 5 mg once daily
  - Adult: 5 mg once daily

**PHARMACOKINETICS**

- Levocetirizine is an isomer of cetirizine.

**CONTRA-INDICATIONS**

Avoid in Acute porphyrias p. 1058

**INTERACTIONS**

→ Appendix 1: antihistamines, non-sedating

**SIDE-EFFECTS**

- **Common**
  - Asthenia, constipation (in children), drowsiness, dry mouth
- **Uncommon**
  - Abdominal pain
- **Frequency not known**
  - Agitation, angioedema, appetite increased, arthralgia, depression, dizziness (very common in children), dyspnoea, hallucination, hepatitis, myalgia, nausea, oedema, palpitations, paraesthesia, seizure, skin reactions, sleep disorders (very common in children), suicidal ideation, syncope, tachycardia, taste altered, tremor, urinary disorders, vertigo, vision disorders, vomiting, weight increased

**SIDE-EFFECTS, FURTHER INFORMATION**

Non-sedating antihistamines such as levocetirizine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**RENAL IMPAIRMENT**

- In adults Avoid if eGFR less than 10 mL/minute/1.73 m².
- In children Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**Dose adjustments**

- In adults 5 mg on alternate days if eGFR 30–50 mL/minute/1.73 m³. 5 mg every 3 days if eGFR 10–30 mL/minute/1.73 m³.

**INTERACTIONS**

→ Appendix 1: antihistamines, non-sedating

**SIDE-EFFECTS**

- **Common or very common**
  - Drowsiness, nervousness (in children)
- **Uncommon**
  - Appetite increased, headache (very common in children), insomnia
- **Rare or very rare**
  - Alopecia, angioedema, dizziness, dry mouth, fatigue (very common in children), gastritis, hepatic function abnormal, oedema, palpitations, rash, seizure, tachycardia

**SIDE-EFFECTS, FURTHER INFORMATION**

Non-sedating antihistamines such as loratadine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe impairment (risk of increased exposure).

**Dose adjustments**

Manufacturer advises initial dose reduction to alternate days in severe impairment.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Loratadine for allergy symptoms www.medicinesforchildren.org.uk/loratadine-allergy-symptoms

Driving and skilled tasks

Although drowsiness is rare, nevertheless patients and their carers should be advised.
that it can occur and may affect performance of skilled
tasks (e.g. cycling or driving); alcohol should be avoided.

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Loratadine 10 mg tablets may be prescribed.
  - Loratadine syrup 5 mg/5 mL may be prescribed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Oral solution**
  - **EXCIPIENTS:** May contain Propylene glycol
  - Loratadine (Non-proprietary)
    - **Loratadine 1 mg per 1 mL**
      - Loratadine 5mg/5ml oral solution | 100 ml (pump) £1.90 DT = £1.55
      - Loratadine 5mg/5ml oral solution sugar free sugar-free | 100 ml (pump)
  - Clarityn (Loratadine)
  - Mizollen (Sanofi)
  - Rupatadine (Non-proprietary)
    - **Rupatadine 5 mg**
      - Rupatadine 5mg modified-release tablets | 30 tablet (£30) £6.92 DT = £5.92

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Non-sedating antihistamines such as rupatadine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.
  - Uncommon Anxiety · arthralgia · back pain · concentration impaired · constipation · cough · diarrhoea · dry throat · eosinophilia (in children) · epistaxis · fever · gastrointestinal discomfort · increased risk of infection · irritability · malaise · myalgia · nasal dryness · nausea · neutropenia (in children) · night sweats (in children) · oropharyngeal pain · skin reactions · thirst · vomiting · weight increase
  - Rare or very rare Palpitations · tachycardia
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Non-sedating antihistamines such as mizolastine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.
  - **PREGNANCY**
    - Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid (no information available).

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid—no information available.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **INDICATIONS AND DOSE**
  - **Symptomatic relief of allergic rhinitis and urticaria**
    - **BY MOUTH USING TABLETS**
      - Child 12-17 years: 10 mg once daily
      - Adult: 10 mg once daily
    - **CAUTIONS**
      - Elderly—limited information available · history of QT-interval prolongation · predisposition to arrhythmia · uncorrected hypokalaemia
    - **INTERACTIONS**
      - Appendix 1: antihistamines, non-sedating
    - **SIDE-EFFECTS**
      - Asthenia · dizziness · drowsiness · dry mouth · headache
      - uncommon Appetite increased · arthralgia · back pain · concentration impaired · constipation · cough · diarrhoea · dry throat · eosinophilia (in children) · epistaxis · fever · gastrointestinal discomfort · increased risk of infection · irritability · malaise · myalgia · nasal dryness · nausea · neutropenia (in children) · night sweats (in children) · oropharyngeal pain · skin reactions · thirst · vomiting · weight increased
    - **Rare or very rare** Palpitations · tachycardia

- **Mizolastine**
  - **INDICATIONS AND DOSE**
    - Symptomatic relief of allergic symptoms such as hay fever, urticaria
    - **BY MOUTH**
      - Child 12-17 years: 10 mg once daily
      - Adult: 10 mg once daily
    - **CONTRA-INDICATIONS**
      - Cardiac disease · hypokalaemia · susceptibility to QT-interval prolongation
    - **INTERACTIONS**
      - Appendix 1: antihistamines, non-sedating
    - **SIDE-EFFECTS**
      - Common or very common Appetite increased · asthenia · diarrhoea · dizziness · dry mouth · gastrointestinal discomfort · headache · nausea · weight increased
      - uncommon Anxiety · arthralgia · back pain · concentration impaired · constipation · cough · diarrhoea · dry throat · eosinophilia (in children) · epistaxis · fever · gastrointestinal discomfort · increased risk of infection · irritability · malaise · myalgia · nasal dryness · nausea · neutropenia (in children) · night sweats (in children) · oropharyngeal pain · skin reactions · thirst · vomiting · weight increased
      - Rare or very rare Palpitations · tachycardia
    - **SIDE-EFFECTS, FURTHER INFORMATION**
      - Non-sedating antihistamines such as mizolastine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.

- **PREGNANCY**
  - Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid (no information available).

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid—no information available.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Rupatadine**
  - **DRUG ACTION**
    - Rupatadine is a second generation non-sedating antihistamine.
  - **INDICATIONS AND DOSE**
    - Symptomatic relief of allergic rhinitis and urticaria
    - **BY MOUTH USING TABLETS**
      - Child 12-17 years: 10 mg once daily
      - Adult: 10 mg once daily
    - **CAUTIONS**
      - Elderly—limited information available · history of QT-interval prolongation · predisposition to arrhythmia · uncorrected hypokalaemia
    - **INTERACTIONS**
      - Appendix 1: antihistamines, non-sedating
    - **SIDE-EFFECTS**
      - Asthenia · dizziness · drowsiness · dry mouth · headache
      - uncommon Appetite increased · arthralgia · back pain · concentration impaired · constipation · cough · diarrhoea · dry throat · eosinophilia (in children) · epistaxis · fever · gastrointestinal discomfort · increased risk of infection · irritability · malaise · myalgia · nasal dryness · nausea · neutropenia (in children) · night sweats (in children) · oropharyngeal pain · skin reactions · thirst · vomiting · weight increased
    - **Rare or very rare** Palpitations · tachycardia
    - **SIDE-EFFECTS, FURTHER INFORMATION**
      - Non-sedating antihistamines such as rupatadine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal. This is because non-sedating antihistamines penetrate the blood brain barrier to a much lesser extent.

- **PREGNANCY**
  - Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid (no information available).

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid—no information available.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Antihistamines**
  - **SEDATING ANTIHISTAMINES**
    - **Alimemazine tartrate**
      - **(Trimipramine tartrate)**
      - **INDICATIONS AND DOSE**
        - **Urticaria** · **Pruritus**
        - **BY MOUTH**
          - Child 2-4 years: 2.5 mg 3–4 times a day
Hepatic impairment

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

### Oral solution

**CAUTIONARY AND ADVISORY LABELS 2**

**Alimemazine tartrate (Non-proprietary)**

- **Alimemazine tartrate 1.5 mg per 1 ml Alimemazine 7.5mg/5ml oral solution** 100 ml £179.55 DT = £179.55
- **Alimemazine tartrate 6 mg per 1 ml Alimemazine 30mg/5ml oral solution** 100 ml £243.51 DT = £243.51
Respiratory system

MEDICINAL FORMS

PROFESSION SPECIFIC INFORMATION

DIRECTIONS FOR ADMINISTRATION

HEPATIC IMPAIRMENT

BREAST FEEDING

PREGNANCY

With parenteral use

With oral use

Drowsiness

Frequency not known

Agitation • appetite decreased • blood disorder • bronchial secretion viscosity increased • depression • diarrhoea • haemolytic anaemia • hypotension • irritability • muscle twitching • muscle weakness • nightmare • palpitations • photosensitivity reaction • skin reactions • tinnitus • urinary retention • vomiting

SPECIFIC SIDE-EFFECTS

Common or very common

With oral use

Drowsiness

Frequency not known

With oral use

Angioedema • arrhythmias • chest tightness • confusion • gastrointestinal discomfort • hepatic disorders

With parenteral use

Central nervous system stimulation • confusional psychosis (in adults) • dyspepsia • gastrointestinal disorder • hepatitis • sedation

SIDE-EFFECTS, FURTHER INFORMATION

Children and elderly patients are more susceptible to side-effects.

PREGNANCY

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

BREAST FEEDING

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

DIRECTIONS FOR ADMINISTRATION

For intravenous injection, give over 1 minute; if small dose required, dilute with Sodium Chloride 0.9%.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Chlorphenamine maleate for allergy symptoms www.medicinesforchildren.org.uk/chlorphenamine-maleate-allergy-symptoms-0

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary

With oral use

Chlorphenamine tablets may be prescribed. Chlorphenamine oral solution may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY

With intramuscular use or intravenous use

Prescription only medicine restriction does not apply to chlorphenamine injection where administration is for saving life in emergency.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Solution for injection

Chlorphenamine maleate (Non-proprietary)

Chlorphenamine maleate 10 mg per 1 ml Chlorphenamine 10mg/1ml solution for injection ampoules | 5 ampoule [PO] £22.48–£22.50 DT + £22.50

Oral solution

CAUTIONARY AND ADVISORY LABELS 2

Chlorphenamine maleate (Non-proprietary)

Chlorphenamine maleate 400 microgram per 1 ml Chlorphenamine 2mg/5ml oral solution sugar free sugar-free | 150 ml | £2.78 DT + £2.21

Allerief (Crescent Pharma Ltd)

Chlorphenamine maleate 400 microgram per 1 ml Allerief 2mg/5ml oral solution sugar free | 150 ml | £2.21 DT + £2.21

Piriton (GlaxoSmithKline Consumer Healthcare)

Chlorphenamine maleate 400 microgram per 1 ml Piriton 2mg/5ml syrup | 150 ml | £2.78 DT + £2.78

Tablet

CAUTIONARY AND ADVISORY LABELS 2

Chlorphenamine maleate (Non-proprietary)

Chlorphenamine maleate 4 mg Chlorphenamine 4mg tablets | 28 tablet [P] £1.09 DT + £0.76

Allerief (Crescent Pharma Ltd)

Chlorphenamine maleate 4 mg Allerief 4mg tablets | 28 tablet [P] £1.74 DT + £0.76

Hayleve (Genesis Pharmaceuticals Ltd)

Chlorphenamine maleate 4 mg Hayleve 4mg tablets | 28 tablet [P] £0.76 DT + £0.76

Piriton (GlaxoSmithKline Consumer Healthcare)

Chlorphenamine maleate 4 mg Piriton 4mg tablets | 500 tablet [P] £0.96

Piriton Allergy 4mg tablets | 30 tablet [P] £2.06 | 60 tablet [P] £3.73

Pollinase (chlorphenamine) (E M Pharma)

Chlorphenamine maleate 4 mg Pollinase Antihistamine 4mg tablets | 30 tablet [P] £1.00

Clemastine

09-Jul-2018

INDICATIONS AND DOSE

Symptomatic relief of allergy such as hay fever, urticaria

BY MOUTH

Adult: 1 mg twice daily, increased if necessary up to 6 mg daily

CONTRA-INDICATIONS

Avoid in Acute porphyrias p. 1058

CAUTIONS

Elderly • epilepsy • prostatic hypertrophy • pyloroduodenal obstruction • stenosing peptic ulcer • susceptibility to angle-closure glaucoma • urinary retention

INTERACTIONS

Appendix 1: antihistamines, sedating

SIDE-EFFECTS

Common or very common

Asthma • sedation

Uncommon

Dizziness

Rare or very rare

Abdominal pain • agitation • constipation • dry mouth • dyspnoea • headache • nausea • palpitations • rash • tachycardia

PREGNANCY

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

BREAST FEEDING

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2

Tavegil (GlaxoSmithKline Consumer Healthcare)

Clemastine (as Clemastine hydrogen fumarate) 1 mg Tavegil 1mg tablets | 60 tablet [P] £6.66 DT = £6.66

Cyproheptadine hydrochloride

30-Jun-2018

INDICATIONS AND DOSE

Symptomatic relief of allergy such as hay fever, urticaria

Pruritus

BY MOUTH

Adult: 4 mg 3 times a day, usual dose 4–20 mg daily; maximum 32 mg per day

CONTRA-INDICATIONS

Avoid in Acute porphyrias p. 1058

CAUTIONS

Epilepsy • prostatic hypertrophy • pyloroduodenal obstruction • susceptibility to angle-closure glaucoma • urinary retention

INTERACTIONS

Appendix 1: antihistamines, sedating
Hydroxyzine hydrochloride 30-Mar-2017

**DRUG ACTION**

Hydroxyzine is a sedating antihistamine which exerts its actions by antagonising the effects of histamine.

**INDICATIONS AND DOSE**

- **Pruritus**
  - **By mouth**
    - Child 6 months-5 years: 5–15 mg daily in divided doses, dose adjusted according to weight; maximum 2 mg/kg per day.
    - Child 6–17 years (body-weight up to 40 kg): Initially 15–25 mg daily in divided doses, dose increased as necessary, adjusted according to weight; maximum 2 mg/kg per day.
    - Child 6–17 years (body-weight >40 kg and above): Initially 15–25 mg daily in divided doses, increased if necessary to 50–100 mg daily in divided doses, dose adjusted according to weight.
    - Adult: Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg 3–4 times a day.
    - Elderly: Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg twice daily.

**SIDE-EFFECTS**


**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitation, and tremor.

**CAUTIONS**

- Elderly: Elderly patients are particularly susceptible to side-effects, particularly CNS effects.
- Children: Children have an increased susceptibility to side-effects; manufacturers advise avoid or reduce dose.
- Interaction: Appendix 1: antihistamines, sedating
- Side-effects: Rare or very rare: Severe cutaneous adverse reactions (SCARs): skin reactions

**SIDE-EFFECTS**

- Paradoxical stimulation may occur rarely, especially with high doses or in the elderly. Drowsiness may diminish after a few days of treatment.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: RISK OF QT-INTERVAL PROLONGATION AND TORSADE DE POINTE (APRIL 2015)

Following concerns of heart rhythm abnormalities, the safety and efficacy of hydroxyzine has been reviewed by the European Medicines Agency. The review concludes that hydroxyzine is associated with a small risk of QT-interval prolongation and torsade de pointes; these events are most likely to occur in patients who have risk factors for QT prolongation, e.g. concomitant use of drugs that prolong the QT-interval, cardiovascular disease, family history of sudden cardiac death, significant electrolyte imbalance (low plasma-potassium or plasma-magnesium concentrations), or significant bradycardia. To minimise the risk of such adverse effects, the following dose restrictions have been made and new cautions and contra-indications added:

- Hydroxyzine is contra-indicated in patients with prolonged QT-interval or who have risk factors for QT-interval prolongation;
- Avoid use in the elderly due to increased susceptibility to the side-effects of hydroxyzine;
- Consider the risks of QT-interval prolongation and torsade de pointes before prescribing to patients taking drugs that lower heart rate or plasma-potassium concentration;
- In children with body-weight up to 40 kg, the maximum daily dose is 2 mg/kg;
- In adults, the maximum daily dose is 100 mg;
- In the elderly, the maximum daily dose is 50 mg (if use of hydroxyzine cannot be avoided);
- The lowest effective dose for the shortest period of time should be prescribed.

**CONTRA-INDICATIONS**

Acquired or congenital QT interval prolongation - predisposition to QT interval prolongation

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- QT interval prolongation: Risk factors for QT interval prolongation include significant electrolyte imbalance, bradycardia, cardiovascular disease, and family history of sudden cardiac death.
- Caution: Bladder outflow obstruction - breathing problems - cardiovascular disease - children - decreased gastrointestinal motility - dementia - elderly - epilepsy - hypertension - hyperthyroidism - myasthenia gravis - prostatic hypertrophy (in adults) - pyloroduodenal obstruction - stenosing peptic ulcer - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

- Elderly: Elderly patients are particularly susceptible to side-effects; manufacturers advise avoid or reduce dose.
- Children: Children have an increased susceptibility to side-effects, particularly CNS effects.
286 Allergic conditions

- **ALLERGY AND CROSS-SENSITIVITY** Manufacturer advises hydroxyzine should be avoided in patients with previous hypersensitivity to cetirizine or other piperazine derivatives, and aminophylline.

- **PREGNANCY** Manufacturers advise avoid—toxicity in animal studies with higher doses. Use in the latter part of the third trimester may cause irritability, paradoxical excitation, and tremor in the neonate.

- **BREAST FEEDING** Manufacturer advises avoid—expected to be present in milk but effect unknown.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment (increased risk of accumulation); avoid in severe impairment.

- **RENAL IMPAIRMENT** Manufacturer advises dose reduction of 33% in mild to moderate impairment.

- **EFFECT ON LABORATORY TESTS** May interfere with methacholine test—manufacturer advises stop treatment 96 hours prior to test. May interfere with skin testing for allergy—manufacturer advises stop treatment one week prior to test.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving or cycling); sedating effects enhanced by alcohol.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

<table>
<thead>
<tr>
<th>DVD</th>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
<th>Hydroxyzine hydrochloride (Non-proprietary)</th>
<th>10 mg</th>
<th>84 tablet (PZN)</th>
<th>£1.20-£1.65 DT = £1.65</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Hydroxyzine hydrochloride 10 mg tablets</td>
<td>28 tablet (PZN)</td>
<td>£0.62-£0.85 DT = £0.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atarax (Alliance Pharmaceuticals Ltd)</td>
<td>Hydroxyzine hydrochloride 10 mg Atarax tablets</td>
<td>84 tablet (PZN)</td>
<td>£1.20 DT = £1.65</td>
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<tr>
<td></td>
<td></td>
<td>Hydroxyzine hydrochloride 25 mg Atarax tablets</td>
<td>28 tablet (PZN)</td>
<td>£0.62 DT = £0.85</td>
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</tbody>
</table>

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitation, and tremor.

- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

<table>
<thead>
<tr>
<th>DVD</th>
<th>CAUTIONARY AND ADVISORY LABELS 2, 21</th>
<th>Zaditen (CD Pharma Srl)</th>
<th>Ketotifen (as Ketotifen fumarate) 200 microgram per 1 ml Zaditen 1mg/5ml elixir sugar-free</th>
<th>300 ml (PZN)</th>
<th>£8.91 DT = £8.91</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zaditen (CD Pharma Srl)</td>
<td>Ketotifen (as Ketotifen fumarate) 1 mg</td>
<td>60 tablet (PZN)</td>
<td>£7.53 DT = £7.53</td>
</tr>
</tbody>
</table>

## Promethazine hydrochloride

- **INDICATIONS AND DOSE**
  - **Symptomatic relief of allergy such as hay fever and urticaria**
  - **Insomnia associated with urticaria and pruritus**
  - **BY MOUTH**
    - Child 2–4 years: 5 mg twice daily, alternatively 5–15 mg once daily, dose to be taken at night
    - Child 5–9 years: 5–10 mg twice daily, alternatively 10–25 mg once daily, dose to be taken at night
    - Child 10–17 years: 10–20 mg 2–3 times a day, alternatively 25 mg once daily, dose to be taken at night, increased if necessary to 25 mg twice daily
  - **Adult:** 10–25 mg 2–3 times a day
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: 25–50 mg (max. per dose 100 mg)

- **Emergency treatment of anaphylactic reactions**
  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: 25–50 mg, to be administered as a solution containing 2.5 mg/mL in water for injections; maximum 100 mg per course

- **Sedation (short-term use)**
  - **BY MOUTH**
    - Child 2–4 years: 15–20 mg
    - Child 5–9 years: 20–25 mg
    - Child 10–17 years: 25–50 mg
    - Adult: 25–50 mg
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: 25–50 mg

- **Nausea** | **Vomiting** | **Vertigo** | **Labyrinthine disorders** | **Motion sickness**
  - **BY MOUTH**
    - Child 2–4 years: 5 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
    - Child 5–9 years: 10 mg, to be taken at bedtime on night before travel, repeat following morning if necessary

- **SIDE-EFFECTS**
  - **Common or very common** Anxiety, insomnia, irritability
  - **Uncommon** Cystitis, dizziness, dry mouth, skin reactions
  - **Rare or very rare** Hepatitis, Stevens-Johnson syndrome, weight increased

- **SIDE-EFFECTS, FURTHER INFORMATION** Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.
**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Solution for injection**

EXCIPIENTS: May contain Sulfites

- Phenergan (Sanofi)
  - Promethazine hydrochloride 25 mg per 1 ml Phenergan 25mg/1ml solution for injection ampoules | 10 ampoule (£1.22) £6.74

**Oral solution**

CAUTIONARY AND ADVISORY LABELS 2

EXCIPIENTS: May contain Sulfites

ELECTROLYTES: May contain Sodium

- Phenergan (Sanofi)
  - Promethazine hydrochloride 1 mg per 1 ml Phenergan 1mg/ml elixir sugar-free | 100 ml (£2.45) £2.85

**Tablet**

CAUTIONARY AND ADVISORY LABELS 2

- Promethazine hydrochloride 10 mg Promethazine hydrochloride 10mg tablets | 56 tablet (£3.56) £3.41
  - Promethazine hydrochloride 25 mg Promethazine hydrochloride 25mg tablets | 56 tablet (£4.65) £4.65
- Phenergan (Sanofi)
  - Promethazine hydrochloride 25 mg Phenergan 25mg tablets | 56 tablet (£4.65) £4.65
  - Sominex (Teva UK Ltd)
  - Promethazine hydrochloride 20 mg Sominex 20mg tablets | 8 tablet (£1.89) £1.65

**VACCINES**

> **ALLERGEN-TYPE VACCINES**

**Bee venom extract**

**INDICATIONS AND DOSE**

Hypersensitivity to bee venom

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**DESENSITISING VACCINES**

In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:

- Seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- Hypersensitivity to wasp and bee venoms.

Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

**CONTRA-INDICATIONS** Consult product literature

**CAUTIONS** Consult product literature

**INTERACTIONS** → Appendix 1: bee venom extract

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION** Life-threatening hypersensitivity reactions can occur. Cardiopulmonary resuscitation must be immediately available. Manufacturer advises monitoring for at least 1 hour after injection.

**PREGNANCY** Avoid.

**PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009) OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN

Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

CONTRA-INDICATIONS

- Should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established

CAUTIONS

GENERAL CAUTIONS

- Epilepsy - prostatic hypertrophy (in adults) - pyloroduodenal obstruction - severe coronary artery disease - susceptibility to angle-closure glaucoma - urinary retention

SPECIFIC CAUTIONS

- With intravenous use: Avoid extravasation with intravenous injection

INTERACTIONS → Appendix 1: antihistamines, sedating

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Arrhythmia - blood disorder - confusion - dizziness - drowsiness - dry mouth - headache - hypotension - jaundice - movement disorders - palpitations - photosensitivity reaction - urinary retention - vision blurred

SPECIFIC SIDE-EFFECTS


- With parenteral use: Appetite decreased - epigastric discomfort - fatigue - haemolytic anaemia - hypersensitivity - muscle spasms - nightmare - restlessness - skin reactions

SIDE-EFFECTS, FURTHER INFORMATION

Elderly patients are more susceptible to anticholinergic side-effects.

PREGNANCY

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

BREAST FEEDING

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

RENAL IMPAIRMENT

Use with caution.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect the performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary

Promethazine Hydrochloride Tablets 10 mg or 25 mg may be prescribed.

Promethazine Hydrochloride Oral Solution (elixir) 5 mg/5 mL may be prescribed.

LESS SUITABLE FOR PRESCRIBING

Promethazine is less suitable for prescribing for sedation.

EXCEPTIONS TO LEGAL CATEGORY

Prescription only medicine restriction does not apply to promethazine hydrochloride injection where administration is for saving life in emergency.
Grass pollen extract

**INDICATIONS AND DOSE**
Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs
- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)
Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs (initiated under specialist supervision)
- **BY MOUTH**
  - Adult: 1 tablet daily, treatment to be started at least 4 months before start of pollen season and continue for up to 3 years

**IMPORTANT SAFETY INFORMATION**
**DESENSITISING VACCINES**
In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergy drugs;
- hypersensitivity to wasp and bee venoms.
Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

**CONTRA-INDICATIONS**
Consult product literature
**CAUTIONS**
Consult product literature
**INTERACTIONS**
Appendix 1: grass pollen extract
**SIDE-EFFECTS**
**SIDE-EFFECTS, FURTHER INFORMATION**
Hypersensitivity reactions to immunotherapy can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

**PREGNANCY**
Should be avoided in pregnant women—consult product literature.

**Tree pollen extract**

**INDICATIONS AND DOSE**
Treatment of seasonal allergic hay fever due to tree pollen in patients who have failed to respond to anti-allergy drugs
- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**
**DESENSITISING VACCINES**
In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergy drugs;
- hypersensitivity to wasp and bee venoms.
Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

**CONTRA-INDICATIONS**
Consult product literature
**CAUTIONS**
Consult product literature
**INTERACTIONS**
Appendix 1: tree pollen extract
**SIDE-EFFECTS**
**SIDE-EFFECTS, FURTHER INFORMATION**
Hypersensitivity reactions to immunotherapy can be life-threatening. Cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

**PREGNANCY**
Should be avoided in pregnant women—consult product literature.
Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy.

www.nice.org.uk/TA246

MEDICAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
- Pharmalgen Wasp Venom (ALK-Abello Ltd)
- Pharmalgen Wasp Venom 120 nanogram powder and solvent for solution for injection vials | 1 vial
- Pharmalgen Wasp Venom 1.2 microgram powder and solvent for solution for injection vials | 1 vial
- Pharmalgen Wasp Venom 12 microgram powder and solvent for solution for injection vials | 1 vial

Pharmalgen® 2012

MEDICINAL FORMS
- Pharmalgen® (Allergy Therapeutics (UK) Ltd)
- Pollinex Trees No 1 suspension for injection 1 ml vials |
- Pollinex Trees No 2 suspension for injection 1 ml vials |
- Pollinex Trees No 3 suspension for injection 1 ml vials |

Each set of different medicines containing the same drug.

Wasp venom extract

INDICATIONS AND DOSE

Hypersensitivity to wasp venom
- BY SUBCUTANEOUS INJECTION
- Adults: (consult product literature)

Contra-indications Consult product literature

Cautions Consult product literature

Interactions Appendix 1: wasp venom extract

Side-effects
SIDE-EFFECTS, FURTHER INFORMATION
Hypersensitivity reactions to wasp venom extracts can be life-threatening;
cardiovascular and respiratory symptoms must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

Pregnancy Avoid.

Prescribing and dispensing information Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing desensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
- Pharmalgen® for bee and wasp venom allergy (February 2012) NICE TA246
- Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:
  - a severe systemic reaction to bee or wasp venom;
  - a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.

Other drugs used for Angioedema Adrenaline/epinephrine, p. 222

Medicines used in hereditary angioedema > Complement regulatory proteins

C1-esterase inhibitor

INDICATIONS AND DOSE
BERINERT®
- Acute attacks of hereditary angioedema (under expert supervision)
- BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
- Adult: 20 units/kg

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
- BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
- Adult: 1000 units for 1 dose, to be administered less than 6 hours before procedure

CINRYZE®
- Acute attacks of hereditary angioedema (under expert supervision)
- BY SLOW INTRAVENOUS INJECTION
- Adult: 1000 units, repeated if necessary for 1 dose, dose may be repeated if necessary after 60 minutes (or sooner for patients experiencing laryngeal attacks or if treatment initiation is delayed)

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
- BY SLOW INTRAVENOUS INJECTION
- Adult: 1000 units for 1 dose, to be administered up to 24 hours before procedure

Long-term prophylaxis of severe, recurrent attacks of hereditary angioedema where acute treatment is inadequate, or when oral prophylaxis is inadequate or not tolerated (under expert supervision)
- BY SLOW INTRAVENOUS INJECTION
- Adult: 1000 units every 3–4 days, interval between doses to be adjusted according to response

CAUTIONS Vaccination against hepatitis A and hepatitis B may be required
290  Allergic conditions

- **SIDE-EFFECTS**
  - Rare or very rare  Dizziness · dyspnoea · flushing · headache · hypersensitivity · hypertension · hypotension · nausea · tachycardia · thrombosis (with high doses) · urticaria

- **PREGNANCY**  Manufacturer advises avoid unless essential.

- **PRESCRIBING AND DISPENSING INFORMATION**  C1-esterase inhibitor is prepared from human plasma.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **SIDE-EFFECTS**
  - uncommon
  - common or very common

- **SIDE-EFFECTS**
  - **CONTRA-INDICATIONS**  Rabbit allergy

- **SIDE-EFFECTS**
  - **COMMON**  Headache
  - **UNCOMMON**  Abdominal discomfort · diarrhoea · nausea · oral paraesthesia · paraesthesia · throat irritation · urticaria · vertigo

- **PREGNANCY**  Use only if potential benefit outweighs risk—toxicity in animal studies.

- **PREGNANCY**  Use only if potential benefit outweighs risk—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

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### All Wales Medicines Strategy Group (AWMSG) decisions

**AWMSG No. 786**  The All Wales Medicines Strategy Group has advised (November 2018) that conestat alfa (Ruconest®) is recommended as an option for use within NHS Wales for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema due to C1 esterase inhibitor deficiency. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for injection**
    - **Conestat alfa 2100 unit**  Ruconest 21,000 unit powder for solution for injection vials  |  1 vial (POD) £75.00

### Drugs used in hereditary angioedema

#### Selective Bradykinin B2 Antagonists

- **Icatibant**

  - **INDICATIONS AND DOSE**
    - **Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency**
      - **BY SUBCUTANEOUS INJECTION**
      - **Adult**  30 mg for 1 dose, then 30 mg after 6 hours if required, then 30 mg after 6 hours if required; maximum 3 doses per day

  - **CAUTIONS**  Ischaemic heart disease · stroke

  - **INTERACTIONS**  → Appendix 1: Icatibant

  - **SIDE-EFFECTS**
    - **Common or very common**  Dizziness · fever · headache · nausea · skin reactions

  - **PREGNANCY**  Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

  - **BREAST FEEDING**  Manufacturer advises avoid for 12 hours after administration.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

- **Scottish Medicines Consortium (SMC) decisions**
  - **SMC No. 476/08**  The Scottish Medicines Consortium has advised (March 2012) that icatibant (Firazyr®) is accepted for use within NHS Scotland for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

- **All Wales Medicines Strategy Group (AWMSG) decisions**
  - **AWMSG No. 3293**  The All Wales Medicines Strategy Group has advised (June 2018) that icatibant acetate (Firazyr®) is recommended as an option for use within NHS Wales for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema due to C1 esterase inhibitor deficiency. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - **Icatibant (as icatibant acetate)**  10 mg per 1 ml  Firazyr 30 mg/3 ml solution for injection pre-filled syringes  |  1 pre-filled disposable injection (POD) £1,395.00

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### Conestat alfa

**20-Feb-2019**

- **INDICATIONS AND DOSE**
  - **Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency**
    - **BY SLOW INTRAVENOUS INJECTION**
    - **Adult**  (body-weight up to 84 kg): 50 units/kg for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day
    - **Adult**  (body-weight 84 kg and above): 4200 units for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day

- **SIDE-EFFECTS**
  - **CONTRA-INDICATIONS**  Rabbit allergy

- **SIDE-EFFECTS**
  - **COMMON**  Headache
  - **UNCOMMON**  Abdominal discomfort · diarrhoea · nausea · oral paraesthesia · paraesthesia · throat irritation · urticaria · vertigo

- **PREGNANCY**  Use only if potential benefit outweighs risk—animal studies.

- **BREAST FEEDING**  Use only if potential benefit outweighs risk—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

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### Scottish Medicines Consortium (SMC) decisions

**SMC No. 745/11**  The Scottish Medicines Consortium has advised (August 2018) that conestat alfa (Ruconest®) is accepted for use within NHS Scotland for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema due to C1 esterase inhibitor deficiency. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.
3 Conditions affecting sputum viscosity

MUCOLYTICS

Acetylcysteine

- **INDICATIONS AND DOSE**
  - **NACSYS® EFFERVESCENT TABLETS**
    - **REDUCTION OF SPUTUM VISCOITY**
      - **BY MOUTH**
      - Adult: 600 mg once daily

- **CAUTIONS**
  - History of peptic ulceration

- **SIDE-EFFECTS**
  - **Uncommon**
    - Diarrhoea, fever, gastrointestinal discomfort, headache, hypotension, nausea, stomatitis, tinnitus, vomiting
  - **Rare or very rare**
    - Haemorrhage
  - **Frequency not known**
    - Face oedema

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: effervescent tablet, granules, effervescent tablet.

  **ELECTROLYTES:** May contain Sodium

  **Acetylcysteine 600 mg NACSYS 600mg effervescent tablets sugar-free** | 30 tablet [POM] £5.50 DT = £89.50

Carbocisteine

- **INDICATIONS AND DOSE**
  - **REDUCTION OF SPUTUM VISCOITY**
    - **BY MOUTH**
    - Adult: Initially 2.25 g daily in divided doses, then reduced to 1.5 g daily in divided doses, as condition improves

- **CONTRA-INDICATIONS**
  - Active peptic ulceration

- **CAUTIONS**
  - History of peptic ulceration (may disrupt the gastric mucosal barrier)

- **SIDE-EFFECTS**
  - Gastrointestinal haemorrhage, skin reactions, Stevens-Johnson syndrome, vomiting

- **PREGNANCY**
  - Manufacturer advises avoid in first trimester.

- **BREAST FEEDING**
  - No information available.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral liquid formulations may include cherry, raspberry, cinnamon, or rum.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Oral solution**
  - **Carbocisteine (Non-proprietary)**
    - Carbocisteine 50 mg per 1 ml Carbocisteine 250mg/5ml oral solution | 300 ml [POM] £18.55 DT = £8.55
    - Carbocisteine 75 mg per 1 ml Carbocisteine 750mg/10ml oral solution 10ml sachets sugar free sugar-free | 15 sachet [POM] £3.85 DT = £3.85
  - **Mucodyne (Sanofi)**
    - Carbocisteine 50 mg per 1 ml Mucodyne Paediatric 250mg/5ml syrup | 125 ml [POM] £12.60
    - Mucodyne 250mg/5ml syrup | 300 ml [POM] £8.39 DT = £8.55

  **Capsule**
  - **Carbocisteine (Non-proprietary)**
    - Carbocisteine 375 mg Carbocisteine 375mg capsules | 120 capsule [POM] £18.98 DT = £4.60

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Erdotin

- **INDICATIONS AND DOSE**
  - Symptomatic treatment of acute exacerbations of chronic bronchitis
  - **BY MOUTH**
  - Adult: 300 mg twice daily for up to 10 days

- **CAUTIONS**
  - History of peptic ulceration (may disrupt the gastric mucosal barrier)

- **SIDE-EFFECTS**
  - Common or very common
    - Epigastric pain, taste altered
  - Uncommon
    - Allergic dermatitis, angioedema, common cold, diarrhoea, dysphagia, headache, nausea, vomiting

- **PREGNANCY**
  - Manufacturer advises avoid—no information available.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in mild to moderate hepatic failure; avoid in severe hepatic failure.

- **Dose adjustments**
  - Manufacturer advises max. 300 mg daily in mild to moderate hepatic failure.

- **RENAL IMPAIRMENT**
  - Avoid if eGFR less than 25 mL/minute/1.73 m²—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) decisions**
  - SMC No. 415/07
  - The Scottish Medicines Consortium (November 2007) has advised that erdotine (Erdotin®) is not recommended for use within NHS Scotland for the symptomatic treatment of acute exacerbations of chronic bronchitis as the economic case was not demonstrated.

  **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - **Erdotin (Galen Ltd)**
    - Erdotin 300 mg Erdotin 300mg capsules | 20 capsule [POM] £5.00 DT = £5.00

3.1 Cystic fibrosis

Cystic fibrosis

**Description of condition**

Cystic fibrosis is a genetic disorder affecting the lungs, pancreas, liver, intestine, and reproductive organs. The main clinical signs are pulmonary disease, with recurrent infections and the production of copious viscous sputum, and malabsorption due to pancreatic insufficiency. Other complications include hepatobiliary disease, osteoporosis, cystic fibrosis-related diabetes, and distal intestinal obstruction syndrome.

**Aims of treatment**

The aim of treatment includes preventing and managing lung infections, loosening and removing thick, sticky mucus from the lungs, preventing or treating intestinal obstruction, and providing sufficient nutrition and hydration.

Lung function is a key predictor of life expectancy in people with cystic fibrosis and optimising lung function is a major aim of care.
Non-drug treatment
Specialist physiotherapists should assess patients with cystic fibrosis and provide advice on airway clearance, nebuliser use, musculoskeletal disorders, physical activity, and urinary incontinence. The importance of airway clearance techniques should be discussed with patients and their parents or carers and appropriate training provided. Patients should be advised that regular exercise improves both lung function and overall fitness.

Drug treatment
Treatment for cystic fibrosis lung disease is based on the prevention of lung infection and the maintenance of lung function. In patients with cystic fibrosis, who have clinical evidence of lung disease, the frequency of routine review should be based on their clinical condition, but adults should be reviewed at least every 3 months. More frequent review is required immediately after diagnosis.

Mucolytics
Patients with cystic fibrosis who have evidence of lung disease should be offered a mucolytic. Dornase alfa p. 293 is the first choice mucolytic. If there is an inadequate response, dornase alfa p. 293 and hypertonic sodium chloride p. 275, or hypertonic sodium chloride p. 275 alone should be considered.

Mannitol dry powder for inhalation p. 295 is recommended as an option when dornase alfa p. 293 is unsuitable (because of ineligibility, intolerance, or inadequate response), when lung function is rapidly declining, and if other osmotic drugs are not considered appropriate (see mannitol p. 295 National funding/access decisions).

Lumacaftor with ivacaftor p. 294 is not recommended for treating cystic fibrosis within its marketing authorisation (see lumacaftor with ivacaftor p. 294 National funding/access decisions).

Pulmonary infection
Staphylococcus aureus
Patients who are not taking prophylaxis and have a new Staphylococcus aureus infection can be given an oral antibiotic. If they are clinically well and if they are clinically well and have pulmonary disease, oral or intravenous (depending on infection severity) broad-spectrum antibacterials with activity against Staph. aureus should be considered (consult local protocol).

A long-term antibacterial should be considered to suppress chronic Staph. aureus respiratory infections in patients whose pulmonary disease is stable. In patients with chronic Staph. aureus respiratory infections who become clinically unwell with pulmonary disease, oral or intravenous (depending on infection severity) broad-spectrum antibacterials with activity against Staph. aureus should be given. In those patients with new evidence of meticillin-resistant Staphylococcus aureus (MRSA) respiratory infection (with or without pulmonary exacerbation), specialist microbiological advice should be sought.

Antibacterials should not be routinely used to suppress MRSA in patients with stable pulmonary disease. If a patient with cystic fibrosis and chronic MRSA respiratory infection becomes unwell with a pulmonary exacerbation or shows a decline in pulmonary function, specialist microbiological advice should be sought.

Pseudomonas aeruginosa
If a patient with cystic fibrosis develops a new Pseudomonas aeruginosa infection, eradication therapy with a course of oral antibacterial should be started (by intravenous injection, if they are clinically unwell), in combination with an inhaled antibacterial. An extended course of oral and inhaled antibacterial should follow (consult local protocol).

If eradication therapy is not successful, sustained treatment with an inhaled antibacterial should be offered. Nebulised colistimethate sodium p. 556 should be considered as first-line treatment (but see also colistimethate sodium by dry powder inhalation p. 556 National funding/access decisions).

In patients with chronic Ps. aeruginosa infection (when treatment has not eradicated the infection) who become clinically unwell with pulmonary exacerbations, an oral antibacterial or a combination of two intravenous antibacterial drugs of different classes (depending on infection severity) should be used. Changing antibacterial regimens should be considered to treat exacerbations (consult local protocol).

Nebulised aztreonam p. 541, nebulised tobramycin, or tobramycin dry powder for inhalation (see tobramycin p. 520 National funding/access decisions) should be considered for those who are deteriorating despite regular inhaled colistimethate sodium p. 556.

Burkholderia cepacia complex
Patients who develop a new Burkholderia cepacia complex infection, should be given eradication therapy with a combination of intravenous antibacterial drugs (specialist microbiological advice should be sought on the choice of antibacterials). There is no evidence to support using antibacterials to suppress chronic Burkholderia cepacia complex infection in patients with cystic fibrosis who have stable pulmonary status.

Specialist microbiological advice should be sought for patients with chronic Burkholderia cepacia complex infection (when treatment has not eradicated the infection) and who become clinically unwell with a pulmonary disease exacerbation.

An inhaled antibacterial should be considered for those who have chronic Burkholderia cepacia complex infection and declining pulmonary status; treatment should be stopped if there is no observed benefit.

Haemophilus influenzae
Haemophilus influenzae infection in the absence of clinical evidence of pulmonary infection should be treated with an appropriate oral antibacterial drug. In those who are unwell with clinical evidence of pulmonary infection, an appropriate antibacterial should be given by mouth or intravenously depending on the severity of the illness (consult local protocol).

Non-tuberculous mycobacteria
Non-tuberculous mycobacterial eradication therapy should be considered for patients with cystic fibrosis who are clinically unwell and whose pulmonary disease has not responded to other recommended treatments. Specialist microbiological advice should be sought on the choice of antibacterial and on the duration of treatment.

Aspergillus fumigatus complex
Treatment with an antifungal drug should only be considered to suppress chronic Aspergillus fumigatus complex respiratory infection in patients with declining pulmonary status. Specialist microbiological advice should be sought on the choice of antifungal drug.

Unidentified infections
An oral or intravenous (depending on the exacerbation severity) broad-spectrum antibacterial should be used for patients who have a pulmonary disease exacerbation and no clear cause. If a causative pathogen is identified, an appropriate treatment should be selected (consult local protocol).

Immunomodulatory drugs
Long-term treatment with azithromycin p. 536 [unlicensed indication], at an immunomodulatory dose, should be offered to patients with deteriorating lung function or repeated pulmonary exacerbations. In those patients with continued deterioration in lung function or continuing pulmonary exacerbations, long-term

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azithromycin p. 536 should be discontinued and the use of an oral corticosteroid considered. 

**Nutrition and exocrine pancreatic insufficiency**

The cystic fibrosis specialist dietitian should offer advice on optimal nutrition. Pancreatin p. 96 should be offered to patients with exocrine pancreatic insufficiency. Dose should be adjusted as needed to minimise any symptoms or signs of malabsorption (see Exocrine pancreatic insufficiency p. 95). An acid-suppressing drug, such as an H2 receptor antagonist or a proton pump inhibitor [unlicensed indications] can be considered for patients who have persistent symptoms or signs of malabsorption.

A short-term trial of an appetite stimulant (for example up to 3 months) [unlicensed indication] can be considered in adult patients if attempts to increase calorie intake are not effective.[8]

**Distal intestinal obstruction syndrome**

Oral or intravenous fluids should be offered to ensure adequate hydration for patients with distal intestinal obstruction syndrome. Meglumine amidotrizoate with sodium amidotrizoate solution (orally or via an enteral tube) should be considered as first-line treatment for distal intestinal obstruction syndrome. An iso-osmotic polyethylene glycol solution (orally or via an enteral tube) can be considered as a second-line treatment. Surgery is a last resort, if prolonged treatment with a polyethylene glycol solution is not effective. Suspected distal intestinal obstruction syndrome should be managed in a specialist cystic fibrosis centre.[9]

**Liver disease**

If liver function blood tests are abnormal in patients with cystic fibrosis, ursodeoxycholic acid p. 89 [unlicensed indication] can be given until liver function is restored.[9]

**Bone mineral density**

Patients should be monitored for cystic fibrosis-related low bone mineral density.[9]

**Cystic fibrosis-related diabetes**

Patients should be monitored for cystic fibrosis-related diabetes.[9]

**Useful Resources**


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<th>MUCOLYTIcs</th>
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<td><strong>Dornase alfa</strong></td>
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<td>(Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase))</td>
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<tr>
<td><strong>Drug Action</strong></td>
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<td><strong>Indications and Dose</strong></td>
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<tr>
<td>Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function</td>
</tr>
<tr>
<td>▶ By Inhalation of Nebulised Solution</td>
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<tr>
<td>Adult: 2500 units once daily, administered by jet nebuliser, patients over 21 years may benefit from twice daily dosage</td>
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<tr>
<td>Dose Equivalence and Conversion</td>
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<tr>
<td><strong>Nebuliser liquid</strong></td>
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<tr>
<td>Dornase alfa 1 mg per 1 ml</td>
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<tr>
<td>Pulzyme 2.5mg nebuliser liquid 2.5ml ampoules <a href="www.pulzyme.com">www.pulzyme.com</a> £496.43 DT + £496.43</td>
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| Ivacaftor | 10-Apr-2019 |
| **Drug Action** | Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) protein potentiator that increases chloride transport in the abnormal CFTR protein. |
| **Indications and Dose** |
| Cystic fibrosis (specialist use only) |
| ▶ By Mouth |
| ▶ Adult: 150 mg every 12 hours |
| **Dose Adjustments Due to Interactions** |
| ▶ Manufacturer advises reduce dose to 150 mg twice a week with concurrent use of potent inhibitors of CYP3A4. |
| ▶ Manufacturer advises reduce dose to 150 mg once daily with concurrent use of moderate inhibitors of CYP3A4. |
| **Contra-Indications** | Organ transplantation (no information available) |
| **Interactions** | → Appendix 1: ivacaftor |
| **Side-effects** |
| Common or very common |
| ▶ Breast abnormalities · diarrhoea · dizziness · ear discomfort · headache · ototoxicity · rash · tympanic membrane haemorrhage |
| Uncommon |
| ▶ Gynaecomastia |
| Frequency not known |
| Hepatic function abnormal |
| Side-Effects, further information |
| Manufacturer advises interrupt treatment if transaminase levels more than 5 times the upper limit of normal or transaminase levels more than 3 times the upper limit of normal and blood bilirubin more than twice the upper limit of normal—consult product literature. |
| **Pregnancy** | Manufacturer advises use only if potential benefit outweighs risk—limited information available. |
| **Breast Feeding** | Manufacturer advises avoid—present in milk in animal studies. |
| **Hepatic Impairment** | Manufacturer advises caution in moderate to severe impairment (limited information available). |
| **Dose Adjustments** | Manufacturer advises reduce dose to 150 mg once daily in moderate impairment; in severe impairment reduce starting dose to 150 mg on alternate days, adjust dosing interval according to clinical response and tolerability. |
| **Renal Impairment** | Caution in severe impairment. |
| **Monitoring Requirements** | Manufacturer advises monitor liver function before treatment, every 3 months during the first year of treatment, then annually thereafter |

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Lumacaftor with ivacaftor

The properties listed below are those particular to the combination only. For the properties of the components please consider, ivacaftor p. 253.

- **INDICATIONS AND DOSE**
  - Cystic fibrosis (specialist use only)
    - **BY MOUTH**
      - Adult: 400/250 mg every 12 hours
  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Manufacturer advises reduce initial dose to 200/125 mg daily for the first week in those also taking a potent inhibitor of CYP3A4.
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Dose expressed as x/y mg of lumacaftor/ivacaftor.
  - **CAUTIONS**
    - Forced expiratory volume in 1 second (FEV1) less than 40% of the predicted normal value—additional monitoring required at initiation of treatment—pulmonary exacerbation—no information available
  - **INTERACTIONS**
    - Appendix 1: ivacaftor - lumacaftor
  - **SIDE-EFFECTS**
    - **Common or very common**
      - Breast abnormalities, diarrhoea, dizziness, ear discomfort, flatulence, headache, menstrual cycle irregularities, nausea, ototoxicity, rash, tympanic membrane hyperaemia, vomiting
    - **Uncommon**
      - Gynaecomastia, hepatic encephalopathy, hepatitis cholestatic, hypertension
    - **Frequency not known**
      - Cataract, chest pain
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Manufacturer advises interrupt treatment if transaminase levels more than 5 times the upper limit of normal or transaminase levels more than 3 times the upper limit of normal and blood bilirubin more than twice the upper limit of normal—consult product literature.
  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).
  - **DOSE ADJUSTMENTS**
    - Manufacturer advises dose reduction of evening dose to 200/125 mg in moderate impairment; in severe impairment, dose reduction to 200/125 mg every 12 hours is advised.
  - **PRE-TREATMENT SCREENING**
    - If the patient’s genotype is unknown, a validated genotyping method should be performed to confirm the presence of the F508del mutation on both alleles of the CFTR gene before starting treatment.
  - **MONITORING REQUIREMENTS**
    - Manufacturer advises monitor blood pressure periodically during treatment.
  - **EFFECT ON LABORATORY TESTS**
    - False positive urine screening tests for tetrahydrocannabinol have been reported—manufacturer advises consider alternative confirmatory method.
  - **DIRECTIONS FOR ADMINISTRATION**
    - Tablets should be taken with fat-containing food.
  - **PATIENT AND CARER ADVICE**
    - Patients or carers should be given advice on how to administer ivacaftor tablets.

24 Apr 2019
Mannitol

- **INDICATIONS AND DOSE**
  - Treatment of cystic fibrosis as an add-on therapy to standard care
    - **BY INHALATION OF POWDER**
    - Adult: Maintenance 400 mg twice daily, an initiation dose assessment must be carried out under medical supervision, for details of the initiation dose regimen, consult product literature

- **CONTRA-INDICATIONS**
  - Bronchial hyperresponsiveness to inhaled mannitol - impaired lung function (forced expiratory volume in 1 second < 50% of predicted) - non-CF bronchiectasis

- **CAUTIONS**
  - Asthma - haemoptysis

- **SIDE-EFFECTS**
  - Common or very common Chest discomfort - condition aggravated - cough - haemoptysis - headache - respiratory disorders - throat complaints - vomiting

- **PREGNANCY**
  - Manufacturer advises avoid.

- **BREAST FEEDING**
  - Manufacturer advises avoid.

- **PRE-TREATMENT SCREENING**
  - Patients must be assessed for bronchial hyperresponsiveness to inhaled mannitol before starting the therapeutic dose regimen; an initiation dose assessment must be carried out under medical supervision—for details of the initiation dose regimen, consult product literature.

- **DIRECTIONS FOR ADMINISTRATION**
  - The dose should be administered 5–15 minutes after a bronchodilator and before physiotherapy; the second daily dose should be taken 2–3 hours before bedtime.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer mannitol inhalation powder.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Mannitol dry powder for inhalation for treating cystic fibrosis (November 2012) NICE TA266
      - Mannitol (Bronchitol®) dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:
        - who cannot use dornase alfa (rhDNase) because of ineligibility, intolerance or inadequate response to rhDNase, and
        - whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually), and
        - for whom other osmotic agents are not considered appropriate.
      - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, until they and their NHS clinician consider it appropriate to stop.
      - www.nice.org.uk/guidance/ta266

- **Scottish Medicines Consortium (SMC) decisions**
  - SMC No. 83/13
    - The Scottish Medicines Consortium has advised (December 2013) that mannitol (Bronchitol®) is accepted for restricted use within NHS Scotland for the treatment of cystic fibrosis in adults as an add-on therapy to best standard of care. Mannitol is restricted to patients who are not currently using dornase alfa due to lack of response, intolerance, or ineligibility and have rapidly declining lung function and in whom other osmotic agents are considered unsuitable.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Inhalation powder**
    - Osmohale (Mawdsley-Brooks & Company Ltd)
      - Mannitol 5 mg Osmohale 5mg inhalation powder capsules
        - 1 capsule £0.11
      - Mannitol 10 mg Osmohale 10mg inhalation powder capsules
        - 1 capsule £0.22
      - Mannitol 20 mg Osmohale 20mg inhalation powder capsules
        - 1 capsule £0.22
      - Mannitol 40 mg Osmohale 40mg inhalation powder capsules
        - 15 capsule £0.65
    - Bronchitol (Chiesi Ltd)
      - Mannitol 40 mg Bronchitol 40mg inhalation powder capsules with two devices
        - 280 capsule £23.16
    - Bronchitol 40mg inhalation powder capsules with device
      - 10 capsule £0.95

Tezacaftor with ivacaftor

- **INDICATIONS AND DOSE**
  - Cystic fibrosis (in combination with ivacaftor) (specialist use only)
    - **BY MOUTH**
      - Adult: 100/150 mg, to be taken in the morning and, ivacaftor 150 mg to be taken in the evening

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - With concurrent use of potent CYP3A4 inhibitors, manufacturer advises reduce dose to 100/150 mg tezacaftor/ivacaftor twice a week, taken approximately 3–4 days apart; the evening dose of ivacaftor should not be taken.
  - With concurrent use of moderate CYP3A4 inhibitors, manufacturer advises reduce dose to 100/150 mg tezacaftor/ivacaftor every other morning, with ivacaftor 150 mg taken in the mornings alternate to tezacaftor/ivacaftor; the evening dose of ivacaftor should not be taken.

- **DOSE EQUIVALENCE AND CONVERSION**
  - Combination dose expressed as x/y mg of tezacaftor/ivacaftor.

- **INTERACTIONS**
  - **Appendix 1: ivacaftor - tezacaftor**

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain - breast abnormalities - diarrhoea - dizziness - ear discomfort - headache - nausea - ototoxicity - rash - tympanic membrane hyperaemia
  - Uncommon Gynaecostasia
  - Frequency not known Hepatic function abnormal

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Manufacturer advises interrupt treatment if transaminase levels more than 3 times the upper limit of normal or transaminase levels more than 3 times the upper limit of normal and blood bilirubin more than twice the upper limit of normal—consult product literature.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).
  - **Dose adjustments**
    - Manufacturer advises omit evening dose of ivacaftor in moderate to severe impairment; in severe impairment, adjust dosing interval according to clinical response and tolerability.
4 Cough and congestion

Aromatic inhalations, cough preparations and systemic nasal decongestants

Aromatic inhalations in adults

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis; boiling water should not be used owing to the risk of scalding. In practice, inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis.

Cough preparations in adults

Cough suppressants

Cough may be a symptom of an underlying disorder, such as asthma, gastro-oesophageal reflux disease, or rhinitis, which should be addressed before prescribing cough suppressants. Cough may be a side-effect of another drug, such as an ACE inhibitor, or it can be associated with smoking or environmental pollutants. Cough can also have a significant habit component. When there is no identifiable cause, cough suppressants may be useful, for example if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

There is some evidence to suggest that codeine phosphate p. 454 provides no benefit for symptoms of acute cough. Codeine phosphate is also constipating and can cause dependence; dextromethorphan and pholcodine below have fewer side-effects.

Sedating antihistamines are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

Palliative care

Diamorphine hydrochloride p. 456 and methadone hydrochloride p. 502 have been used to control distressing cough in terminal lung cancer although morphine p. 463 is now preferred. In other circumstances they are contra-indicated because they induce sputum retention and ventilatory failure as well as causing opioid dependence. Methadone hydrochloride linctus should be avoided because it has a long duration of action and tends to accumulate.

Demulcent and expectorant cough preparations

Demulcent cough preparations contain soothing substances such as syrup or glycerol and some patients believe that such preparations relieve a dry irritating cough. Preparations such as simple linctus have the advantage of being harmless and inexpensive; paediatric simple linctus is particularly useful in children.

Expectorants are claimed to promote expulsion of bronchial secretions, but there is no evidence that any drug can specifically facilitate expectoration.

COUGH AND COLD PREPARATIONS

Pholcodine

- INDICATIONS AND DOSE

Dry cough

- BY MOUTH USING LINCTUS

- Child 6–11 years: 2–5 mg 3–4 times a day

- Child 12–17 years: 5–10 mg 3–4 times a day

An over-the-counter cough medicine containing the expectorant guaifenesin may be used for acute cough; there is some evidence to suggest it may reduce symptoms.

Compound preparations are on sale to the public for the treatment of cough and colds but should not be used in children under 6 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time.

Nasal decongestants, systemic

Nasal decongestants for administration by mouth may not be as effective as preparations for local application but they do not give rise to rebound nasal congestion on withdrawal. Pseudoephedrine hydrochloride p. 1202 is available over the counter; it has few sympathomimetic effects.

Aromatic inhalations in children

The use of strong aromatic decongestants (applied as rubs or to pillows) is not advised for infants under the age of 3 months. Carers of young infants in whom nasal obstruction with mucus is a problem can readily be taught appropriate techniques of suction aspiration but sodium chloride 0.9% p. 1040 given as nasal drops is preferred; administration before feeds may ease feeding difficulties caused by nasal congestion.

Cough preparations in children

The use of over-the-counter cough suppressants containing codeine phosphate should be avoided in children under 12 years and in children of any age known to be CYP2D6 ultra-rapid metabolisers. Cough suppressants containing similar opioid analogues such as dextromethorphan and pholcodine are not generally recommended in children and should be avoided in children under 6 years; dextromethorphan should be avoided in children under 12 years.

MHRA/CHM advice (March 2008 and February 2009)

Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- brompheniramine, chlorphenamine maleate p. 283, diphenhydramine, doxylamine, promethazine, or triprolidine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- Phenylephrine hydrochloride p. 189, pseudoephedrine hydrochloride, ephedrine hydrochloride p. 1202, oxymetazoline, or xylometazoline hydrochloride p. 1203 (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to five days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.
**COUGH AND COLD PREPARATIONS > OTHER**

**Citric acid**

(Formulated as Simple Linctus)

- **INDICATIONS AND DOSE**
  - Cough
    - **BY MOUTH**
      - Adult: 5 mL 3–4 times a day, this dose is for Simple Linctus, BP (2.5%)

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral liquid formulations may include anise.
  - When prepared extemporaneously, the BP states Simple Linctus, BP consists of citric acid monohydrate 2.5%, in a suitable vehicle with an anise flavour.

**MENTHOL AND DERIVATIVES**

**Eucalyptus with menthol**

- **INDICATIONS AND DOSE**
  - Aromatic inhalation for relief of nasal congestion
    - **BY INHALATION**
      - Adult: Add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Menthol and Eucalyptus Inhalation, BP 1980 consists of racementhol or levomenthol 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL

**RESINS**

**Benzoin tincture, compound**

(Friars’ Balsam)

- **INDICATIONS AND DOSE**
  - Aromatic inhalation for relief of nasal congestion
    - **BY INHALATION**
      - Child: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary
      - Adult: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary

- **SIDE-EFFECTS**
  - Skin sensitisation

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Not recommended (applied as a rub or to pillows) for infants under 3 months.
5 Idiopathic pulmonary fibrosis

Other drugs used for idiopathic pulmonary fibrosis
Nintedanib, p. 991

ANTIFIBROTICS

Pirfenidone

02-Feb-2019

- **DRUG ACTION** The exact mechanism of action of pirfenidone is not yet understood, but it is believed to slow down the progression of idiopathic pulmonary fibrosis by exerting both antifibrotic and anti-inflammatory properties.

- **INDICATIONS AND DOSE**
  Treatment of mild to moderate idiopathic pulmonary fibrosis (initiated under specialist supervision)

  ▶ **BY MOUTH**
  - Adult: Initially 267 mg 3 times a day for 7 days, then increased to 534 mg 3 times a day for 7 days, then increased to 801 mg 3 times a day

  **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Caution with concomitant use with ciprofloxacin—reduce dose of pirfenidone to 534 mg three times daily with high-dose ciprofloxacin (750 mg twice daily).

- **CONTRA-INDICATIONS** Cigarette smoking

- **CAUTIONS**
  - Photosensitivity Avoid exposure to direct sunlight—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required (consult product literature).
  - Treatment interruption If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous daily dose without titration.

- **INTERACTIONS** → Appendix 1: pirfenidone

- **SIDE-EFFECTS**
  - **Common or very common** Appetite decreased · arthralgia · asthenia · constipation · cough · diarrhoea · dizziness · drowsiness · dyspnoea · gastrointestinal discomfort · gastrointestinal disorders · headache · hot flush · increased risk of infection · insomnia · musculoskeletal chest pain · myalgia · nausea · photosensitivity reaction · skin reactions · sunburn · taste altered · vomiting · weight decreased
  - **Uncommon** Angioedema
  - **Rare or very rare** Agranulocytosis

  SIDE-EFFECTS, FURTHER INFORMATION Gastrointestinal side-effects may require dose reduction or treatment interruption—consult product literature.

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment (risk of increased exposure); avoid in severe impairment (no information available).

- **RENAL IMPAIRMENT** Avoid use if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor for weight loss.
  - Test liver function before treatment, then at monthly intervals for the next 6 months, and then every 3 months thereafter; review if abnormal liver function tests—dose reduction, treatment interruption or discontinuation may be required (consult product literature).

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks Dizziness or malaise may affect performance of skilled tasks (e.g. driving).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE decisions**
  - Pirfenidone for treating idiopathic pulmonary fibrosis (February 2018) NICE TA504
  - Pirfenidone (Esbriet®) is recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:
    - the patient has a forced vital capacity (FVC) between 50% and 80% predicted, and
    - the manufacturer provides pirfenidone with the discount agreed in the patient access scheme, and
    - treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period).
  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/ta504

  **Scottish Medicines Consortium (SMC) decisions**
  - SMC No. 835/13
  - The Scottish Medicines Consortium has advised (August 2013) that pirfenidone (Esbriet®) is accepted for restricted use within NHS Scotland for the treatment of mild to moderate idiopathic pulmonary fibrosis. Pirfenidone is restricted for use in patients with a predicted forced vital capacity less than or equal to 50%, and only whilst pirfenidone is available at the price agreed in the patient access scheme.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **Esbriet** (Roche Products Ltd)
    - Pirfenidone 267 mg Esbriet 267mg tablets | 63 tablet POM £501.92 | 252 tablet POM £2,007.70
    - Pirfenidone 801 mg Esbriet 801mg tablets | 84 tablet POM £2,007.70

  **Capsule**
  - **Esbriet** (Roche Products Ltd)
    - Pirfenidone 267 mg Esbriet 267mg capsules | 63 capsule POM £501.92 | 252 capsule POM £2,007.70 | 270 capsule POM £2,151.10

  www.getintopharma.com
Respiratory depression, respiratory distress syndrome and apnoea

Overview
Respiratory stimulants (analeptic drugs) have a limited place in the treatment of ventilatory failure in patients with chronic obstructive pulmonary disease. They are effective only when given by intravenous injection or infusion and have a short duration of action. Their use has largely been replaced by ventilatory support including nasal intermittent positive pressure ventilation. However, occasionally when ventilatory support is contra-indicated and in patients with hypercapnic respiratory failure who are becoming drowsy or comatose, respiratory stimulants in the short term may arouse patients sufficiently to co-operate and clear their secretions.

Respiratory stimulants can also be harmful in respiratory failure since they stimulate non-respiratory as well as respiratory muscles. They should only be given under expert supervision in hospital and must be combined with active physiotherapy. There is at present no oral respiratory stimulant available for long-term use in chronic respiratory failure.

Respiratory stimulants

Doxapram hydrochloride

**INDICATIONS AND DOSE**

**Postoperative respiratory depression**
- **INITIALLY BY INTRAVENOUS INJECTION**
- **Adult:** Initially 1–1.5 mg/kg, to be administered over at least 30 seconds, repeated if necessary after intervals of one hour, alternatively (by intravenous infusion) 2–3 mg/minute, adjusted according to response

**Acute respiratory failure**
- **BY INTRAVENOUS INFUSION**
- **Adult:** 1.5–4 mg/minute, adjusted according to response, to be given concurrently with oxygen and whenever possible monitor with frequent measurement of blood gas tensions

**CONTRA-INDICATIONS**
Cerebral oedema · cerebrovascular accident · coronary artery disease · epilepsy and other convulsive disorders · hyperthyroidism · physical obstruction of respiratory tract · severe hypertension · status asthmaticus

**CAUTIONS**
Give with beta₂ agonist in bronchoconstriction · give with oxygen in severe irreversible airways obstruction or severely decreased lung compliance (because of increased work load of breathing) · hypertension · impaired cardiac reserve · phaeochromocytoma

**INTERACTIONS**
Appendix 1: doxapram

**SIDE-EFFECTS**
Arrhythmias · chest discomfort · confusion · cough · dizziness · dyspnoea · fever · flushing · hallucination · headache · hyperhidrosis · movement disorders · nausea · neuromuscular dysfunction · oral disorders · perineal warmth · reflexes abnormal · respiratory disorders · seizure · urinary disorders · vomiting

**PREGNANCY**
No evidence of harm, but manufacturer advises avoid unless benefit outweighs risk.

**HEPATIC IMPAIRMENT**
Manufacturer advises use with caution.

**MONITORING REQUIREMENTS**
Frequent arterial blood gas and pH measurements are necessary during treatment to ensure correct dosage.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Doxapram hydrochloride (Non-proprietary)**
  - Doxapram hydrochloride 20 mg per 1 ml
  - Doxapram 100mg/5ml solution for injection ampoules · 5 ampoule £12.65

**Infusion**
- **Doxapram hydrochloride (Non-proprietary)**
  - Doxapram hydrochloride 2 mg per 1 ml
  - Doxapram 1g/500ml infusion bags · 1 bag £0.94

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Chapter 4
Nervous system

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1 Dementia

Description of condition
Dementia is a progressive clinical syndrome characterised by a range of cognitive and behavioural symptoms that can include memory loss, problems with reasoning and communication, a change in personality, and a reduced ability to carry out daily activities such as washing or dressing. Alzheimer’s disease is the most common type of dementia; other common types of dementia include vascular dementia (due to cerebrovascular disease), dementia with Lewy bodies, mixed dementia, and frontotemporal dementia.

Aims of treatment
The aim of treatment is to promote independence, maintain function, and manage symptoms of dementia.

Non-drug treatment
Patients with all types of mild-to-moderate dementia presenting with cognitive symptoms should be given the opportunity to participate in a structured group cognitive stimulation programme. Group reminiscence therapy (use of life stories to improve psychological well-being), and cognitive rehabilitation or occupational therapy to support daily functional ability, should also be considered.

Management of cognitive symptoms
Some commonly prescribed drugs are associated with increased antimuscarinic (anticholinergic) burden, and therefore cognitive impairment; their use should be minimised. Drugs with antimuscarinic effects include some antidepressants (e.g. amitriptyline hydrochloride p. 372, paroxetine p. 366), antihistamines (e.g. chlorphenamine maleate p. 283, promethazine hydrochloride p. 286), antipsychotics (e.g. olanzapine p. 398, quetiapine p. 401), and urinary antispasmodics (e.g. solifenacin succinate p. 779, tolerodine tartrate p. 780).

Alzheimer’s disease
In newly diagnosed patients, drug treatment should only be initiated under the advice of a specialist clinician experienced in the management of Alzheimer’s disease. In patients with mild-to-moderate Alzheimer’s disease, monotherapy with donepezil hydrochloride p. 301, galantamine p. 302, or rivastigmine p. 303 (acetylcholinesterase inhibitors) are first-line treatment options. If acetylcholinesterase inhibitors are not tolerated or contra-indicated, memantine hydrochloride p. 304 is a suitable alternative in patients with moderate Alzheimer’s disease. Memantine hydrochloride is the drug of choice in patients with severe Alzheimer’s disease.

In patients already receiving an acetylcholinesterase inhibitor to treat Alzheimer’s disease, the addition of memantine hydrochloride should be considered if they develop moderate or severe disease; in this case, memantine hydrochloride can be initiated in primary care without advice from a specialist clinician.

In patients with moderate Alzheimer’s disease, discontinuing acetylcholinesterase inhibitor treatment can cause a substantial worsening in cognitive function; treatment discontinuation should not be based on disease severity alone.

Non-Alzheimer’s dementia
Donepezil hydrochloride [unlicensed indication] or rivastigmine [unlicensed indication] should be given to patients with mild-to-moderate dementia with Lewy bodies; galantamine [unlicensed indication] can be considered only if treatment with both donepezil hydrochloride or rivastigmine is not tolerated. Donepezil hydrochloride [unlicensed indication] or rivastigmine [unlicensed indication] can also be considered in patients with severe dementia with Lewy bodies. Memantine hydrochloride [unlicensed indication] can be considered as an alternative in patients with dementia with Lewy bodies in whom acetylcholinesterase inhibitors are contra-indicated or not tolerated.

Acetylcholinesterase inhibitors [unlicensed indication] or memantine hydrochloride [unlicensed indication] should only be considered in patients with vascular dementia if they have suspected co-morbid Alzheimer’s disease, Parkinson’s disease dementia, or dementia with Lewy bodies.
Acetylcholinesterase inhibitors and memantine hydrochloride are not recommended in patients with frontotemporal dementia or cognitive impairment caused by multiple sclerosis.

For management of Parkinson’s disease dementia see Parkinson’s disease p. 409.

Management of non-cognitive symptoms

Agitation, aggression, distress and psychosis

Patients with dementia should be offered psychosocial and environmental interventions such as counselling and management of pain and delirium to reduce distress.

Antipsychotic drugs should only be offered to patients with dementia if they are either at risk of harming themselves or others, or experiencing agitation, hallucinations or delusions that are causing them severe distress. The CHM/MHRA has reported (2009) an increased risk of stroke and a small increased risk of death when antipsychotic drugs are used in elderly patients with dementia. The balance of risks and benefits should be carefully assessed, including any previous history of stroke or transient ischaemic attack and any risk factors for cerebrovascular disease such as hypertension, diabetes, smoking, and atrial fibrillation.

Antipsychotic drugs should be used at the lowest effective dose and for the shortest time possible, with a regular review at least every 6 weeks.

In patients who have dementia with Lewy bodies or Parkinson’s disease dementia, antipsychotic drugs can worsen the motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions. See also management of psychotic symptoms in Parkinson’s disease p. 409.

Depression and anxiety

Psychological treatments (e.g. cognitive behavioural therapy (CBT), multisensory stimulation, relaxation, or animal-assisted therapies) should be considered for patients with mild-to-moderate dementia who have mild to moderate depression or anxiety; antidepressants should be reserved for pre-existing severe mental health problems.

Sleep disturbances

Patients should be offered non-drug treatment approaches to manage sleep problems and insomnia, including sleep hygiene education, exposure to daylight, and increasing exercise and activity.

Useful Resources


Other drugs used for Dementia Risperidone, p. 402

ANTICHLINOSTERASES CENTRALLY ACTING

Donepezil hydrochloride

25-Jul-2018

● INDICATIONS AND DOSE Mild to moderate dementia in Alzheimer’s disease

▶ BY MOUTH

Adults: Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime

● CAUTIONS Asthma - chronic obstructive pulmonary disease - sick sinus syndrome - supraventricular conduction abnormalities - susceptibility to peptic ulcers

● INTERACTIONS Appendix 1: anticholinesterases, centrally acting

● SIDE-EFFECTS

▶ Common or very common: Aggression - agitation - appetite decreased - common cold - diarrhoea - dizziness - fatigue - gastrointestinal disorders - hallucination - headache - injury - muscle cramps - nausea - pain - skin reactions - sleep disorders - syncope - urinary incontinence - vomiting

▶ Uncommon: Bradycardia - gastrointestinal haemorrhage - hyposalivation - seizure

▶ Rare or very rare: Cardiac conduction disorders – extrapyramidal symptoms – hepatic disorders – neuroleptic malignant syndrome – rhabdomyolysis

SIDE-EFFECTS FURTHER INFORMATION

Dose should be started low and increased if tolerated and necessary.

● HEPATIC IMPAIRMENT

Manufacturer advises caution (risk of increased exposure in mild to moderate impairment; no information available in severe impairment).

Dose adjustments

Manufacturer advises dose escalation should be performed according to individual tolerability in mild to moderate impairment.

● DIRECTIONS FOR ADMINISTRATION

Donepezil orodispersible tablet should be placed on the tongue, allowed to disperse, and swallowed.

● PATIENT AND CARER ADVICE

Patient or carers should be given advice on how to administer donepezil hydrochloride orodispersible tablets.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (updated June 2018)

NICE TA217

The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine, and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer’s disease under all of the conditions specified below and in recommendation 1.5.5 of the NICE guideline on dementia.

If prescribing an AChE inhibitor (donepezil, galantamine, or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/guidance/ta217

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Oral solution

Donepezil hydrochloride (Non-proprietary) Donepezil hydrochloride 1 mg per 1 ml Donepezil 1mg/ml oral solution sugar free sugar-free £1.00 50p

Orodispersible tablet

Donepezil hydrochloride (Non-proprietary) Donepezil hydrochloride 5 mg Donepezil 5mg orodispersible tablets sugar free sugar-free £7.29–£8.87 7.36

Donepezil hydrochloride 10 mg Donepezil 10mg orodispersible tablets sugar free sugar-free £7.95–£8.73 8.26

Aricept Evess (Eisai Ltd)

Donepezil hydrochloride 5 mg Aricept Evess 5mg orodispersible tablets sugar-free £9.85 9.85

Donepezil hydrochloride 10 mg Aricept Evess 10mg orodispersible tablets sugar-free £8.89 8.89

www.getintopharma.com
Nervous system

HEPATIC IMPAIRMENT

Breast feeding

DRUG ACTION
Galantamine is a reversible inhibitor of acetylcholinesterase and it also has nicotinic receptor agonist properties.

INDICATIONS AND DOSE
Mild to moderately severe dementia in Alzheimer’s disease

Adult: 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for at least 4 weeks; maintenance 8–12 mg twice daily

CAUTIONS
Avoid in gastro-intestinal obstruction, avoid in urinary outflow obstruction, avoid whilst recovering from bladder surgery, avoid whilst recovering from gastrointestinal surgery, cardiac disease, chronic obstructive pulmonary disease, congestive heart failure, electrolyte disturbances, history of seizures, history of severe asthma, pulmonary infection, sick sinus syndrome, supraventricular conduction abnormalities, susceptibility to peptic ulcers, unstable angina

INTERACTIONS
Appendix 1: anticholinesterase, centrally acting

SIDE-EFFECTS

Common or very common
- Appetite decreased
- Arrhythmias
- Asthenia
- Depression
- Diarrhoea
- Dizziness
- Drowsiness
- Fall
- Gastrointestinal discomfort
- Hallucinations
- Headache
- Hypertension
- Malaise
- Muscle spasms
- Nausea
- Skin reactions
- Syncope
- Tremor
- Vomiting
- Weight decreased

Uncommon
- Atrioventricular block
- Bradycardia
- Flushing
- Hyperhidrosis
- Hypersomnia
- Hypotension
- Muscle weakness
- Palpitations
- Paraesthesia
- Seizure
- Taste altered
- Tinnitus
- Vision blurred

Rare or very rare
- Hepatitis
- Severe cutaneous adverse reactions (SCARs)

SIDE-EFFECTS, FURTHER INFORMATION
Manufacturer advises increasing dose according to response and tolerability.

Serious skin reactions
Serious skin reactions (including Stevens–Johnson syndrome and acute generalized exanthematous pustulosis) have been reported—manufacturer advises discontinue at the first appearance of skin rash.

Pregnancy
Use with caution—toxicity in animal studies.

Breast feeding
Avoid—no information available.

Hepatic impairment
Manufacturer advises caution in moderate impairment (risk of increased plasma concentrations); avoid in severe impairment (no information available).

Dose adjustments
Manufacturer advises for immediate-release preparations in moderate impairment, initially 4 mg once daily (preferably in the morning) for at least 7 days, then 4 mg twice daily for at least 4 weeks; maximum 8 mg twice daily.

Manufacturer advises for modified-release preparations in moderate impairment, initially 8 mg on alternate days (preferably in the morning) for 7 days, then 8 mg once daily for 4 weeks; maximum 15 mg daily.

Renal impairment
Avoid if eGFR less than 30 mL/minute/1.73 m².

Patient and carer advice
Manufacturer recommends that patients are warned of the signs of serious skin reactions; they should be advised to stop taking galantamine immediately and seek medical advice if symptoms occur.

National funding/access decisions

NICE decisions

Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (updated June 2018) NICE TA217

The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine, and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer’s disease under all of the conditions specified below and in recommendation 1.5.5 of the NICE guideline on dementia.

If prescribing an AChE inhibitor (donepezil, galantamine, or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/guidance/ta217

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Oral solution

CAUTIONARY AND ADVISORY LABELS 3, 21

Galantamine (as Galantamine hydrobromide) 4 mg per 1 ml Galantamine 20 mg/ml oral solution sugar-free free sugar-free | 100 ml £120.00 DT = £120.00

Galzemic (Creo Pharma Ltd)
Galantamine (as Galantamine hydrobromide) 4 mg per 1 ml Galzemic 4 mg/ml oral solution sugar-free | 100 ml £90.00 DT = £120.00

Reminyl (Shire Pharmaceuticals Ltd)
Galantamine (as Galantamine hydrobromide) 4 mg per 1 ml Reminyl 4 mg/ml oral solution sugar-free | 100 ml £120.00 DT = £120.00

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 3, 21, 25

Acumor XL (Mylan)
Galantamine (as Galantamine hydrobromide) 8 mg per 1 capsule £49.26 DT = £51.88

Galantamine (as Galantamine hydrobromide) 16 mg per 1 capsule £61.65 DT = £64.90

Galantamine (as Galantamine hydrobromide) 24 mg per 1 capsule £75.81 DT = £79.80

Consion XL (Dr Reddy’s Laboratories (UK) Ltd)
Galantamine (as Galantamine hydrobromide) 8 mg per 1 capsule £25.94 DT = £51.88

Galantamine (as Galantamine hydrobromide) 16 mg per 1 capsule £32.45 DT = £64.90

Galantamine (as Galantamine hydrobromide) 24 mg per 1 capsule £39.90 DT = £79.80

www.getintopharma.com
Rivastigmine

**DRUG ACTION** Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterases.

**INDICATIONS AND DOSE**

**Mild to moderate dementia in Alzheimer’s disease**

_**BY MOUTH**_

- **Adult:** Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitrate from 1.5 mg twice daily

_**BY TRANSDERMAL APPLICATION USING PATCHES**_

- **Adult:** Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increase to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated; use caution in patients with body-weight less than 50 kg, if treatment interrupted for more than 3 days, retitrate from 4.6 mg/24 hours patch

**Mild to moderate dementia in Parkinson’s disease**

_**BY MOUTH**_

- **Adult:** Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3–6 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, retitrate from 1.5 mg twice daily

**DOSE EQUIVALENCE AND CONVERSION**

- When switching from oral to transdermal therapy, patients taking 3–6 mg by mouth daily should initially switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 9 mg by mouth daily should switch to 9.5 mg/24 hours patch if oral dose stable and well tolerated; if oral dose not stable or well tolerated, patients should switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 12 mg by mouth daily should switch to 9.5 mg/24 hours patch. The first patch should be applied on the day following the last oral dose

**CAUTIONS** Bladder outflow obstruction - bowel abnormalities - duodenal ulcers - gastric ulcers - history of asthma - history of chronic obstructive pulmonary disease - history of seizures - risk of fatal overdose with patch administration errors - sick sinus syndrome - susceptibility to ulcers

**INTERACTIONS** → Appendix 1: anticholinesterases, centrally acting

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Anxiety, appetite decreased, arrhythmias, asthenia, dehydration, depression, diarrhoea, dizziness, drowsiness, fall, gastrointestinal discomfort, headache, hyperhidrosis, hypersalivation, hypertension, movement disorders, nausea, skin reactions, syncope, tremor, urinary incontinence, urinary tract infection, vomiting, weight decreased

- **Uncommon** Aggression, atrophicventricular block

- **Rare or very rare** Pancreatitis, seizure

- **Frequency not known** Hepatitis

**SPECIFIC SIDE-EFFECTS**

- **Common or very common**
  - With oral use: Confusion, gait abnormal, hallucinations, malaise, parkinsonism, sleep disorders
  - With oral use: Hypotension
304 Dementia

Nervous System

- With transdermal use Gastric ulcer
- Rare or very rare
- With oral use Angina pectoris, gastrointestinal disorders, gastrointestinal haemorrhage
- Frequency not known
- With transdermal use Hallucination, nightmare

SIDE-EFFECTS, FURTHER INFORMATION Dose should be started low and increased according to response if tolerated. Treatment should be interrupted if dehydration resulting from prolonged vomiting or diarrhoea occurs and withheld until resolution—retitrate dose if necessary.

Transdermal administration is less likely to cause side-effects.

HEPATIC IMPAIRMENT Manufacturer advises caution (risk of increased exposure; no information available in severe impairment).

Dose adjustments Manufacturer advises cautious dose titration according to individual tolerability.

RENAL IMPAIRMENT Dose adjustments Titrate according to individual tolerability.

MONITORING REQUIREMENTS Monitor body-weight.

DIRECTIONS FOR ADMINISTRATION
- With transdermal use Apply patches to clean, dry, non-hairy, non-irritated skin on back, upper arm, or chest, removing after 24 hours and sating a replacement patch on a different area (avoid using the same area for 14 days).

PATIENT AND CARER ADVICE

EXELOM™ PATCHES Advise patients and carers of patch administration instructions, particularly to remove the previous day’s patch before applying the new patch—consult product literature.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (updated June 2018)

NICE TA217

The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine, and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer’s disease under all of the conditions specified below and in recommendation 1.5.5 of the NICE guideline on dementia.

If prescribing an AChE inhibitor (donepezil, galantamine, or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

Healthcare professionals should not rely solely on assessment scales to determine the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

www.nice.org.uk/guidance/ta217

EXELOM™ PATCHES

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (October 2007) that Exelon™ patches should be restricted for use in patients with moderately severe Alzheimer’s disease under the conditions of the NICE guidance (September 2007) and when a transdermal patch is an appropriate choice of formulation.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral solution

CAUTIONARY AND ADVISORY LABELS 21

- Rivastigmine (Non-proprietary)
- Rivastigmine (as Rivastigmine hydrogen tartrate) 2 mg per 1 ml Rivastigmine 2mg/ml oral solution sugar free sugar-free 120 ml (PSt) £66.82 DT = £66.82

Capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

- Rivastigmine (Non-proprietary)
- Rivastigmine (as Rivastigmine hydrogen tartrate) 1.5 mg Rivastigmine 1.5mg capsules | 28 capsule (PSt) £28.26 DT = £12.52 | 56 capsule (PSt) £5.04
- Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Rivastigmine 3mg capsules | 28 capsule (PSt) £33.25 DT = £3.16 | 56 capsule (PSt) £5.22-£6.32
- Rivastigmine (as Rivastigmine hydrogen tartrate) 4.5 mg Rivastigmine 4.5mg capsules | 28 capsule (PSt) £33.25 DT = £23.53 | 56 capsule (PSt) £28.66-£47.06
- Rivastigmine (as Rivastigmine hydrogen tartrate) 5 mg Rivastigmine 5mg capsules | 28 capsule (PSt) £29.17 DT = £12.32 | 56 capsule (PSt) £31.78-£58.34
- Nimvastid (Consilient Health Ltd)
- Nimvastid (as Rivastigmine hydrogen tartrate) 1.5 mg Nimvastid 1.5mg capsules | 28 capsule (PSt) £28.26 DT = £2.55
- Nimvastid (as Rivastigmine hydrogen tartrate) 3 mg Nimvastid 3mg capsules | 28 capsule (PSt) £28.26 DT + £3.16
- Nimvastid (as Rivastigmine hydrogen tartrate) 4.5 mg Nimvastid 4.5mg capsules | 28 capsule (PSt) £28.26 DT = £23.53
- Nimvastid (as Rivastigmine hydrogen tartrate) 6 mg Nimvastid 6mg capsules | 28 capsule (PSt) £28.26 DT = £29.17

Transdermal patch

- Almuriva (Sandoz Ltd)
- Almuriva (as Rivastigmine hydrogen tartrate) 1.5 mg Almuriva 1.5mg/24hours transdermal patches | 30 patch (PSt) £77.97 DT = £77.97
- Almuriva (as Rivastigmine hydrogen tartrate) 2 mg Almuriva 2mg/24hours transdermal patches | 30 patch (PSt) £77.97 DT = £19.97
- Alzest (Dr Reddy’s Laboratories (UK) Ltd)
- Alzest (as Rivastigmine hydrogen tartrate) 2 mg Alzest 2mg/24hours transdermal patches | 30 patch (PSt) £35.09 DT = £77.97
- Alzest (as Rivastigmine hydrogen tartrate) 3 mg Alzest 3mg/24hours transdermal patches | 30 patch (PSt) £19.97 DT = £19.97
- Voleze (Advanz Pharma)
- Voleze (as Rivastigmine hydrogen tartrate) 2 mg Voleze 2mg/24hours transdermal patches | 30 patch (PSt) £77.97 DT = £77.97
- Voleze (as Rivastigmine hydrogen tartrate) 3 mg Voleze 3mg/24hours transdermal patches | 30 patch (PSt) £19.97 DT = £19.97

DOPAMINERGIC DRUGS > NMDA RECEPTOR ANTAGONISTS

Memantine hydrochloride

DRUG ACTION Memantine is a glutamate receptor antagonist.

INDICATIONS AND DOSE Moderate to severe dementia in Alzheimer’s disease

- BY MOUTH
- Adult: Initially 5 mg once daily, then increased in steps of 5 mg every week; usual maintenance 20 mg daily; maximum 20 mg per day

www.getintopharma.com
Epilepsy and other seizure disorders

2 Epilepsy and other seizure disorders

Epilepsy

Epilepsy control

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the presenting epilepsy syndrome should first be considered. If the syndrome is not clear, the seizure type should determine the choice of treatment. Concomitant medication, co-morbidity, age, and sex should also be taken into account.

The dosage frequency is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage adherence with the prescribed regimen. Most antiepileptics, when used in the usual dosage, can be given...
twice daily. Lamotrigine p. 318, perampanel p. 322, phenobarbital p. 335, and phenytoin p. 323, which have long half-lives, can be given once daily at bedtime. However, with large doses, some antiepileptics may need to be given more frequently to avoid adverse effects associated with high peak plasma-drug concentration.

Management

When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried; the diagnosis should be checked before starting an alternative drug if the first drug showed lack of efficacy. The change from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions. If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy. A single antiepileptic drug should be prescribed wherever possible.

MHRA/CHM advice: Antiepileptic drugs: updated advice on switching between different manufacturers’ products (November 2017)

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of antiepileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

- Different antiepileptic drugs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control;
- Antiepileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product. These categories are listed below;
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product this should be prescribed either by specifying a brand name, or the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder);
- This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Please report on a Yellow Card any suspected adverse reactions to antiepileptic drugs;
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);
- Usual dispensing practice can be followed when a specific product is not stated.

Category 2

Clobazam p. 336, clonazepam p. 337, eslicarbazepine acetate p. 313, lamotrigine, oxcarbazepine p. 321, perampanel, rufinamide p. 326, topiramate p. 331, valproate, zonisamide p. 334. For these drugs, the need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency, treatment history, and potential implications to the patient of having a breakthrough seizure. Non-clinical factors as for Category 3 drugs should also be considered.

Category 3

Brivaracetam p. 310, ethosuximide p. 314, gabapentin p. 315, lacosamide p. 317, levetiracetam p. 320, pregabalin p. 324, tiagabine p. 331, vigabatrin p. 333. For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer’s product as therapeutic equivalence can be assumed, however, other factors are important when considering whether switching is appropriate. Differences between alternative products (e.g. product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.

Antiepileptic hypersensitivity syndrome

Antiepileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide); rarely cross-sensitivity occurs between some of these antiepileptic drugs. Some other antiepileptics (eslicarbazepine, stiripentol, and zonisamide) have a theoretical risk. The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, the patient must not be re-exposed, and expert advice should be sought.

Risk of suicidal thoughts and behaviour

The MHRA has advised (August 2008) that all antiepileptic drugs are associated with a small increased risk of suicidal thoughts and behaviour. Symptoms may occur as early as one week after starting treatment. Patients should be advised to seek medical advice if they develop any mood changes, distressing thoughts, or feelings about suicide or harming themselves, and should be referred for appropriate treatment if necessary.

Interactions

Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or inhibition; displacement from protein binding sites is not usually a problem. These interactions are highly variable and unpredictable.

Withdrawal

Antiepileptic drugs should be withdrawn under specialist supervision. Avoid abrupt withdrawal, particularly of barbiturates and benzodiazepines, because this can precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.

The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant
Epilepsy and other seizure disorders

...risk of seizure recurrence on drug withdrawal. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

Driving
If a driver has a seizure (of any type) they must stop driving immediately and inform the Driver and Vehicle Licensing Agency (DVLA).

- Patients who have had a first unprovoked epileptic seizure or a single isolated seizure must not drive for 6 months; driving may then be resumed, provided the patient has been assessed by a specialist as fit to drive and investigations do not suggest a risk of further seizures.
- Patients with established epilepsy may drive a motor vehicle provided they are not a danger to the public and are compliant with treatment and follow up. To continue driving, these patients must be seizure-free for at least one year (or have a pattern of seizures established for one year where there is no influence on their level of consciousness or the ability to act); also, they must not have a history of unprovoked seizures.

Note: additional criteria apply for drivers of large goods or passenger carrying vehicles—consult DVLA guidance.

- Patients who have had a seizure while asleep are not permitted to drive for one year from the date of each seizure, unless:
  - a history or pattern of sleep seizures occurring only ever while asleep has been established over the course of at least one year from the date of the first sleep seizure; or
  - an established pattern of purely asleep seizures can be demonstrated over the course of three years if the patient has previously had seizures whilst awake (or awake and asleep).

The DVLA recommends that patients should not drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months after their last dose. If a seizure occurs due to a prescribed change or withdrawal of epilepsy treatment, the patient will have their driving license revoked for 1 year; relicensing may be considered earlier if treatment has been reinstated for 6 months and no further seizures have occurred.

Pregnancy
Women of child-bearing potential should discuss with a specialist the impact of both epilepsy, and its treatment, on the outcome of pregnancy.

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and particularly if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of serious developmental disorders (up to 30–40% risk) and congenital malformations (approx. 10% risk). Valproate must not be used in females of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and alternative treatments are ineffective or not tolerated; during pregnancy, it must not be used for epilepsy, unless it is the only possible treatment. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. Topiramate carries an increased risk of congenital malformations (including cleft palate, hypospadias, and anomalies involving various body systems) if taken in the first trimester of pregnancy. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

Prescribers should also consider carefully the choice of antiepileptic therapy in pre-pubescent girls who may later become pregnant. Women of child-bearing potential who take antiepileptic drugs should be given advice about the need for an effective contraception method to avoid unplanned pregnancy—for further information, see Conception and contraception in the individual drug monographs. Some antiepileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives.

Women who want to become pregnant should be referred to a specialist for advice in advance of conception. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester.

If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus. To reduce the risk of neural tube defects, folate supplementation is advised before conception and throughout the first trimester. In the case of sodium valproate p. 327 and valproic acid p. 354 an urgent consultation is required to reconsider the benefits and risks of valproate therapy.

The concentration of antiepileptic drugs in the plasma can change during pregnancy. Doses of phenytoin, carbamazepine, and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth should be monitored.

Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol. Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with antiepileptics.

Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital.

Epilepsy and Pregnancy Register
All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

Breast-feeding
Women taking antiepileptic monotherapy should generally be encouraged to breast-feed; if a woman is on combination therapy or if there are other risk factors, such as premature birth, specialist advice should be sought.

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones. Infants should also be monitored for adverse effects associated with the antiepileptic drug particularly with newer antiepileptics, if the antiepileptic is readily transferred into breast-milk causing high infant serum-drug concentrations (e.g. ethosuximide, lamotrigine, primidone, and zonisamide), or if slower metabolism in the infant causes drugs to accumulate (e.g. phenobarbital and lamotrigine). Serum-drug concentration monitoring should be undertaken in breast-fed infants if suspected adverse reactions develop; if toxicity develops it may be necessary to introduce formula feeds to limit the infant’s drug exposure, or to wean the infant off breast-milk altogether.

Primidone, phenobarbital, and the benzodiazepines are associated with an established risk of drowsiness in breast-fed babies and caution is required.

Withdrawal effects may occur in infants if a mother suddenly stops breast-feeding, particularly if she is taking phenobarbital, primidone, or lamotrigine.
Focal seizures with or without secondary generalisation
Carbamazepine p. 311 and lamotrigine p. 318 are first-line options for newly diagnosed focal seizures; oxcarbazepine p. 321, sodium valproate p. 327 and levetiracetam p. 320 may be used if carbamazepine or lamotrigine are unsuitable or not tolerated. If monotherapy is unsuccessful with two of these first-line antiepileptic drugs, adjunctive treatment may be considered. Options for adjunctive treatment include carbamazepine, clobazam p. 336, gabapentin p. 315, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate p. 331. If adjunctive treatment is ineffective or not tolerated, a tertiary epilepsy specialist should be consulted who may consider eslicarbazepine acetate p. 313, lacosamide p. 317, phenobarbital p. 335, phenytoin p. 323, pregabalin p. 324, tiagabine p. 331, vigabatrin p. 333 and zonisamide p. 334.

Generalised seizures
Tonic-clonic seizures
Sodium valproate is the first-line treatment for newly diagnosed generalised tonic-clonic seizures (except in female patients who are premenopausal, see Valproate below). Lamotrigine is the alternative choice if sodium valproate is not suitable, but may exacerbate myoclonic seizures. In those with established epilepsy with generalised tonic-clonic seizures only, lamotrigine or sodium valproate may be prescribed as the first-line treatment. Carbamazepine and oxcarbazepine may also be considered in newly diagnosed and established tonic-clonic seizures, but may exacerbate myoclonic and absence seizures. Clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate may be used as adjunctive treatment if monotherapy is ineffective or not tolerated.

Absence seizures
Ethosuximide p. 314, or sodium valproate (except in female patients who are premenopausal, see Valproate below), are the drugs of choice in absence seizures and syndromes; lamotrigine is a suitable alternative when ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. Sodium valproate should be used as the first choice if there is a high risk of generalised tonic-clonic seizures. A combination of any two of these drugs may be used if monotherapy is ineffective. Clobazam, clonazepam p. 337, levetiracetam, topiramate or zonisamide may be considered by a tertiary epilepsy specialist if adjunctive treatment fails. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are not recommended in absence seizures or syndromes.

Myoclonic seizures
Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. Sodium valproate is the drug of choice in newly diagnosed myoclonic seizures (except in female patients who are premenopausal, see Valproate below); topiramate and levetiracetam are alternative options if sodium valproate is unsuitable but consideration should be given to the less favourable side-effect profile of topiramate. A combination of two of these drugs may be used if monotherapy is ineffective or not tolerated. If adjunctive treatment fails, a tertiary epilepsy specialist should be consulted and may consider clobazam, clonazepam, zonisamide or piracetam p. 406. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are not recommended for the treatment of myoclonic seizures.

Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that coexist with myoclonic seizures in idiopathic generalised epilepsy.

Anticonvulsants
Carbamazepine and lamotrigine are alternative options if sodium valproate is not suitable, but may exacerbate myoclonic seizures due to the risk of seizure exacerbation. They may respond poorly to the traditional drugs. Sodium valproate is the drug of choice (except in female patients who are premenopausal, see Valproate below); lamotrigine can be added as adjunctive treatment. If adjunctive treatment is ineffective or not tolerated, a tertiary epilepsy specialist should be consulted, and may consider rufinamide p. 325 or topiramate. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin are not recommended in atonic and tonic seizures.

Epilepsy syndromes
Some drugs are licensed for use in particular epilepsy syndromes. The epilepsy syndromes are specific types of epilepsy that are characterised according to the number of features including seizure type, age of onset, and EEG characteristics. For more information on epilepsy syndromes in children see BNF for children.

Dravet syndrome
A tertiary specialist should be involved in decisions regarding treatment of Dravet syndrome. Sodium valproate (except in pregnancy or females of childbearing potential, see Valproate below) or topiramate are first-line treatment options in children with Dravet syndrome. Clobazam or stiripentol p. 330 may be considered as adjunctive treatment in children and adults if first-line treatments are ineffective or not tolerated. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin should not be used as they may exacerbate myoclonic seizures.

Lennox-Gastaut syndrome
A tertiary specialist should be involved in decisions regarding treatment of Lennox-Gastaut syndrome. Sodium valproate is the first-line drug for treating children with Lennox-Gastaut syndrome (except in pregnancy or females of childbearing potential, see Valproate below); lamotrigine can be used as adjunctive treatment in children and adults if sodium valproate is unsuitable, ineffective or not tolerated. If adjunctive treatment is ineffective or not tolerated, rufinamide and topiramate may be considered by tertiary specialists. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin should not be used. Felbamate [unlicensed] may be used in tertiary specialist centres when all other treatment options have failed.

Antiepileptic drugs
Carbamazepine and related antiepileptics
Carbamazepine is a drug of choice for simple and complex focal seizures and is a first-line treatment option for generalised tonic-clonic seizures. It can be used as adjunctive treatment for focal seizures when monotherapy has been ineffective. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly. Carbamazepine may exacerbate tonic, atonic, myoclonic and absence seizures and is therefore not recommended if these seizures are present.

Oxcarbazepine is licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures. It can also be considered for the treatment of primary generalised tonic-clonic seizures [unlicensed]. Oxcarbazepine is not recommended in tonic, atonic, absence or myoclonic seizures due to the risk of seizure exacerbation.

Eslicarbazepine acetate p. 313 is licensed for adjunctive treatment in adults with focal seizures with or without secondary generalisation.
Epilepsy and other seizure disorders

Ethosuximide
Ethosuximide p. 314 is a first-line treatment option for absence seizures. It may also be prescribed as adjunctive treatment for absence seizures when monotherapy is ineffective. Ethosuximide is also licensed for myoclonic seizures.

Gabapentin and pregabalin
Gabapentin p. 315 and pregabalin p. 324 are used for the treatment of focal seizures with or without secondary generalisation. They are not recommended if tonic, atonic, absence or myoclonic seizures are present. Both are also licensed for the treatment of neuropathic pain. Pregabalin is licensed for the treatment of generalised anxiety disorder.

Lamotrigine
Lamotrigine p. 318 is an antiepileptic drug recommended as a first-line treatment for focal seizures and primary and secondary generalised tonic-clonic seizures. It is also licensed for typical absence seizures in children (but efficacy may not be maintained in all children) and is an unlicensed treatment option in adults if first-line treatments have been unsuccessful. Lamotrigine can also be used as adjunctive treatment in atonic or tonic seizures if first-line treatment has failed [unlicensed]. Myoclonic seizures may be exacerbated by lamotrigine and it can cause serious rashes especially in children; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration, whereas the enzyme-inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. When the potential for interaction is not known, treatment should be initiated with lower doses, such as those used with valproate.

Levetiracetam and brivaracetam
Levetiracetam p. 320 is used for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures. Levetiracetam may be prescribed alone and in combination for the treatment of myoclonic seizures, and under specialist supervision for absence seizures [both unlicensed].

Brivaracetam p. 310 is used as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation.

Phenobarbital and primidone
Phenobarbital p. 335 is effective for tonic-clonic and focal seizures but may be sedative in adults. It may be tried for atypical absence, tonic, and tonic seizures. Rebound seizures may be a problem on withdrawal.

Primidone p. 336 is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. A low initial dose of primidone is essential.

Phenytoin
Phenytoin p. 323 is licensed for tonic-clonic and focal seizures but may exacerbate absence or myoclonic seizures and should be avoided if these seizures are present. It has a narrow therapeutic index and the relationship between dose and plasma-drug concentration is non-linear; small dosage increases in some patients may produce large increases in plasma concentration with acute toxic side-effects. Similarly, a few missed doses or a small change in drug absorption may result in a marked change in plasma-drug concentration. Monitoring of plasma-drug concentration improves dosage adjustment.

When only parenteral administration is possible, fosphenytoin sodium p. 314, a pro-drug of phenytoin, may be convenient to give. Unlike phenytoin (which should only be given intravenously), fosphenytoin sodium may also be given by intramuscular injection.

Rufinamide
Rufinamide p. 326 is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It may be considered by a tertiary specialist for the treatment of refractory tonic or atonic seizures [unlicensed].

Topiramate
Topiramate p. 331 can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation. It can be used as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome and for absence, tonic and atonic seizures under specialist supervision [unlicensed]. It can also be considered as an option in myoclonic seizures [unlicensed]. Female patients should be fully informed of the risks related to the use of topiramate during pregnancy and the need to use effective contraception—for further information, see Conception and contraception and Pregnancy in the topiramate drug monograph.

Valproate
Sodium valproate p. 327 is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised tonic-clonic seizures, focal seizures, generalised absences and myoclonic seizures, and can be tried in atypical absence seizures. It is recommended as a first-line option in atonic and tonic seizures. Sodium valproate has widespread metabolic effects and monitoring of liver function tests and full blood count is essential. Because of its high teratogenic potential, valproate must not be used in females of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and alternative treatments are ineffective or not tolerated. During pregnancy, it must not be used for epilepsy unless it is the only possible treatment. For further information see Important safety information, Conception and contraception, and Pregnancy in the sodium valproate and valproate drug p. 354 drug monographs.

Valproic acid (as semisodium valproate) is licensed for acute mania associated with bipolar disorder.

Zonisamide
Zonisamide p. 334 can be used alone for the treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy, and as adjunctive treatment for refractory focal seizures with or without secondary generalisation in adults and children aged 6 years and above. It can also be used under the supervision of a specialist for refractory absence and myoclonic seizures [unlicensed indications].

Benzodiazepines
Clobazam p. 336 may be used as adjunctive therapy in the treatment of generalised tonic-clonic and refractory focal seizures. It may be prescribed under the care of a specialist for refractory absence and myoclonic seizures. Clonazepam p. 337 may be prescribed by a specialist for refractory absence and myoclonic seizures, but its sedative side-effects may be prominent.

Other drugs
Acetazolamide p. 1181, a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation. Piracetam p. 406 is used as adjunctive treatment for cortical myoclonus.

Status epilepticus
Convulsive status epilepticus
Immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine p. 1080 should be considered if alcohol
abuse is suspected; pyridoxine hydrochloride p. 1080 should be given if the status epilepticus is caused by pyridoxine hydrochloride deficiency.

Seizures lasting longer than 5 minutes should be treated urgently with intravenous lorazepam p. 339 (repeated once after 10 minutes if seizures recur or fail to respond). Intravenous diazepam p. 343 is effective but it carries a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Patients should be monitored for respiratory depression and hypotension.

Where facilities for resuscitation are not immediately available, diazepam p. 343 can be administered as a rectal solution or midazolam p. 340 oromucosal solution can be given into the buccal cavity.

**Important**

If, after initial treatment with benzodiazepines, seizures recur or fail to respond 25 minutes after onset, phenytoin sodium, fosphenytoin sodium p. 314, or phenobarbital sodium should be used; contact intensive care unit if seizures continue. If these measures fail to control seizures 45 minutes after onset, anaesthesia with thiopental sodium p. 338, midazolam, or a non-barbiturate anaesthetic such as propofol p. 1330 (unlicensed indication), should be instituted with full intensive care support.

**Phenytoin sodium** can be given by slow intravenous injection, followed by the maintenance dosage if appropriate.

Alternatively, fosphenytoin sodium (a pro-drug of phenytoin), can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin sodium. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin sodium should be expressed in terms of phenytoin sodium.

**Non-convulsive status epilepticus**

The urgency to treat non-convulsive status epilepticus depends on the severity of the patient’s condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

**Febrile convulsions**

*Brief febrile convulsions* need no specific treatment; antipyretic medication (e.g. paracetamol p. 444), is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. *Prolonged febrile convulsions* (those lasting 5 minutes or longer), or *recurrent febrile convulsions* without recovery must be treated actively (as for convulsive status epilepticus). Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated.

**Other drugs used for Epilepsy and other seizure disorders** Magnesium sulfate, p. 1051

### ANTIEPILEPTICS

#### Brivaracetam

**INDICATIONS AND DOSE**

Adjunctive therapy of focal seizures with or without secondary generalisation

- **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- Adult: Initially 25–50 mg twice daily, adjusted according to response; usual maintenance 25–100 mg twice daily (max. per dose 100 mg twice daily)

**INTERACTIONS** → Appendix 1: antiepileptics

**SIDE-EFFECTS**

- **Common or very common**
  - Anxiety
  - Appetite decreased
  - Constipation
  - Cough
  - Depression
  - Dizziness
  - Drowsiness
  - Fatigue
  - Increased risk of infection
  - Insomnia
  - Irritability
  - Nausea
  - Vertigo
  - Vomiting
- **Uncommon**
  - Aggression
  - Psychotic disorder
- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—limited information available. See also Pregnancy in Epilepsy p. 305.
- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in *animal* studies.
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution (risk of increased exposure).
- **DOSAGE ADJUSTMENTS**
  - Manufacturer advises consider initial dose of 25 mg twice daily; max. maintenance dose of 75 mg twice daily (limited information available).
- **TREATMENT CESSATION**
  - Manufacturer advises avoid abrupt withdrawal—reduce daily dose in steps of 50 mg at weekly intervals, then reduce to 20 mg daily for a final week.

**DIRECTIONS FOR ADMINISTRATION**

- **With intravenous use**
  - For intermittent *intravenous infusion*, manufacturer advises dilute in *Glucose* 5% or *Sodium Chloride* 0.9% or *Lactated Ringer’s solution*; give over 15 minutes.
- **With oral use**
  - Manufacturer advises oral solution can be diluted in water or juice shortly before swallowing.

**PREScribing and dispensing information**

Manufacturer advises if switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the total daily dose and the frequency of administration should be maintained.

**PATIENT AND CARER ADVICE**

- **Missed doses**
  - Manufacturer advises if one or more doses are missed, a single dose should be taken as soon as possible and the next dose should be taken at the usual time.
- **Driving and skilled tasks**
  - Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1160/16

The *Scottish Medicines Consortium* has advised (July 2016) that *Brivaracetam* is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with refractory epilepsy. Treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy.

**All Wales Medicines Strategy Group (AWMSG) decisions**

AWMSG No. 3387

The *All Wales Medicines Strategy Group* has advised (December 2018) that *Brivaracetam* is recommended as an option for restricted use within NHS Wales. *Brivaracetam* should be restricted for
use in the treatment of patients with refractory epilepsy, who remain uncontrolled with, or are intolerant to, other adjunctive anti-epileptic medicines, within its licensed indication as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 4 years of age with epilepsy. Brivaracetam (Briviact®) is not recommended for use within NHS Wales outside of this subpopulation.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
CAUTIONARY AND ADVISORY LABELS 2 ELECTROLYTES: May contain Sodium
▶ Briviact (UCB Pharma Ltd) ▼
Brivaracetam 10 mg per 1 ml Briviact 50mg/5ml solution for injection vials 10 vial (POM) £222.75

Oral solution
CAUTIONARY AND ADVISORY LABELS 2, 8 EXCIPIENTS: May contain Sorbitol ELECTROLYTES: May contain Sodium
▶ Briviact (UCB Pharma Ltd) ▼
Brivaracetam 10 mg per 1 ml Briviact 10mg/ml oral solution sugar-free 300 ml (POM) £155.83 DT £115.83

Tablet
CAUTIONARY AND ADVISORY LABELS 2, 8, 25
▶ Briviact (UCB Pharma Ltd) ▼
Brivaracetam 10 mg Briviact 10mg tablets 14 tablet (POM) £34.64 DT £34.64
Brivaracetam 25 mg Briviact 25mg tablets 56 tablet (POM) £129.64 DT £129.64
Brivaracetam 50 mg Briviact 50mg tablets 56 tablet (POM) £129.64 DT £129.64
Brivaracetam 75 mg Briviact 75mg tablets 56 tablet (POM) £129.64 DT £129.64
Brivaracetam 100 mg Briviact 100mg tablets 56 tablet (POM) £129.64 DT £129.64

Carbamazepine

26-Jun-2018

● INDICATIONS AND DOSE
Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: Initially 100–200 mg 1–2 times a day, increased gradually according to response; usual dose 200 mg 3–4 times a day, increased if necessary up to 1.6 g daily

Focal and generalised tonic-clonic seizures
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 1 month–11 years: Initially 5 mg/kg once daily, dose to be taken at night, alternatively initially 2.5 mg/kg twice daily, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 5 mg/kg 2–3 times a day, increased if necessary up to 20 mg/kg daily
Child 12–17 years: Initially 100–200 mg 1–2 times a day, then increased to 200–400 mg 2–3 times a day, increased if necessary up to 1.8 g daily, dose should be increased slowly

DOSE EQUIVALENCE AND CONVERSION
Suppositories of 125 mg may be considered to be approximately equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).

CARBAGEN® SR
Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures
▶ BY MOUTH
Adult: Initially 100–400 mg daily in 1–2 divided doses, increased in steps of 100–200 mg every 2 weeks, dose should be increased slowly; usual dose 0.8–1.2 g daily in 1–2 divided doses, increased if necessary up to 1.6–2 g daily in 1–2 divided doses
Elderly: Reduce initial dose

Trigeminal neuralgia
▶ BY MOUTH
Adult: Initially 100–200 mg daily in 1–2 divided doses, some patients may require higher initial dose, increase gradually according to response; usual dose 600–800 mg daily in 1–2 divided doses, increased if necessary up to 1.6 g daily in 1–2 divided doses

Prophylaxis of bipolar disorder unresponsive to lithium
▶ BY MOUTH
Adult: Initially 400 mg daily in 1–2 divided doses, increased until symptoms controlled; usual dose 400–600 mg daily in 1–2 divided doses; maximum 1.6 g per day

Focal and generalised tonic-clonic seizures | Prophylaxis of bipolar disorder
▶ BY MOUTH
Child 5–11 years: Initially 5 mg/kg daily in 1–2 divided doses, then increased in steps of 2.5–5 mg/kg every 3–7 days as required, dose should be increased slowly; maintenance 10–15 mg/kg daily in 1–2 divided doses, increased if necessary up to 20 mg/kg daily in 1–2 divided doses
Child 12–17 years: Initially 100–400 mg daily in 1–2 divided doses, then increased to 400–1200 mg daily in 1–2 divided doses, increased if necessary up to 1.8 g daily in 1–2 divided doses, dose should be increased slowly

TEGRETOL® PROLONGED RELEASE
Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures
▶ BY MOUTH
Adult: Initially 100–400 mg daily in 2 divided doses, increased in steps of 100–200 mg every 2 weeks, dose should be increased slowly; usual dose 0.8–1.2 g daily in 2 divided doses, increased if necessary up to 1.6–2 g daily in 2 divided doses
Epilepsy and other seizure disorders

Focal and generalised tonic-clonic seizures | Prophylaxis of bipolar disorder

**BY MOUTH**

- Child 5–11 years: Initially 5 mg/kg daily in 2 divided doses, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 10–15 mg/kg daily in 2 divided doses, increased if necessary up to 20 mg/kg daily in 2 divided doses.
- Child 12–17 years: Initially 100–400 mg daily in 2 divided doses, dose should be increased slowly; maintenance 400–1200 mg daily in 2 divided doses, increased if necessary up to 1.8 g daily in 2 divided doses.

**Trigeminal neuralgia**

- **BY MOUTH**
  - Child: Initially 400 mg daily in 2 divided doses, increased until symptoms controlled; usual dose 400–600 mg daily in 2 divided doses; maximum 1.6 g per day.

**INTERACTIONS**

- **Blood, hepatic, or skin disorders**
  - Carbamazepine should be avoided unless no alternative (such as phenytoin).
  - Cross-sensitivity reported with oxcarbazepine and with hypersensitivity syndrome associated with carbamazepine.
  - Monitoring blood counts and hepatic and renal function tests (but evidence of practical value uncertain).

**CONTRA-INDICATIONS**

- Acute porphyrias.
- Severe, progressive, or associated with clinical symptoms of porphyria cutanea tarda.

**UNLICENSED USE**

- In adults Not licensed for use in adult alcohol withdrawal. Use off-label neuropathy is an unlicensed indication.

**CAUTIONS**

- **Cardiac disease**
  - Use in diabetic neuropathy is an unlicensed indication.
  - Cardiac disease.

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058.
- AV conduction abnormalities (unless paced).
- History of bone-marrow depression.

**SIDE-EFFECTS**

- **Common or very common**
  - Dizziness, drowsiness, dry mouth, eosinophilia, fatigue, fluid imbalance, gastrointestinal discomfort, headache, hypotension, leucopenia, movement disorders, nausea, oedema, skin reactions, thrombocytopenia, vision disorders, vomiting, weight increased.

- **Uncommon**
  - Constipation, diarrhoea, eye disorders, tic, tremor.

- **Rare or very rare**
  - Aggression, agranulocytosis, albuminuria, alopecia, anaemia, angioedema, anxiety, appetite decreased, arthralgias, arthritides, azotaemia, bone disorders, bone marrow disorders, cardiac conduction disorders, circulatory collapse, confusion, congestive heart failure, conjunctivitis, coronary artery disease aggravated, depression, dyspepsia, embolism and thrombosis, erythema nodosum, fever, folate deficiency, galactorrhoea, gynaecomastia, haematuria, haemolytic anaemia, hallucinations, hearing impairment, hepatic disorders, hirsutism, hyperacidity, hyperhidrosis, hypersensitivity, hypertension, hypogammaglobulinaemia, hypotension, lens opacity, leucocytosis, lymphadenopathy, meningitis, muscle complaints, muscle weakness, nephritis, tubulointerstitial, nervous system disorder, neuroleptic malignant syndrome, oral disorders, pancreatitis, paraesthesia, paresis, peripheral neuropathy, photosensitivity reaction, pneumonia, pneumonitis, pseudolymphoma, psychosis, red blood cell abnormalities, renal impairment, severe cutaneous adverse reactions (SCARs), sexual dysfunction, speech impairment, spermatogenesis abnormal, syncope, systemic lupus erythematosus (SLE), taste altered, tinnitus, urinary disorders, vanishing bile duct syndrome, vasculitis.

**FREQUENCY not known**

- Bone fracture, colitis, human herpesvirus 6 infection reactivation, memory loss, nail loss.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Some side-effects (such as headache, ataxia, drowsiness, nausea, vomiting, blurring of vision, dizziness and allergic skin reactions) are dose-related, and may be dose-limiting. These side-effects are more common at the start of treatment and in the elderly.

**OVERDOSE**

- For details on the management of poisoning, see Active elimination techniques, under Emergency treatment of poisoning p. 1395.

**ALLERGY AND CROSS-SENSITIVITY**

- Antiepileptic hypersensitivity syndrome associated with carbamazepine.

**PREGNANCY**

- See Pregnancy in Epilepsy p. 305.

**MONITORING**

- Doses should be adjusted on the basis of plasma drug concentration monitoring.

**BREAST FEEDING**

- Amount probably too small to be harmful.

**HEPATIC IMPAIRMENT**

- Manufacture advises caution and close monitoring—no information available.

**RENAL IMPAIRMENT**

- Use with caution.

**PRE-TREATMENT SCREENING**

- Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

**MONITORING REQUIREMENTS**

- Plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre) measured after 1–2 weeks.

**Manufacturers**

- Blood counts and hepatic and renal function tests (but evidence of practical value uncertain).

**TREATMENT CESSATION**

- When stopping treatment with carbamazepine for bipolar disorder, reduce the dose gradually over a period of at least 4 weeks.

**DIRECTIONS FOR ADMINISTRATION**

- In children Oral liquid has been used rectally—should be retained for at least 2 hours (but may have laxative effect).

**TREGRETOL® PROLONGED RELEASE**

- Tegretol® Prolonged Release tablets can be halved but should not be chewed.

**PRESCRIBING AND DISPENSING INFORMATION**

- Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

**PATIENT AND CARER ADVICE**

- Blood, hepatic, or skin disorders.

- Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop.
Epilepsy and other seizure disorders

Medicines for Children leaflet: Carbamazepine (oral) for preventing seizures www.medicinesforchildren.org.uk/carbamazepine-oral-preventing-seizures-0

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Carbamazepine Tablets may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 3, 8, 25

- Carbagen SR (Mylan)
- Carbamazepine 200 mg. Carbagen SR 200mg tablets | 56 tablet | £4.16 DT = £5.20
- Carbamazepine 400 mg. Carbagen SR 400mg tablets | 56 tablet | £8.20 DT = £10.24
- Tegretol Retard (Novartis Pharmaceuticals UK Ltd)
- Carbamazepine 200 mg. Tegretol Prolonged Release 200mg tablets | 56 tablet | £5.20 DT = £5.20
- Carbamazepine 400 mg. Tegretol Prolonged Release 400mg tablets | 56 tablet | £10.24 DT = £10.24

**Tablet**

CAUTIONARY AND ADVISORY LABELS 3, 8

- Carbagen
- Carbamazepine 100 mg. Carbagen 100mg tablets | 28 tablet | £5.74 | 84 tablet | £2.07 (Hospital only)
- Carbamazepine 200 mg. Carbagen 200mg tablets | 28 tablet | £4.99 | 84 tablet | £3.83 (Hospital only)
- Carbamazepine 400 mg. Carbagen 400mg tablets | 28 tablet | £4.27 | 56 tablet | £5.02 (Hospital only)
- Tegretol (Novartis Pharmaceuticals UK Ltd)
- Carbamazepine 100 mg. Tegretol 100mg tablets | 84 tablet | £2.07 DT = £2.07
- Carbamazepine 200 mg. Tegretol 200mg tablets | 84 tablet | £3.83 DT = £3.83
- Carbamazepine 400 mg. Tegretol 400mg tablets | 56 tablet | £5.02 DT = £5.02

**Suppository**

CAUTIONARY AND ADVISORY LABELS 3, 8

- Carbamazepine (Non-proprietary)
- Carbamazepine 125 mg Carbamazepine 125mg suppositories | 5 suppository | £12.00 DT = £12.00
- Carbamazepine 250 mg Carbamazepine 250mg suppositories | 5 suppository | £14.00 DT = £14.00

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 3, 8

- Carbamazepine (Non-proprietary)
- Carbamazepine 20 mg per 1 ml Carbamazepine 100mg/5ml oral suspension sugar free sugar-free | 300 ml | £8.25 DT = £8.04
- Tegretol (Novartis Pharmaceuticals UK Ltd)
- Carbamazepine 20 mg per 1 ml Tegretol 100mg/5ml liquid sugar-free | 300 ml | £6.12 DT = £8.04

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**Eliscarbazepine acetate**

20-Nov-2018

**INDICATIONS AND DOSE**

Monotherapy of focal seizures with or without secondary generalisation

- **BY MOUTH**
  - Adult: Initially 400 mg once daily for 1–2 weeks, then increased to 800 mg once daily, then increased if necessary to 1.2 g once daily (max. per dose 1.6 g)
  - Elderly: Initially 400 mg once daily for 1–2 weeks, then increased to 800 mg once daily (max. per dose 1.2 g)

Adjuvative therapy of focal seizures with or without secondary generalisation

- **BY MOUTH**
  - Adult: Initially 400 mg once daily for 1–2 weeks, then increased to 800 mg once daily (max. per dose 1.2 g)

**CONTRA-INDICATIONS** Second- or third-degree AV block

**CAUTIONS** Elderly · hyponatraemia · PR-interval prolongation

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**INTERACTIONS** → Appendix 1: antiepileptics

**SIDE-EFFECTS**

- Common or very common Appetite decreased · asthenia · concentration impaired · diarrhoea · dizziness · drowsiness · electrolyte imbalance · gait abnormal · headaches · movement disorders · nausea · skin reactions · sleep disorders · vertigo · vision disorders · vomiting

- Uncommon Alopecia · anaemia · anxiety · bradycardia · chest pain · chills · confusion · constipation · depression · dry mouth · eye disorders · flushing · gastritis · gastrointestinal discomfort · haemorrhage · hearing impairment · hyperhidrosis · hypertension · hypotension · hypothyroidism · increased risk of infection · liver disorder · malaise · mood altered · muscle weakness · myalgia · pain in extremity · palpitations · peripheral coldness · peripheral neuropathy · peripheral oedema · psychomotor retardation · psychotic disorder · sensation abnormal · speech impairment · tinnitus · toothache · weight decreased

- Frequency not known Angioedema · leucopenia · pancreatitis · severe cutaneous adverse reactions (SCARs) · thrombocytopenia

**ALLERGY AND CROSS-SENSITIVITY**

Antiepileptic hypersensitivity syndrome theoretically associated with eslicarbazepine. See under Epilepsy p. 305 for more information.

**PREGNANCY**

Manufacturer advises minimum effective doses and monotherapy if possible—reproductive toxicity in animal studies.

Monitoring. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in mild to moderate impairment—limited information; avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**

Manufacturer advises avoid if creatinine creatinine clearance less than 30 mL/minute.

Dose adjustments. Manufacturer advises reduce initial dose to 200 mg once daily or 400 mg every other day for 2 weeks, then increase to 400 mg once daily if creatinine clearance 30–60 mL/minute. The dose may be further increased based on individual response.

**PRE-TREATMENT SCREENING**

Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

**MONITORING REQUIREMENTS**

Monitor plasma-sodium concentration in patients at risk of hyponatraemia and discontinue treatment if hyponatraemia occurs.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations. Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks. Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness, somnolence and visual disorders.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 592/09

The Scottish Medicines Consortium has advised (November 2010) that eslicarbazepine (Zebinix®) is accepted for restricted use within NHS Scotland as adjuvant therapy in adults with focal seizures with or without secondary generalisation. It is restricted for use in refractory epilepsy.
Epilepsy and other seizure disorders

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in patients who have been heavily pre-treated and remain uncontrolled with existing anti-epileptic drugs. This advice is contingent upon the continuing availability of the patient access scheme in Scotland.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS**: B
- Zebinix (Eisai Ltd)
- Eslicarbazepine acetate 50 mg per 1 ml Zebinix 50mg/1ml oral suspension sugar-free | 200 ml | £56.67

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**: B
- Zebinix (Eisai Ltd)
- Eslicarbazepine acetate 200 mg Zebinix 200mg tablets | 60 tablet | £68.00 DT = £68.00
- Eslicarbazepine acetate 800 mg Zebinix 800mg tablets | 30 tablet | £136.00 DT = £136.00

**SIDE-EFFECTS**

- **Absence seizures**: Atypical absence seizures (adjunct)
- **Myoclonic seizures**
  
  - **By mouth**
  
  - **Child 1 month–5 years**: Initially 5 mg/kg twice daily (max. per dose 125 mg), dose to be increased every 5–7 days; maintenance 10–20 mg/kg twice daily (max. per dose 500 mg), total daily dose may rarely be given in 3 divided doses.
  
  - **Child 6–17 years**: Initially 250 mg twice daily, then increased in steps of 250 mg every 5–7 days; usual dose 500–750 mg twice daily, increased if necessary up to 1 g twice daily.
  
  - **Adult**: Initially 500 mg daily in 2 divided doses, then increased in steps of 250 mg every 5–7 days; usual dose 1–1.5 g daily in 2 divided doses, increased if necessary up to 2 g daily.

**CAUTIONS**

Avoid in Acute porphyrias p. 1058

**INTERACTIONS** Appendix 1: antiepileptics

**SIDE-EFFECTS**

- Aggression, agranulocytosis, appetite decreased, blood disorder, bone marrow disorders, concentration impaired, depression, diarrhoea, dizziness, drowsiness, erythema nodosum, fatigue, gastrointestinal discomfort, generalised tonic-clonic seizure, headache, hiccups, leucopenia, libido increased, lupus-like syndrome, mood altered, movement disorders, nausea, nephrotic syndrome, oral disorders, psychosis, rash, sleep disorders, Stevens–Johnson syndrome, vaginal haemorrhage, vision disorders, vomiting, weight decreased

**SIDE-EFFECTS, FURTHER INFORMATION**

Blood counts required if features of fever, sore throat, mouth ulcers, bruising or bleeding.

**PREGNANCY**

See also Pregnancy in Epilepsy p. 305.

**Monitoring**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**

Present in milk. Hyperexcitability and sedation reported.

**HEPATIC IMPAIRMENT**

Use with caution.

**RENA L IMPAIRMENT**

Use with caution.

**PATIENT AND CARER ADVICE**

Blood disorders. Patients or their carers should be told how to recognise signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, mouth ulcers, bruising, or bleeding develop.

**INTERACTIONS**

Appendix 1: antiepileptics

**SIDE-EFFECTS**

- Common or very common: Asthenia, chills, dizziness, drowsiness, dry mouth, dysarthria, euphoric mood, headache, hypotension, movement disorders, nausea, nystagmus, sensation abnormal, skin reactions, stupor.

**MEDI CINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS**: B
- Ethosuximide (Non-proprietary)
- Ethosuximide 50 mg per 1 ml Ethosuximide 250mg/5ml syrup | 200 ml | £173.00 DT = £173.00
- Ethosuximide 250mg/5ml oral solution sugar free sugar-free | 125 ml | £108.12–108.13 sugar-free | 250 ml | £216.25

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS**: B
- Ethosuximide (Non-proprietary)
- Ethosuximide 250 mg Ethosuximide 250mg capsules | 36 capsule | £173.00 DT = £173.00

**DRUG ACTION**

Fosphenytoin is a pro-drug of phenytoin.
taste altered - tinnitus - tremor - vasodilation - vertigo - vision disorders - vomiting

- **Uncommon** Cardiac arrest - confusion - hearing impairment - muscle complaints - muscle weakness - nervousness - oral disorders - reflexes abnormal - severe cutaneous adverse reactions (SCARs) - systemic lupus erythematosus (SLE) - thinking abnormal

- **Frequency not known** Acute psychosis - agranulocytosis - appetite disorder - atrial conduction depression (more common if injection too rapid) - atrioventricular block - bone disorders - bone fracture - bone marrow disorders - bradycardia - cardiotoxicity - cerebrovascular insufficiency - circulatory collapse (more common if injection too rapid) - coarsening of the facial features - constipation - delirium - Dupuytren's contracture - encephalopathy - granulocytopenia - groin tingling - hair changes - hepatic disorders - hyperglycaemia - hypersensitivity - insomnia - leucopenia - lymphadenopathy - nephritis - tubulointerstitial - Peyronie's disease - polyarteritis nodosa - polynephritis - purple glove syndrome - thrombocytopenia - toxic seizure - ventricular conduction depression (more common if injection too rapid) - ventricular fibrillation (more common if injection too rapid)

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Fosphenytoin** has been associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia, and heart block have also been reported. The following reactions are recommended: monitor heart rate, blood pressure, and respiratory function for duration of infusion; observe patient for at least 30 minutes after infusion; if hypotension occurs, reduce infusion rate or discontinue; reduce dose or infusion rate in elderly, and in renal or hepatic impairment.

- **Allergy and cross-sensitivity** Cross-sensitivity reported with carbamazepine.

- **Pregnancy** See also Pregnancy in Epilepsy p. 305. Changes in plasma-protein binding may cause interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction.

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **Breast feeding** Small amounts present in milk, but not known to be harmful.

- **Hepatic impairment** Manufacturer advises caution—monitor free plasma-phenytoin concentration (rather than total plasma-phenytoin concentration) in hepatic impairment or hypoalbuminaemia and in hyperbilirubinaemia.

- **Dose adjustments** Manufacturer advises a 10–25% reduction in dose or infusion rate (except in the treatment of status epilepticus) in hepatic impairment or hypoalbuminaemia.

- **Renal impairment** Dose adjustments Consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus).

- **Pre-treatment screening** HLA-B*1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

- **Monitoring requirements** Manufacturer recommends blood counts (but evidence of practical value uncertain).

- With intravenous use Monitor heart rate, blood pressure, ECG, and respiratory function for duration of infusion.

- **Directions for administration** For intermittent intravenous infusion (Pro-Epanutin®), give in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of 1.5–25 mg (phenytoin sodium equivalent (PE))/mL.

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**Epilepsy and other seizure disorders**

- **Prescribing and dispensing information** Prescriptions for fosphenytoin should state the dose in terms of phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Electrolytes:** May contain phosphate
- **Pro-Epanutin (Pfizer Ltd)**

Fosphenytoin sodium 75 mg per 1 ml Pro-Epanutin 750mg/10ml concentrate for solution for injection vials | 10 vial | £400.00

(Hospital only)

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**Gabapentin**

- **Indications and dose** Adjunctive treatment of focal seizures with or without secondary generalisation

  - **by mouth**

    - Child 6–11 years: 10 mg/kg once daily (max. per dose 300 mg) on day 1, then 10 mg/kg twice daily (max. per dose 300 mg) on day 2, then 10 mg/kg 3 times a day (max. per dose 300 mg) on days 3; usual dose 25–35 mg/kg daily in 3 divided doses; some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate. Daily dose maximum to be given in 3 divided doses; maximum 70 mg/kg per day.

    - Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.

    - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.

    - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day).

**Monotherapy for focal seizures with or without secondary generalisation**

- **by mouth**

    - Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.

    - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day).

**Peripheral neuropathic pain**

- **by mouth**

    - Adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg.

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Migraine prophylaxis
- **BY MOUTH**
  - Adult: Initially 300 mg daily, then increased to up to 2.4 g daily in divided doses, adjusted according to response

Menopausal symptoms, particularly hot flushes, in women with breast cancer
- **BY MOUTH**
  - Adult: 300 mg 3 times a day, initial dose should be lower and titrated up over three days

**UNLICENSED USE**
- In children  Not licensed at doses over 50 mg/kg daily in children under 12 years.
- In adults  Not licensed for migraine prophylaxis. **(Caution)** Not licensed for menopausal symptoms.

**IMPORTANT SAFETY INFORMATION**

The levels of propylene glycol, saccharin and aspartame in some products may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rosemont brand) are given to adolescents or adults with low body-weight (39.50 kg) — consult product literature.

MHRA/CHM ADVICE: GABAPENTIN (NEURONTIN®): RISK OF SEVERE RESPIRATORY DEPRESSION (OCTOBER 2017)

Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants, and elderly people might be at higher risk of experiencing severe respiratory depression and dose adjustments may be necessary in these patients.

MHRA/CHM ADVICE: GABAPENTIN (NEURONTIN®) AND RISK OF ABUSE AND DEPENDENCE: NEW SCHEDULING REQUIREMENTS FROM 1 APRIL (APRIL 2019)

Following concerns about abuse, gabapentin has been reclassified as a Class C controlled substance and is now a Schedule 3 drug, but is exempt from safe custody requirements. Healthcare professionals should evaluate patients carefully for a history of drug abuse before prescribing gabapentin, and observe patients for signs of abuse and dependence. Patients should be informed of the potential risks of interactions between gabapentin and alcohol, and with other medicines that cause CNS depression, particularly opioids.

**CAUTIONS**
- Diabetes mellitus - elderly (in adults) - high doses of oral solution in adolescents and adults with low body-weight - history of psychotic illness - history of substance abuse - mixed seizures (including absences)

**INTERACTIONS**  → Appendix 1: Antiepileptics

**SIDE-EFFECTS**
- **Uncommon** Cognitive impairment - palpitations
- **Frequency not known** Acute kidney injury - alopecia - angioedema - breast enlargement - drug use disorders - gynaecomastia - hallucination - hepatic disorders - hyponatraemia - pancreatitis - rhombomylolysis - severe cutaneous adverse reactions (SCARs) - thrombocytopena - tinnitus - urinary incontinence
- **PREGNANCY**  Manufacturer advises avoid unless benefit outweighs risk — toxicity reported. See also Pregnancy in Epilepsy p. 305.
- **BREAST FEEDING**  Present in milk — manufacturer advises use only if potential benefit outweighs risk. See also Breast-feeding in Epilepsy p. 305.

**RENAI IMPAIRMENT**
- **Dose adjustments**  → in adults  Manufacturer advises reduce dose to 600–1800 mg daily in 3 divided doses if creatinine clearance 50–79 ml/minute. Manufacturer advises reduce dose to 300–900 mg daily in 3 divided doses if creatinine clearance 30–49 ml/minute. Manufacturer advises reduce dose to 150–600 mg daily in 3 divided doses if creatinine clearance 15–29 ml/minute (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days).

Manufacturer advises reduce dose to 150–300 mg daily in 3 divided doses if creatinine clearance is less than 15 ml/minute (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days) — further dose reductions may be required in proportion to creatinine clearance, consult product literature.
- **In children** Reduce dose if estimated glomerular filtration rate less than 80 ml/minute/1.73 m²; consult product literature.

**MONITORING REQUIREMENTS**  Monitor for signs of gabapentin abuse.

**EFFECT ON LABORATORY TESTS**  False positive readings with some urinary protein tests.

**DIRECTIONS FOR ADMINISTRATION** Capsules can be opened but the bitter taste is difficult to mask.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Gabapentin for neuropathic pain; www.medicinesforchildren.org.uk/gabapentin-neuropathic-pain

Medicines for Children leaflet: Gabapentin for preventing seizures; www.medicinesforchildren.org.uk/gabapentin-preventing-seizures

Patient leaflet: NHS England has produced a patient leaflet with information on the reclassification of gabapentin.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 3, 5, 8, 25**
- Gabapentin (Non-proprietary)
  - Gabapentin 600 mg  |  Gabapentin 600 mg tablets | 100 tablet  |  £10.00 DT  |  £5.99  |  **(C2)**
  - Gabapentin 800 mg  |  Gabapentin 800 mg tablets | 100 tablet  |  £7.00 DT  |  £25.96  |  **(C3)**
- Neurontin (Pfizer Ltd)
  - Gabapentin 600 mg  |  Neurontin 600 mg tablets | 100 tablet  |  £9.29 DT  |  £5.99  |  **(C2)**
  - Gabapentin 800 mg  |  Neurontin 800 mg tablets | 100 tablet  |  £9.13 DT  |  £25.96  |  **(C3)**

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 3, 5, 8**

**EXCIPIENTS:**  May contain Propylene glycol

**ELECTROLYTES:**  May contain Potassium, sodium

**Gabapentin (Non-proprietary)**
- Gabapentin 50 mg per 1 ml  |  Gabapentin 500mg/ml oral solution sugar free sugar-free  |  150 ml  |  £99.00 DT  |  £5.99  |  **(C3)**

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 3, 5, 8, 25**

**Gabapentin (Non-proprietary)**
- Gabapentin 100 mg  |  Gabapentin 100mg capsules | 100 capsule  |  £12.92 DT  |  £8.49  |  **(C3)**
- Gabapentin 300 mg  |  Gabapentin 300mg capsules | 100 capsule  |  £42.40 DT  |  £13.15  |  **(C3)**
- Gabapentin 400 mg  |  Gabapentin 400mg capsules | 100 capsule  |  £60.06 DT  |  £13.86  |  **(C3)**

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**Lacosamide**

22-Feb-2018

- **INDICATIONS AND DOSE**
  - **Monotherapy of focal seizures with or without secondary generalisation**
    - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
      - Child (body-weight 50 kg and above): Initially 50 mg twice daily, then increased to 100 mg twice daily, after one week, alternatively initially 100 mg twice daily; increased in steps of 50 mg twice daily (max. per dose 300 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals
      - Child 4-17 years (body-weight up to 50 kg): (consult product literature)
      - Adult: Initially 50 mg twice daily, then increased to 100 mg twice daily, after one week, alternatively initially 100 mg twice daily; increased in steps of 50 mg twice daily (max. per dose 300 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals
      - Adult: Loading dose 200 mg, followed by 100 mg twice daily, to be given 12 hours after initial dose; increased in steps of 50 mg twice daily (max. per dose 200 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals
    - **Adjunctive treatment of focal seizures with or without secondary generalisation**
      - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
      - Child (body-weight 50 kg and above): Initially 50 mg twice daily, then increased to 100 mg twice daily, after one week; increased in steps of 50 mg twice daily (max. per dose 200 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals
      - Child 4-17 years (body-weight up to 50 kg): (consult product literature)
      - Adult: Initially 50 mg twice daily, then increased to 100 mg twice daily, after one week; increased in steps of 50 mg twice daily (max. per dose 200 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals
    - **Adjunctive treatment of focal seizures with or without secondary generalisation (alternative loading dose regimen when it is necessary to rapidly attain therapeutic plasma concentrations) (under close medical supervision)**
      - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
      - Child (body-weight 50 kg and above): Loading dose 200 mg, followed by 100 mg twice daily, to be given 12 hours after initial dose; increased in steps of 50 mg twice daily (max. per dose 200 mg twice daily) if necessary and if tolerated, dose to be increased at weekly intervals

- **SIDE-EFFECTS**
  - Common or very common: Asthenia, concentration impaired, confusion, constipation, depression, diarrhea, dizziness, drowsiness, dry mouth, dysarthria, dyspepsia, flatulence, gait abnormal, headache, insomnia, mood altered, movement disorders, muscle spasms, nausea, vertigo, vision disorders, vomiting
  - Uncommon: Aggression, agitation, angioedema, arrhythmias, atrioventricular block, hallucination, psychotic disorder, suicidal tendencies, syncope
  - Frequency not known: Agranulocytosis

- **ALLERGY AND CROSS-SENSITIVITY**
  - Antiepileptic hypersensitivity syndrome associated with lacosamide. See under Epilepsy p. 305 for more information.
  - **PREGNANCY**
  - See also Pregnancy in Epilepsy p. 305.
  - Monitoring: The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution (risk of increased exposure), particularly in severe impairment (no information available).

- **SIDE-EFFECTS**
  - **ASTHENIA**
  - **CONFUSION**
  - **DEPRESSION**
  - **DIZZINESS**
  - **DYSPEPSIA**

- **INTERACTIONS**
  - **CONTRA-INDICATIONS**: Second- or third-degree AV block
  - **CAUTIONS**: Conduction problems - elderly (in adults) - risk of PR-interval prolongation - severe cardiac disease

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - **SMC No. 532/09**
      - The Scottish Medicines Consortium has advised (February 2009) that lacosamide (Vimpat®) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.
    - **SMC No. 1301/18**
      - The Scottish Medicines Consortium has advised (February 2018) that lacosamide (Vimpat®) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in adolescents and children from 4 years of age with epilepsy. It is restricted for specialist use in refractory epilepsy.
  - **All Wales Medicines Strategy Group (AWMSG) decisions**
    - **AWMSG No. 3343**
      - The All Wales Medicines Strategy Group has advised (March 2018) that lacosamide (Vimpat®) is recommended as an option for use within NHS Wales as adjunctive therapy in

- **Flavours of syrup may include strawberry.**

- **PATIENT AND CARER ADVICE**

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Manufacturer advises consider dose reduction—consult product literature.

- **RENA L IMPAI RMENT**
  - Manufacturer advises avoid—present in milk in animal studies.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use: For intermittent intravenous infusion, manufacturer advises give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9% or Lactated Ringer’s Solution; give over 15–60 minutes—gives doses greater than 200 mg over at least 30 minutes.

- **ADDITIONAL INFORMATION**
  - Flavours of syrup may include strawberry.
the treatment of focal seizures with or without secondary generalisation in children from 4 years of age up to 15 years of age with epilepsy.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**
  
  ELECTROLYTES: May contain Sodium

  **Vimpat** (UCB Pharma Ltd)

  Lacosamide 10 mg per 1 ml Vimpat 200mg/20ml solution for infusion via 1 vial (PVD) £29.70

  **Oral solution**

  CAUTIONARY AND ADVISORY LABELS

  **Vimpat** (UCB Pharma Ltd)

  Lacosamide 10 mg per 1 ml Vimpat 10mg/ml syrup sugar-free 200 ml (PVD) £25.74 DT = £25.74

  **Tablet**

  CAUTIONARY AND ADVISORY LABELS

  **Vimpat** (UCB Pharma Ltd)

  Lacosamide 50 mg Vimpat 50mg tablets | 14 tablet (PVD) £10.81

  Lacosamide 100 mg Vimpat 100mg tablets | 14 tablet (PVD) £21.62

  Lacosamide 150 mg Vimpat 150mg tablets | 14 tablet (PVD) £32.44

  Lacosamide 200 mg Vimpat 200mg tablets | 56 tablet (PVD) £144.16 DT = £144.16

- **INDICATIONS AND DOSE**

  **Lamotrigine**

  01-Aug-2018

  **Monotherapy of focal seizures**

  | Monotherapy of primary and secondary generalised tonic-clonic seizures |
  | Monotherapy of seizures associated with Lennox-Gastaut syndrome |

  | BY MOUTH |
  | Child 12-17 years: Initially 25 mg once daily for 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days |
  | Adult: Initially 25 mg once daily for 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |

  **Adjunctive therapy of focal seizures**

  | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures with valproate |
  | Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome with valproate |

  | BY MOUTH |
  | Child 2-11 years: Initially 300 micrograms/kg daily in 1–2 divided doses for 14 days, then increased in steps of up to 600 micrograms/kg every 7–14 days; maintenance 1–10 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day |
  | Adult: Initially 25 mg once daily for 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |

  **Adjunctive therapy of focal seizures without enzyme inducing drugs**

  | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures without enzyme inducing drugs |
  | Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes without enzyme inducing drugs |

  | BY MOUTH |
  | Child 2-11 years: Initially 2 mg once daily on alternate days for first 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day |
  | Child 2-11 years (body-weight up to 13 kg): Initially 2 mg once daily on alternate days for first 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |
  | Child 2-11 years (body-weight 13 kg and above): Initially 150 micrograms/kg once daily for 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |
  | Child 12-17 years: Initially 25 mg once daily for 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |
  | Adult: Initially 25 mg once daily for 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |

  **Epilepsy and other seizure disorders**

  | Monotherapy of seizures associated with Lennox-Gastaut syndrome |
  | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures |

  | BY MOUTH |
  | Child 12-17 years: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |
  | Adult: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days |
Monotherapy or adjunctive therapy of bipolar disorder (without enzyme inducing drugs) without valproate

- **BY MOUTH**
- **Adult:** Initially 25 mg once daily for 14 days, then 50 mg daily in 1–2 divided doses for further 14 days, then 100 mg daily in 1–2 divided doses for further 7 days; maintenance 200 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day

**Adjuvant therapy of bipolar disorder with valproate**

- **BY MOUTH**
- **Adult:** Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then 50 mg daily in 1–2 divided doses for further 7 days; maintenance 100 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

**Adjuvant therapy of bipolar disorder (with enzyme inducing drugs) without valproate**

- **BY MOUTH**
- **Adult:** Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased to 100 mg twice daily for further 7 days, then increased to 150 mg twice daily for further 7 days; maintenance 200 mg twice daily, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

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**SAFE PRACTICE**

Do not confuse the different combinations or indications.

- **CAUTIONS**
  - Myoclonic seizures (may be exacerbated). Parkinson’s disease (may be exacerbated)(in adults)
- **INTERACTIONS**
  - Appendix 1: antiepileptics
- **SIDE-EFFECTS**
  - Common or very common: Aggression, agitation, arthralgia, diarrhoea, dizziness, drowsiness, dry mouth, fatigue, headache, irritability, nausea, pain, rash, sleep disorders, tremor, vomiting
  - Uncommon: Alopecia, movement disorders, vision disorders
  - Rare or very rare: Confusion, conjunctivitis, disseminated intravascular coagulation, face oedema, fever, hallucination, hepatitis, herpes infection, hypersensitivity syndrome, lymphadenopathy, meningitis, aseptic, multi-organ failure, nystagmus, seizure, severe cutaneous adverse reactions (SCARs), tic

**SIDE-EFFECTS, FURTHER INFORMATION**

Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have developed (especially in children); most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

- **ALLERGY AND CROSS-SENSITIVITY**
  - Antiepileptic hypersensitivity syndrome associated with lamotrigine. See under Epilepsy p. 305 for more information.
- **PREGNANCY**
  - See also Pregnancy in Epilepsy p. 305.
- **Monitoring**
  - Doses should be adjusted on the basis of plasma-drug concentration monitoring.
- **BREAST FEEDING**
  - Present in milk, but limited data suggest no harmful effect on infant.
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in moderate to severe impairment.
  - Dose adjustments: Manufacturer advises dose reduction of approx. 50% in moderate impairment, and approx. 75% in severe impairment; adjust according to response.
- **RENAL IMPAIRMENT**
  - Caution in renal failure; metabolite may accumulate.
  - Dose adjustments: Consider reducing maintenance dose in significant impairment.
- **TREATMENT CESSATION**
  - Avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic lamotrigine product.
  - Switching between formulations: Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.
- **PATIENT AND CARER ADVICE**
  - Skin reactions: Warn patients and carers to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop.
  - Blood disorders: Patients and their carers should be alert for symptoms and signs suggestive of bone-marrow failure, such as anaemia, bruising, or infection. Aplastic anaemia, bone-marrow depression, and pancytopenia have been associated rarely with lamotrigine.
  - Medicines for Children leaflet: Lamotrigine for preventing seizures www.medicinesforchildren.org.uk/lamotrigine-preventing-seizures

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Dispersible tablet**

**CAUTIONARY AND ADVISORY LABELS 8, 13**

- **Lamotrigine (Non-proprietary)**
  - Lamotrigine 5 mg: Lamotrigine 5mg dispersible tablets sugar-free
  - 28 tablet (PSt) £15.00 DT + £6.86
  - Lamotrigine 25 mg: Lamotrigine 25mg dispersible tablets sugar-free
  - 56 tablet (PSt) £20.00 DT + £2.20
  - Lamotrigine 100 mg: Lamotrigine 100mg dispersible tablets sugar-free
  - 56 tablet (PSt) £58.68 DT + £3.99
- **Lamictal** (GlaxoSmithKline UK Ltd)
  - Lamotrigine 2 mg: Lamictal 2mg dispersible tablets sugar-free
  - 30 tablet (PSt) £18.81 DT + £18.81
  - Lamotrigine 5 mg: Lamictal 5mg dispersible tablets sugar-free
  - 28 tablet (PSt) £9.38 DT + £6.86
  - Lamotrigine 25 mg: Lamictal 25mg dispersible tablets sugar-free
  - 56 tablet (PSt) £23.53 DT + £2.20
  - Lamotrigine 100 mg: Lamictal 100mg dispersible tablets sugar-free
  - 56 tablet (PSt) £69.04 DT + £3.99

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 8**

- **Lamotrigine (Non-proprietary)**
  - Lamotrigine 25 mg: Lamotrigine 25mg tablets
  - 56 tablet (PSt) £8.80 DT + £4.25

www.getintopharma.com
Adjunctive therapy of focal seizures with or without seizures

Adjunctive therapy of myoclonic seizures and tonic-clonic seizures

Adult:

- Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

**INDICATIONS AND DOSE**

**Monotherapy of focal seizures with or without secondary generalisation**

- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Child 12–17 years: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

**Adjunctive therapy of focal seizures with or without secondary generalisation**

- **BY MOUTH**
  - Child 1–5 months: Initially 7 mg/kg once daily, then increased in steps of up to 7 mg/kg twice daily (max. per dose 21 mg/kg twice daily), dose to be increased every 2 weeks
  - Child 6 months–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

- **BY INTRAVENOUS INFUSION**
  - Child 4–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks
  - Adult: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks

**Adjunctive therapy of myoclonic seizures and tonic-clonic seizures**

- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Child 12–17 years (body-weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks
  - Child 12–17 years (body-weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks

**SIDE-EFFECTS**

- Common or very common: Anxiety, appetite decreased, asthenia, behaviour abnormal, cough, depression, diarrhoea, dizziness, drowsiness, gastrointestinal discomfort, headache, increased risk of infection, insomnia, mood altered, movement disorders, nausea, skin reactions, vertigo, vomiting

- Uncommon: Alopecia, concentration impaired, confusion, hallucination, leucopenia, muscle weakness, myalgia, paraesthesia, psychotic disorder, suicidal tendencies, thrombocytopenia, vision disorders, weight changes

- Rare or very rare: Acute kidney injury, agranulocytosis, haematopoietic disorders, hyponatraemia, neutropenia, pancreatitis, pancytopenia, personality disorder, rhabdomyolysis, severe cutaneous adverse reactions (SCARs), thinking abnormal

**PREGNANCY**

See also Pregnancy in Epilepsy p. 305.

**Monitoring**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

It is recommended that the fetal growth should be monitored.

**BREAST FEEDING**

Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

- In adults: Halve dose in severe hepatic impairment if eGFR less than 60 mL/minute/1.73 m².
- In children: Halve dose in severe hepatic impairment if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

**RENAL IMPAIRMENT**

- **Dose adjustments**
  - In children: Reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m² (consult product literature).
  - In adults: Maximum 2 g daily if eGFR 50–80 mL/minute/1.73 m², Maximum 1.5 g daily if eGFR 30–50 mL/minute/1.73 m², Maximum 1 g daily if eGFR less than 30 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

- In intravenous use: For intravenous infusion (Kepra®), dilute requisite dose with at least 100 mL Glucose 5% or Sodium Chloride 0.9%; give over 15 minutes.
- With oral use: For administration of oral solution, requisite dose may be diluted in a glass of water.

**PRESCRIBING AND DISPENSING INFORMATION**

If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Levetiracetam for preventing seizures www.medicinesforchildren.org.uk/levetiracetam-preventing-seizures
Adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

**BY MOUTH**
- Child 6-17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maximum 15 mg/kg twice daily; maximum 46 mg/kg per day
- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**Treatment of primary generalised tonic-clonic seizures**

**BY MOUTH**
- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- In adjunctive therapy, the dose of concomitant antiepileptics may need to be reduced when using high doses of oxcarbazepine.

**SIDE-EFFECTS**
- In adults
  - Not licensed for the treatment of primary generalised tonic-clonic seizures.

**UNLICENSED USE**
- In adults
  - Not licensed for the treatment of primary generalised tonic-clonic seizures.

**CAUTIONS**
- Avoid in Acute porphyrias p. 1058 • Cardiac conduction disorders • Heart failure • Hyponatraemia

**INTERACTIONS**
- Appendix 1: Antiepileptics

**PRE-TREATMENT SCREENING**
- Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

**INDICATIONS AND DOSE**

Monotherapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

**BY MOUTH**
- Child 6-17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maximum 46 mg/kg per day
- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**OXCARBAZEPINE**

**Epilepsy and other seizure disorders**

**MEDIINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Granules**

**CAUTIONARY AND ADVISORY LABELS**
- Adult:
  - Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**
- Adult:
  - Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**Solution for infusion**

**ELECTROLYTES**: May contain Sodium
- Adult:
  - Initially 300 mg/kg twice daily; maximum 46 mg/kg per day
  - Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS**
- Adult:
  - Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses
MONITORING REQUIREMENTS
- Monitor plasma-sodium concentration in patients at risk of hyponatraemia.
- Monitor body-weight in patients with heart failure.

PRESCRIBING AND DISPENSING INFORMATION
Patients may need to be maintained on a specific manufacturer’s branded or generic oxcarbazepine product.

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

PATIENT AND CARER ADVICE
Blood, hepatic, or skin disorders Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as lethargy, confusion, muscular twitching, fever, rash, blistering, mouth ulcers, bruising, or bleeding develop.

Medicines for Children: Oxcarbazepine for preventing seizures see medicinesforchildren.org.uk/oxcarbazepine-preventing-seizures

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Oral suspension

- Tripteral (Novartis Pharmaceuticals UK Ltd)

Oxcarbazepine 60 mg per 1 ml Trileptal 60mg/ml oral suspension sugar-free | 250 ml (POM) £46.96 DT = £48.96

Tablet

- Oxcarbazepine (Non-proprietary)

Oxcarbazepine 150 mg Oxcarbazepine 150mg tablets | 50 tablet (POM) £12.42 DT = £13.37

Oxcarbazepine 300 mg Oxcarbazepine 300mg tablets | 50 tablet (POM) £24.88 DT = £26.87

Oxcarbazepine 600 mg Oxcarbazepine 600mg tablets | 50 tablet (POM) £48.96 DT = £53.71

Tripteral (Novartis Pharmaceuticals UK Ltd)

Oxcarbazepine 150 mg Trileptal 150mg tablets | 50 tablet (POM) £12.24 DT = £13.37

Oxcarbazepine 300 mg Trileptal 300mg tablets | 50 tablet (POM) £24.48 DT = £26.87

Oxcarbazepine 600 mg Trileptal 600mg tablets | 50 tablet (POM) £48.96 DT = £53.71

MANUFACTURERS
- Fycompa (Eisai Ltd)

Perampanel 2 mg Fycompa 2mg tablets | 7 tablet (POM) £35.00 DT = £36.00

Perampanel 4 mg Fycompa 4mg tablets | 28 tablet (POM) £40.00 DT = £41.00

Perampanel 6 mg Fycompa 6mg tablets | 28 tablet (POM) DT = £40.00

Perampanel 8 mg Fycompa 8mg tablets | 28 tablet (POM) £40.00 DT = £42.00

Perampanel 10 mg Fycompa 10mg tablets | 28 tablet (POM) £40.00 DT = £42.00

Perampanel 12 mg Fycompa 12mg tablets | 28 tablet (POM) £40.00 DT = £42.00

INDICATIONS AND DOSE

Adjunctive treatment of focal seizures with or without secondary generalised seizures

BY MOUTH

Child 12–17 years: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at intervals of at least every 2 weeks, adjusted according to response; maintenance 4–8 mg once daily; maximum 12 mg per day.

Adult: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at intervals of at least every 2 weeks, adjusted according to response; maintenance 4–8 mg once daily; maximum 12 mg per day.

Adjunctive treatment of primary generalised tonic-clonic seizures

BY MOUTH

Child 12–17 years: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at intervals of at least every 2 weeks, adjusted according to response, maintenance up to 8 mg once daily; maximum 12 mg per day.

Adult: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at intervals of at least every 2 weeks, adjusted according to response, maintenance up to 8 mg once daily; maximum 12 mg per day.

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Titrate at intervals of at least 1 week with concomitant carbamazepine, fosphenytoin, oxcarbazepine, or phenytoin.

INTERACTIONS

Appendix 1: antiepileptics

SIDE-EFFECTS

- Common or very common Anxiety - appetite abnormal - back pain - behaviour abnormal - confusion - dizziness - drowsiness - dysarthria - fatigue - gait abnormal - irritability - movement disorders - nausea - vertigo - vision disorders - weight increased

PREGNANCY

Manufacturer advises avoid. See also Pregnancy in Epilepsy p. 305.

Monitoring The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING

Avoid — present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

Dose adjustments Manufacturer advises maximum 8 mg per day in mild to moderate impairment.

RENAL IMPAIRMENT

Avoid in moderate or severe impairment.

PRESCRIBING AND DISPENSING INFORMATION

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients may need to be maintained on a specific manufacturer’s branded or generic perampanel product.

PATIENT AND CARER ADVICE

Driving and skilled tasks Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness and drowsiness.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
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Phenytoin 19-Apr-2017

- **INDICATIONS AND DOSE**
  - **Tonic-clonic seizures** | Focal seizures
    - **BY MOUTH**
      - Child 1 month–11 years: Initially 1.5–2.5 mg/kg twice daily, then adjusted according to response to 2.5–5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), dose also adjusted according to plasma-phenytoin concentration; maximum 300 mg per day
      - Child 12–17 years: Initially 75–150 mg twice daily, then adjusted according to response to 150–200 mg twice daily (max. per dose 300 mg twice daily), dose also adjusted according to plasma-phenytoin concentration
  - **Loading dose**
    - **BY MOUTH**
      - Child: Initially 2.5 mg/kg twice daily, then adjusted according to response to 4–8 mg/kg daily, dose also adjusted according to plasma-phenytoin concentration; maximum 300 mg per day
  - **Status epilepticus** | Acute symptomatic seizures associated with head trauma or neurosurgery
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Child 1 month–11 years: Loading dose 20 mg/kg, then (by slow intravenous injection or by intravenous infusion) 2.5–5 mg/kg twice daily
      - Child 12–17 years: Loading dose 20 mg/kg, then (by intravenous infusion or by slow intravenous injection) up to 100 mg 3–4 times a day
      - Adult: Loading dose 20 mg/kg (max. per dose 2 g), then (by intravenous infusion or by slow intravenous injection or by mouth) maintenance 100 mg every 6–8 hours adjusted according to plasma-phenytoin concentration monitoring

- **DOSE EQUIVALENT AND CONVERSION**
  - Preparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base (such as Epanutin Infatabs® and Epanutin® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy. However, if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma-phenytoin concentration monitoring is recommended.

- **UNLICENSED USE**

- **SIDE-EFFECTS**
  - With intravenous use. Phenytoin doses in BNF publications may differ from those in product literature.

- **INTERACTIONS**
  - **Appendix 1: antiepileptics**

- **CONTRA-INDICATIONS**
  - **GENERAL CONTRA-INDICATIONS**
    - Acute porphyrias p. 1058
  - **SPECIFIC CONTRA-INDICATIONS**
    - With intravenous use
      - Second- and third-degree heart block.
      - Sino-atrial block.
      - Atrioventricular conduction depression (more common if injection too rapid).
      - Tonic seizure (more common if injection too rapid).
      - Ventricular conduction depression (more common if injection too rapid).
      - Ventricular fibrillation (more common if injection too rapid).
      - With oral use
        - Electrolyte imbalance.
        - Pneumonitis.
        - Vitamin D deficiency.
      - With parenteral use
        - Arrhythmias.
        - Atrial conduction depression (more common if injection too rapid).
        - Cardiac arrest.
        - Extravasation necrosis.
        - Hypotension.
        - Injection site necrosis.
        - Purpura.
        - Respiratory arrest.
        - Respiratory disorders.
        - Seizure (more common if injection too rapid).
        - Venricular conduction depression.

- **SAFETY INFORMATION**
  - **NHS IMPROVEMENT PATIENT SAFETY ALERT: RISK OF DEATH AND SEVERE HARM FROM ERROR WITH INJECTABLE PHENYTOIN (NOVEMBER 2016)**
    - Use of injectable phenytoin is error-prone throughout the prescribing, preparation, administration and monitoring processes; all relevant staff should be made aware of appropriate guidance on the safe use of injectable phenytoin to reduce the risk of error.
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**Bradycardia and hypotension** With intravenous use; reduce rate of administration if bradycardia or hypotension occurs.

**Overdose** Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia.

- **ALLERGY AND CROSS-SENSITIVITY** Cross-sensitivity reported with carbamazepine. Antiepileptic hypersensitivity syndrome associated with phenytoin. See under Epilepsy p. 305 for more information.

- **PREGNANCY** See also Pregnancy in Epilepsy p. 305.

- **MONITORING REQUIREMENTS**

- **PRE-TREATMENT SCREENING** HLAB*^®^ 1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

- **MONITORING REQUIREMENTS**

- **Blood counts** Manufacturer recommends blood counts (but evidence of practical value uncertain).

- **Adults** The usual total plasma-phenytoin concentration for optimum response is 10–20 mg/litre (or 40–80 micromol/litre). In pregnancy, the elderly, and certain disease states where protein binding may be reduced, careful interpretation of total plasma-phenytoin concentration is necessary; it may be more appropriate to measure free plasma-phenytoin concentration.

- **Children** Therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding. Trough plasma concentration for optimum response: neonate—3 months, 6–15 mg/litre (25–60 micromol/litre); child 3 months–18 years, 10–20 mg/litre (40–80 micromol/litre).

- **With intravenous use** Monitor ECG and blood pressure.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises each injection or infusion should be preceded and followed by an injection of Sodium Chloride 0.9% through the same needle or catheter to avoid local venous irritation.

- **Intravenous injection** Give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). Manufacturer advises for intravenous infusion, dilute to a concentration not exceeding 10 mg/ml with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron). Give at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). Complete administration within 1 hour of preparation.

- **PREGNANCY** See also Pregnancy in Epilepsy p. 305.

- **Monitoring** Changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction.

- **Doses** Should be adjusted on the basis of plasma-drug concentration monitoring.

- **BREAST FEEDING** Small amounts present in milk, but not known to be harmful.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (increased risk of accumulation and toxicity due to decreased protein binding in hepatic impairment, hypoalbuminaemia, or hyperbilirubinaemia).

- **Dose adjustments** • With oral use Manufacturer advises consider dose reduction.

- **With intravenous use** Manufacturer advises consider maintenance dose reduction.

- **PRE-TREATMENT SCREENING** HLAB*^®^ 1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

- **MONITORING REQUIREMENTS**

- **Blood counts** Manufacturer recommends blood counts (but evidence of practical value uncertain).

- **In adults** The usual total plasma-phenytoin concentration for optimum response is 10–20 mg/litre (or 40–80 micromol/litre). In pregnancy, the elderly, and certain disease states where protein binding may be reduced, careful interpretation of total plasma-phenytoin concentration is necessary; it may be more appropriate to measure free plasma-phenytoin concentration.

- **In children** Therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding. Trough plasma concentration for optimum response: neonate—3 months, 6–15 mg/litre (25–60 micromol/litre); child 3 months–18 years, 10–20 mg/litre (40–80 micromol/litre).

- **With intravenous use** Monitor ECG and blood pressure.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises each injection or infusion should be preceded and followed by an injection of Sodium Chloride 0.9% through the same needle or catheter to avoid local venous irritation.

- **With intravenous use in children** For intravenous injection, give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). Manufacturer advises for intravenous infusion, dilute to a concentration not exceeding 10 mg/ml with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron). Give at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). Complete administration within 1 hour of preparation.

- **With intravenous use in adults** Manufacturer advises for intravenous infusion, give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute) or lower may be more appropriate in some patients (including the elderly and those with heart disease). Manufacturer advises for intravenous infusion, dilute in 50–100 ml Sodium Chloride 0.9% (final concentration not to exceed 10 mg/ml) and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute) or lower may be more appropriate in some patients (including the elderly and those with heart disease). Complete administration within 1 hour of preparation.

- **PRESCRIBING AND DISPENSING INFORMATION** Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

- **PATIENT AND CARER ADVICE** Blood or skin disorders Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Tablet**

- **CAUTIONARY AND ADVISORY LABELS** B

- **Phenytoin (Non-proprietary)**

- **Phenytoin sodium 100 mg** Phenytoin sodium 100mg tablets | 28 tablet | £3.00 DT | £11.03

- **Solution for injection**

- **EXCIPIENTS:** May contain Alcohol, propylene glycol

- **ELECTROLYTES:** May contain Sodium

- **Phenytoin (Non-proprietary)**

- **Phenytoin sodium 50 mg per 1 ml** Phenytoin sodium 250mg/5ml solution for injection ampoules | 5 ampoule | £2.40 (Hospital only)

- **Epanutin (Pfizer Ltd)**

- **Phenytoin sodium 50 mg per 1 ml** Epanutin Ready-Mixed Parenteral 250mg/5ml solution for injection ampoules | 10 ampoule | £48.79 (Hospital only)

- **Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS** B

- **Phenytoin (Non-proprietary)**

- **Phenytoin sodium 6 mg per 1 ml** Epanutin 30mg/5ml oral suspension | 500 ml | £4.27 DT | £4.27

- **Chewable tablet**

- **CAUTIONARY AND ADVISORY LABELS** B, 24

- **Phenytoin (Non-proprietary)**

- **Phenytoin sodium 50 mg** Epanutin Infatabs 50mg chewable tablets | 200 tablet | £13.18 DT | £13.18

- **Capsule**

- **CAUTIONARY AND ADVISORY LABELS** B

- **Phenytoin (Non-proprietary)**

- **Phenytoin sodium 25 mg** Phenytoin sodium 25mg capsules | 28 capsule | £1.24 DT | £1.24

- **Phenytoin sodium 50 mg** Phenytoin sodium 50mg capsules | 28 capsule | £1.07 DT | £1.07

- **Phenytoin sodium 100 mg** Phenytoin sodium 100mg capsules | 84 capsule | £6.75 DT | £8.36

- **Phenytoin sodium 300 mg** Phenytoin sodium 300mg capsules | 28 capsule | £9.11 DT | £9.11

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| Pregabalin | 22-May-2019 |

- **INDICATIONS AND DOSE**

- **Peripheral and central neuropathic pain**

- **BY MOUTH**

- **Adults** Initially 150 mg daily in 2–3 divided doses, then increased if necessary to 300 mg daily in 2–3 divided doses, dose to be increased after 3–7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses, dose to be increased after 7 days

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www.getintopharma.com
Adju~nctive therapy for focal seizures with or without secondary generalisation

BY MOUTH

Adult: Initially 25 mg twice daily, then increased in steps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2–3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses

Generalised anxiety disorder

BY MOUTH

Adult: Initially 150 mg daily in 2–3 divided doses, then increased in steps of 150 mg daily if required, dose to be increased at 7 day intervals, increased if necessary up to 600 mg daily in 2–3 divided doses

UNLICENSED USE Pregabalin doses in BNF may differ from those in product literature.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: PREGABALIN (LYRICA)® AND RISK OF ABUSE AND DEPENDENCE: NEW SCHEDULING REQUIREMENTS FROM 1 APRIL (2019)

Following concerns about abuse, pregabalin has been reclassified as a Class C controlled substance and is now a Schedule 3 drug, but is exempt from safe custody requirements. Healthcare professionals should evaluate patients carefully for a history of drug abuse before prescribing pregabalin, and observe patients for signs of abuse and dependence. Patients should be informed of the potentially fatal risks of interactions between pregabalin and alcohol, and with other medicines that cause CNS depression, particularly opioids.

CAUTIONS Conditions that may precipitate encephalopathy: history of substance abuse – severe congestive heart failure

INTERACTIONS → Appendix 1: antiepileptics

SIDE-EFFECTS

Common or very common Abdominal distension • appetite abnormal • asthenia • cervical spasm • concentration impaired • confusion • constipation • diarrhoea • dizziness • drowsiness • dry mouth • feeling abnormal • gait abnormal • gastrointestinal disorders • headache • increased risk of infection • joint disorders • memory loss • mood altered • movement disorders • muscle complaints • nausea • oedema • pain • sensation abnormal • sexual dysfunction • sleep disorders • speech impairment • vertigo • vision disorders • vomiting • weight changes

Uncommon Aggression • anxiety • arrhythmias • atrioventricular block • breath abnormalities • chest tightness • chills • consciousness impaired • cough • depression • dry eye • dysphoria • epistaxis • eye discomfort • eye disorders • eye inflammation • fever • hallucination • hyperacusia • hypertension • hypoglycaemia • hypotension • malaise • menstrual cycle irregularities • nasal complaints • neutropenia • oral disorders • peripheral coldness • psychiatric disorders • reflexes decreased • skin reactions • sneezing • sweat changes • syncope • taste loss • thirst • urinaiy disorders • vasodilatation

Rare or very rare Altered smell sensation • ascites • dysgraphia • dysphagia • gynaecomastia • hepatic disorders • pancreatitis • QT interval prolongation • renal impairment • rhabdomyolysis • Stevens-Johnson syndrome • throat tightness

Frequency not known Drug use disorders

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk → toxicity in animal studies. See also Pregnancy in Epilepsy p. 305.

BREAST FEEDING See Breast-feeding in Epilepsy p. 305.

RENAL IMPAIRMENT

Dose adjustments Initially 75 mg daily and maximum 300 mg daily if eGFR 30–60 mL/minute/1.73 m². Initially 25–50 mg daily and maximum 150 mg daily in 1–2 divided doses if eGFR 15–30 mL/minute/1.73 m². Initially 25 mg once daily and maximum 75 mg once daily if eGFR less than 15 mL/minute/1.73 m².

MONITORING REQUIREMENTS Monitor for signs of pregabalin abuse.

TREATMENT CESSATION Avoid abrupt withdrawal (taper over at least 1 week).

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include strawberry.

PATIENT AND CARER ADVICE Patient leaflet. NHSE England has produced a patient leaflet with information on the reclassiﬁcation of pregabalin.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (July 2007) that pregabalin (Lyrica)® is not recommended for the treatment of central neuropathic pain. The Scottish Medicines Consortium has advised (April 2009) that pregabalin (Lyrica)® is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in adults who have not achieved adequate pain relief with, or have not tolerated, first- or second-line treatments; discontinue treatment if sufﬁcient benefit is not achieved within 8 weeks of reaching the maximum tolerated dose.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Oral solution

CAUTIONARY AND ADVISORY LABELS 3, 8

Pregabalin (Non-proprietary)

Pregabalin 20 mg per 1 ml Pregabalin 20mg/ml oral solution sugar free sugar-free 473 ml (Potr) £9.48 DT + £9.48 (OCD) | 500 ml (Potr) £75.00-105.16 (OCD)

Lyrica (Pfizer Ltd)

Pregabalin 20 mg per 1 ml Lyrica 20mg/ml oral solution sugar-free 473 ml (Potr) £9.48 DT + £9.48 (OCD)

Capsule

CAUTIONARY AND ADVISORY LABELS 3, 8

Pregabalin (Non-proprietary)

Pregabalin 25 mg Pregabalin 25mg capsules 56 capsule (Potm) £64.40 DT = £2.98 (C03) | 84 capsule (Potm) £4.47-£96.60 (C03)

Pregabalin 50 mg Pregabalin 50mg capsules 56 capsule (Pom) £8.96 (C03) | 84 capsule (Pom) £96.60 DT + £3.40 (C03)

Pregabalin 75 mg Pregabalin 75mg capsules 14 capsule (Pom) £3.23 (C03) | 56 capsule (Pom) £64.40 DT + £2.83 (C03)

Pregabalin 100 mg Pregabalin 100mg capsules 84 capsule (Pom) £96.60 DT + £4.27 (C03)

Pregabalin 150 mg Pregabalin 150mg capsules 56 capsule (Pom) £64.40 DT + £3.67 (C03)

Pregabalin 200 mg Pregabalin 200mg capsules 84 capsule (Pom) £96.60 DT + £5.21 (C03)

Pregabalin 225 mg Pregabalin 225mg capsules 56 capsule (Pom) £64.40 DT + £3.99 (C03)

Pregabalin 300 mg Pregabalin 300mg capsules 56 capsule (Pom) £64.40 DT + £4.92 (C03)

Alzain (Dr Reddy’s Laboratories (UK) Ltd)

Pregabalin 25 mg Alzain 25mg capsules 56 capsule (Pom) £4.99 DT = £2.98 (C03)

Pregabalin 50 mg Alzain 50mg capsules 84 capsule (Pom) £5.99 (C03) | 84 capsule (Pom) £16.99 DT + £3.40 (C03)

Pregabalin 75 mg Alzain 75mg capsules 56 capsule (Pom) £5.99 DT = £2.83 (C03)

Pregabalin 100 mg Alzain 100mg capsules 84 capsule (Pom) £16.99 DT + £4.27 (C03)

Pregabalin 150 mg Alzain 150mg capsules 56 capsule (Pom) £6.99 DT = £3.67 (C03)

Pregabalin 200 mg Alzain 200mg capsules 84 capsule (Pom) £8.99 DT = £5.21 (C03)
Epilepsy and other seizure disorders

**By mouth**

- **Lyrica** (Pfizer Ltd)
- **Axalid** (Kent Pharmaceuticals Ltd)

**Rufinamide**

15-May-2019

**Indications and dose**

**Adjuvant treatment of seizures in Lennox-Gastaut syndrome without valproate (initiated by a specialist)**

- **By mouth**
  - Child 1-3 years: Initially 5 mg/kg twice daily, then increased in steps of up to 5 mg/kg twice daily (max. per dose 22.5 mg/kg twice daily), adjusted according to response, dose to be increased at intervals of not less than 3 days to the target dose (maximum dose), each dose should be given to the nearest 0.5 mL.
  - Child 4-7 years (body-weight up to 30 kg): Initially 100 mg twice daily, then increased in steps of 100 mg twice daily (max. per dose 500 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 3 days.
  - Child 4-17 years (body-weight 30-50 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 900 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days.
  - Adult (body-weight 30-50 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 800 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days.
  - Adult (body-weight 50-100 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 800 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days.
  - Adult (body-weight >100 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 800 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days.
Epilepsy and other seizure disorders

- **CAUTIONS** Patients at risk of further shortening of QTc interval
- **INTERACTIONS** → Appendix 1: antiepileptics
- **SIDE-EFFECTS**
  - **Common or very common** Anxiety, appetite decreased, back pain, constipation, diarrhoea, dizziness, drowsiness, eating disorder, epistaxis, fatigue, gait abnormal, gastrointestinal discomfort, headache, increased risk of infection, insomnia, movement disorders, nausea, nystagmus, oligomenorrhoea, seizures, skin reactions, tremor, vertigo, vision disorders, vomiting, weight decreased
  - **Uncommon** Hypersensitivity
  - **ALLERGY AND CROSS-SENSITIVITY** Antiepileptic hypersensitivity syndrome associated with Rufinamide. See under Epilepsy p. 305 for more information.
  - **PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy in Epilepsy p. 305.
  - **BREAST FEEDING** Manufacturer advises avoid—no information available.
  - **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).
  - **Dose adjustments** Manufacturer advises cautious dose titration in mild to moderate impairment.
  - **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises tablets may be crushed and given in half a glass of water.
  - **PRESCRIBING AND DISPENSING INFORMATION**
    - **Switching between formulations** Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.
    - **Patients may need to be maintained on a specific manufacturer’s branded or generic Rufinamide product.**
  - **PATIENT AND CARER ADVICE** Counselling on antiepileptic hypersensitivity syndrome is advised.
    - Medicines for Children leaflet: Rufinamide for preventing seizures
      - www.medicinesforchildren.org.uk/rufinamide-preventing-seizures
    - **Driving and skilled tasks** Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness, somnolence and blurred vision.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - **Scottish Medicines Consortium (SMC) decisions**
      - SMC No. 416/07
        - The Scottish Medicines Consortium has advised (November 2008) that Rufinamide (Inovelon®) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.
      - SMC No. 795/12
        - The Scottish Medicines Consortium has advised (July 2012) that Rufinamide 40 mg/ml oral suspension (Inovelon®) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.
      - SMC No. SMC2146
        - In children The Scottish Medicines Consortium has advised (April 2019) that Rufinamide (Inovelon®) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox–Gastaut syndrome in patients aged 1 year up to 4 years. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
    - **Oral suspension**
      - CAUTIONARY AND ADVISORY LABELS 8, 21
      - EXCIPIENTS: May contain Propylene glycol
        - Inovelon (Eisai Ltd)
          - Rufinamide 40 mg per 1 ml Inovelon 40mg/ml oral suspension sugar-free | 460 ml [PSM] £94.71 DT = £94.71
    - **Tablet**
      - CAUTIONARY AND ADVISORY LABELS 8, 21
        - Inovelon (Eisai Ltd)
          - Rufinamide 100 mg Inovelon 100mg tablets | 10 tablet [PSM] £5.15 DT = £5.15
          - Rufinamide 200 mg Inovelon 200mg tablets | 60 tablet [PSM] £61.77 DT = £61.77
          - Rufinamide 400 mg Inovelon 400mg tablets | 60 tablet [PSM] £102.96 DT = £102.96

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**Sodium valproate**

- **INDICATIONS AND DOSE**
  - **All forms of epilepsy**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Child 1–17 years: Initially 600 mg daily in 1–2 divided doses, increased in steps of 100–200 mg every 3 days; maximum 2.5 g daily
      - Child 12–17 years: Initially 600 mg daily in 1–2 divided doses, increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily in 2 divided doses; maximum 2.5 g per day
      - Adult: Initially 600 mg daily in 1–2 divided doses, then increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily in 2 divided doses; maximum 2.5 g per day
  - **INITIATION of valproate treatment**
    - Initially by intravenous injection
      - Adult: Initially 10 mg/kg, (usually 400–800 mg), followed by (by intravenous infusion or by intravenous injection) up to 2.5 g daily in 2–4 divided doses, alternatively (by continuous intravenous infusion) up to 2.5 g daily; (by intravenous injection or by intravenous infusion or by continuous intravenous infusion) usual dose 1–2 g daily, alternatively (by intravenous injection or by intravenous infusion or by continuous intravenous infusion) usual dose 20–30 mg/kg daily, intravenous injection to be administered over 3–5 minutes
  - **Continuation of valproate treatment**
    - **BY INTRAVENOUS INJECTION**
      - Adult: If switching from oral therapy to intravenous therapy give the same dose as current oral daily dose, give over 3–5 minutes by intravenous injection or in 2–4 divided doses by intravenous infusion
  - **Migraine prophylaxis**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 200 mg twice daily, then increased if necessary to 1.2–1.5 g daily in divided doses

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**BNF 78**

**Nervous System**

www.getintopharma.com


**Epilepsy and other seizure disorders**

**EPILIM CHRONO®**

*All forms of epilepsy*
  - **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**EPISENTA® CAPSULES**

*All forms of epilepsy*
  - **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**Mania**
  - **BY MOUTH**
  - Adult: Initially 750 mg daily in 1–2 divided doses, adjusted according to response, usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring

**EPISENTA® GRANULES**

*All forms of epilepsy*
  - **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**Mania**
  - **BY MOUTH**
  - Adult: Initially 750 mg daily in 1–2 divided doses, adjusted according to response, usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring

**EPIVAL®**

*All forms of epilepsy*
  - **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**EPISENTA®**

*All forms of epilepsy*
  - **BY MOUTH**
  - Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

**SIDE-EFFECTS**

- Not licensed for migraine prophylaxis.

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058 - known or suspected mitochondrial disorders (higher rate of acute liver failure and liver-related deaths)
- Personal or family history of severe hepatic dysfunction
- Systemic lupus erythematosus CAUTIONS, FURTHER INFORMATION

- Consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- Liver toxicity - Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy.
- Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

**INTERACTIONS** → Appendix 1: antiepileptics

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common: Abdominal pain - agitation - alopecia (regrowth may be curly) - anemia - behaviour abnormal - concentration impaired - confusion - deafness - diarrhoea - drowsiness - haemorrhage - hallucination -
headache • hepatic disorders • hypersensitivity • hyponatraemia • memory loss • menstrual cycle irregularities • movement disorders • nail disorder • nausea • nystagmus • oral disorders • seizures • stupor • thrombocytopenia • tremor • urinary disorders • vomiting • weight increased

Uncommon Androgenetic alopecia • angioedema • bone disorders • bone fracture • bone marrow disorders • coma • encephalopathy • hair changes • hypothyroidism • leucopenia • pancreatitis • paraesthesia • Parkinsonism • peripheral oedema • pleural effusion • renal failure • SIADH • skin reactions • vasculitis • virilism

Rare or very rare Agranulocytosis • cerebral atrophy • cognitive disorder • dementia • diplopia • gynaecomastia • hyperammonaemia • hypothyroidism • infertility male • learning disability • myelodysplastic syndrome • nephritis • tubulointerstitial • polycystic ovaries • red blood cell abnormalities • rhabdomyolysis • severe cutaneous adverse reactions (SCARs) • systemic lupus erythematosus (SLE) • urine abnormalities

Frequency not known Alertness increased

Specific side-effects

Common or very common

With intravenous use Dizziness

Side-effects, further information

Hepatic dysfunction Withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control.

Pancreatitis Discontinue treatment if symptoms of pancreatitis develop.

Conception and contraception The MHRA advises that all women and girls of childbearing potential being treated with valproate medicines must be supported on a Pregnancy Prevention Programme—pregnancy should be excluded before treatment initiation and highly effective contraception must be used during treatment.

Pregnancy For migraine prophylaxis [unlicensed] and bipolar disorder, the MHRA advises that valproate must not be used. For epilepsy, the MHRA advises valproate must not be used unless there is no suitable alternative treatment; in such cases, access to counselling about the risks should be provided (see Healthcare Professional Guide for more information) and a Risk Acknowledgement Form signed by both specialist and patient. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Neonatal bleeding (related to hypofibrinemia) reported. Neonatal hepatotoxicity also reported. See also Pregnancy in Epilepsy p. 305.

Monitoring Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

Breast feeding Present in milk—risk of haematological disorders in breast-fed newborns and infants.

Hepatic impairment Manufacturer advises avoid.

Renal impairment Dose adjustments Reduce dose.

Monitoring requirements Plasma-valproate concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful.

Monitor liver function before therapy and during first 6 months especially in patients most at risk.

Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.
**Epilepsy and other seizure disorders**


Medicines for Children leaflet: Sodium valproate and pregnancy - information for parents and carers www.medicinesforchildren.org.uk/sodium-valproate-and-pregnancy-information-parents-and-carers

**EPILIM® CAPSULES** Patients and carers should be counselled on the administration of capsules.

**EPILIM® GRANULES** Patients and carers should be counselled on the administration of granules.

**EPISENTA®** Patients and carers should be counselled on the administration of capsules.

**EPISENTA® GRANULES** Patients and carers should be counselled on the administration of granules.

*● MEDICINAL FORMS* There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral solution sugar free, gastro-resistant tablets, gastro-resistant tablets resistant.

### Modified-release tablet

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21, 25**

- **Epilim Chrono®**
  - Sodium valproate 200 mg Epilim Chrono 200 tablets | 30 tablet [PoS] £3.50 | 100 tablet [PoS] £11.65 DT = £11.65
  - Sodium valproate 300 mg Epilim Chrono 300 tablets | 30 tablet [PoS] £5.24 | 100 tablet [PoS] £17.47 DT = £17.47
  - Sodium valproate 500 mg Epilim Chrono 500 tablets | 30 tablet [PoS] £8.73 | 100 tablet [PoS] £28.10 DT = £28.10
  - Epival CR (Chanelle Medical UK Ltd)
  - Sodium valproate 300 mg Epival CR 300mg tablets | 100 tablet [PoS] £17.47 DT = £17.47
  - Sodium valproate 500 mg Epival CR 500mg tablets | 100 tablet [PoS] £25.10 DT = £25.10

### Gastro-resistant tablet

**CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 25**

- **Sodium valproate (non-proprietary)**
  - Sodium valproate 200 mg Sodium valproate 200mg gastro-resistant tablets | 100 tablet [PoS] £2.40 DT = £2.40
  - Sodium valproate 500 mg Sodium valproate 500mg gastro-resistant tablets | 100 tablet [PoS] £4.76 DT = £4.76
  - Epilim®
    - Sodium valproate 200 mg Epilim 200 gastro-resistant tablets | 30 tablet [PoS] £2.31 | 100 tablet [PoS] £7.70 DT = £7.70
    - Sodium valproate 500 mg Epilim 500 gastro-resistant tablets | 30 tablet [PoS] £5.78 | 100 tablet [PoS] £15.25 DT = £15.25

### Tablet

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21**

- **Epilim®**
  - Sodium valproate 100 mg Epilim 100mg tablets | 30 tablet [PoS] £1.68 | 100 tablet [PoS] £5.60 DT = £5.60

### Solution for injection

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21**

- **Sodium valproate (non-proprietary)**
  - Sodium valproate 100 per 1 ml Sodium valproate 400mg/4ml solution for injection ampoules | 5 ampoule [PoS] £73.90 DT = £73.90
  - Episenta (Desitin Pharma Ltd)
  - Sodium valproate 100 per 1 ml Episenta 300mg/3ml solution for injection ampoules | 5 ampoule [PoS] £35.00 DT = £35.00

### Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21**

- **Episenta®** (Desitin Pharma Ltd)
  - Sodium valproate 150 mg Episenta 150mg modified-release capsules | 100 capsule [PoS] £7.00 DT = £7.00
  - Sodium valproate 300 mg Episenta 300mg modified-release capsules | 100 capsule [PoS] £13.00 DT = £13.00

### Oral solution

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21**

- **Sodium valproate (non-proprietary)**
  - Sodium valproate 40 per 1 ml Sodium valproate 200mg/5ml oral solution sugar free | 300 ml [PoS] £3.97 DT = £3.97
  - Epilim®
    - Sodium valproate 40 per 1 ml Epilim 200mg/5ml oral solution sugar-free | 300 ml [PoS] £3.80 DT = £3.80
    - Epilim 200mg/5ml syrup | 300 ml [PoS] £3.93 DT = £3.93

### Modified-release granules

**CAUTIONARY AND ADVISORY LABELS 8, 10, 21**

- **Epilim Chronosphere®**
  - Sodium valproate 50 mg Epilim Chronosphere MR 50mg granules | 30 sachet [PoS] £30.00 DT = £30.00

Sodium valproate 100 mg Epilim Chronosphere MR 100mg granules sachets sugar-free | 30 sachet [PoS] £30.00 DT = £30.00

Sodium valproate 250 mg Epilim Chronosphere MR 250mg granules sachets sugar-free | 30 sachet [PoS] £30.00 DT = £30.00

Sodium valproate 500 mg Epilim Chronosphere MR 500mg granules sachets sugar-free | 30 sachet [PoS] £30.00 DT = £30.00

Sodium valproate 1 gram Epilim Chronosphere MR 1000mg granules sachets sugar-free | 30 sachet [PoS] £30.00 DT = £30.00

- **Episenta®** (Desitin Pharma Ltd)
  - Sodium valproate 500 mg Episenta 500mg modified-release granules sachets sugar-free | 100 sachet [PoS] £21.00 DT = £21.00

Sodium valproate 1 gram Episenta 1000mg modified-release granules sachets sugar-free | 100 sachet [PoS] £41.00 DT = £41.00

**Stiripentol**

**INDICATIONS AND DOSE**

Adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome) in combination with clobazam and valproate (under expert supervision)

- **BY MOUTH**
  - Adult: Doses of up to 50 mg/kg daily in 2–3 divided doses should be continued for as long as efficacy is observed.

**DOSE EQUIVALENCE AND CONVERSION**

Stiripentol capsules and oral powder sachets are not bioequivalent. If a switch of formulation is required, manufacturer advises this is done under clinical supervision in case of intolerance.

**CONTRA-INDICATIONS** History of psychosis in the form of episodes of delirium.

**INTERACTIONS** → Appendix 1: antiepileptics

**SIDE-EFFECTS**

- Common or very common: Agitation, appetite decreased, behaviour abnormal, drowsiness, irritability, movement disorders, muscle tone decreased, nausea, neutropenia, sleep disorders, vomiting, weight decreased.

- Uncommon: Diplopia, fatigue, photosensitivity reaction, skin reactions.

- Rare or very rare: Thrombocytopenia.

**ALLERGY AND CROSS-SENSITIVITY** Antiepileptic hypersensitivity syndrome theoretically associated with stiripentol. See under Epilepsy p. 305 for more information.

**PREGNANCY** See also Pregnancy in Epilepsy p. 305. Monitoring: The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING** Present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid (no information available).

**RENAL IMPAIRMENT** Avoid—no information available.

**MONITORING REQUIREMENTS** Perform full blood count and liver function tests prior to initiating treatment and every 6 months thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2017) that stiripentol (Diacomit®) is accepted for use within NHS Scotland in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy whose seizures are not adequately controlled with clobazam and valproate.
**Epilepsy and other seizure disorders**

**Monitoring** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment (risk of increased exposure); avoid in severe impairment.

- **Dose adjustments** Manufacturer advises dose reduction and/or longer dose interval with careful titration in mild to moderate impairment.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Tiagabine for preventing seizures
  - Driving and skilled tasks May impair performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Powder**
  - CAUTIONARY AND ADVISORY LABELS: 1, 8, 13, 21
  - EXCIPIENTS: May contain Aspartame
  - **Diacomit** (Alan Pharmaceuticals)
  - Stripentol 250 mg: Diacomit 250mg oral powder sachets | 60 sachet [POM] £284.00 DT = £284.00
  - Stripentol 500 mg: Diacomit 500mg oral powder sachets | 60 sachet [POM] £493.00 DT = £481.00

- **Capsule**
  - CAUTIONARY AND ADVISORY LABELS: 1, 8, 21
  - **Diacomit** (Alan Pharmaceuticals)
  - Stripentol 250 mg: Diacomit 250mg capsules | 60 capsule [POM] £284.00 DT = £284.00
  - Stripentol 500 mg: Diacomit 500mg capsules | 60 capsule [POM] £493.00 DT = £481.00

**Topiramate**

**INDICATIONS AND DOSE**

Monotherapy of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation

- **BY MOUTH**
  - Child 6-17 years: Initially 0.5–1 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 50 mg twice daily (max. per dose 7.5 mg/kg twice daily), if child cannot tolerate titration regimens recommended above then smaller steps or longer interval between steps may be used; maximum 500 mg per day.
  - Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 100–200 mg daily in 2 divided doses, adjusted according to response, doses of 1 g daily have been used in refractory epilepsy; maximum 500 mg per day.

**Adjunctive treatment of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation**

- **BY MOUTH**
  - Child 2–17 years: Initially 1–3 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be taken at night, then increased in steps of 0.5–1.5 mg/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), if child cannot tolerate recommended titration regimen then smaller steps or longer interval between steps may be used; maximum 400 mg per day.
  - Adult: Initially 25–50 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 200–400 mg daily in 2 divided doses; maximum 400 mg per day.

**Adverse effects**

- **Common or very common** Abdominal pain - behaviour abnormal - concentration impaired - depression - diarrhoea - dizziness - emotional lability - fatigue - gait abnormal - insomnia - nausea - nervousness - speech disorder - tremor - vision disorders - vomiting
- **Uncommon** Drowsiness - psychosis - skin reactions
- **Rare or very rare** Delusions - hallucination
- **PREGNANCY** See also Pregnancy in Epilepsy p. 305.

**Medicines for Children leaflet: Tiagabine for preventing seizures**

- Driving and skilled tasks May impair performance of skilled tasks (e.g. driving).

**Tablet**

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS: 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabitril (Teva UK Ltd)</td>
<td>Tiagabine (as Tiagabine hydrochloride monohydrate)</td>
</tr>
<tr>
<td>5 mg Gabitril 5mg tablets</td>
<td>100 tablet [POM] £52.04 DT = £52.04</td>
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<tr>
<td>Tiagabine (as Tiagabine hydrochloride monohydrate)</td>
<td>10 mg Gabitril 10mg tablets</td>
</tr>
<tr>
<td>Tiagabine (as Tiagabine hydrochloride monohydrate)</td>
<td>15 mg Gabitril 15mg tablets</td>
</tr>
</tbody>
</table>

**Stripentol 250 mg**

- Diacomit 250mg oral powder sachets | 60 sachet [POM] £284.00 DT = £284.00
- Stripentol 500 mg: Diacomit 500mg oral powder sachets | 60 sachet [POM] £493.00 DT = £481.00

**Stripentol 500 mg**

- Diacomit 500mg capsules | 60 capsule [POM] £493.00 DT = £481.00

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332 Epilepsy and other seizure disorders

Migraine prophylaxis

BY MOUTH

Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25 mg every week; usual dose 50–100 mg daily in 2 divided doses; maximum 200 mg per day.

CAUTIONS Avoid in Acute porphyrias p. 1058. risk of metabolic acidosis - risk of nephrolithiasis—ensure adequate hydration (especially in strenuous activity or warm environment).

INTERACTIONS → Appendix 1: antiepileptics.

SIDE-EFFECTS

Common or very common Alopecia, anaemia, anxiety, appetite abnormal, asthenia, behaviour abnormal, cognitive impairment, confusion, constipation, cough, depression, diarrhoea, dizziness, drowsiness, dry mouth, dypsnoea, ear discomfort, eye disorders, feeling abnormal, fever (in children), gait abnormal, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, hypersensitivity, joint disorders, malaise, memory loss, mood altered, movement disorders, muscle complaints, muscle weakness, nasal complaints, nasopharyngitis, nausea, oral disorders, pain, seizures, sensation abnormal, skin reactions, sleep disorders, speech impairment, taste altered, tinnitus, tremor, urinary disorders, vertigo (in children), vision disorders, vomiting (in children), weight changes.

Uncommon Abnormal sensation in eye, anhidrosis, arrhythmias, aura, cerebellar syndrome, consciousness impaired, crying, drooling, dry eye, dysgraphia, dysphonia, eosinophilia (in children), facial swelling, hallucinations, hearing impairment, hyperthermia (in children), hypokalaemia, hypertension, influenza like illness, learning disability (in children), leucopenia, lymphadenopathy, metabolic acidosis, musculoskeletal stiffness, palpitations, pancreatitis, paranasal sinus hypersecretion, peripheral coldness, peripheral neuropathy, polydipsia, psychotic disorder, renal pain, sexual dysfunction, smell altered, suicidal tendencies, syncope, thinking abnormal, thirst, thrombocytopenia, vasodilation.

Rare or very rare Eye inflammation, face oedema, glaucoma, hepatic disorders, limb discomfort, neutropenia, Raynaud’s phenomenon, renal tubular acidosis, severe cutaneous adverse reactions (SCARs), unresponsive to stimulants.

SIDE-EFFECTS, FURTHER INFORMATION Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. If raised intra-ocular pressure occurs: seek specialist ophthalmological advice; use appropriate measures to reduce intra-ocular pressure and stop topiramate as rapidly as feasible.

CONCEPTION AND CONTRACEPTION Manufacturer advises perform pregnancy test before the initiation of treatment—a highly effective contraceptive method is advised in women of child-bearing potential; patients should be fully informed of the risks related to the use of topiramate during pregnancy.

PREGNANCY Increased risk of major congenital malformations following exposure during the first trimester. For migraine prophylaxis manufacturer advises avoid. For epilepsy manufacturer advises consider alternative treatment options. See also Pregnancy in Epilepsy p. 305.

Monitoring Manufacturer advises in case of administration during first trimester, careful prenatal monitoring should be performed.

It is recommended that the fetal growth should be monitored.

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING Manufacturer advises avoid—present in milk.

HEPATIC IMPAIRMENT Use with caution in moderate to severe impairment—clearance may be reduced.

Renal Impairment Use with caution.

Dose adjustments In adults Half usual starting and maintenance dose if eGFR less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration.

In children Half usual starting and maintenance dose if estimated glomerular filtration less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration.

DIRECTIONS FOR ADMINISTRATION TOPAMAX® CAPSULES Swallow whole or sprinkle contents of capsule on soft food and swallow immediately without chewing.

PRESCRIBING AND DISPENSING INFORMATION Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic topiramate product.


TOPAMAX® CAPSULES Patients or carers should be given advice on how to administer Topamax® Sprinkle capsules.

M EDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Oral suspension

Topiramate (Non-proprietary)

Topiramate 10 mg per 1 ml Topiramate 50mg/5ml oral suspension sugar free sugar-free | 150 ml P MS £12.99 + VAT £14.98

Topiramate 20 mg per 1 ml Topiramate 100mg/5ml oral suspension sugar free sugar-free | 280 ml P MS £195.69 + VAT £239.57

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 8

Topiramate (Non-proprietary)

Topiramate 25 mg Topiramate 25mg tablets | 60 tablet P MS £10.00 DT + £6.12

Topiramate 50 mg Topiramate 50mg tablets | 60 tablet P MS £36.75 DT + £9.33

Topiramate 100 mg Topiramate 100mg tablets | 60 tablet P MS £137.54 DT + £14.83

Topiramate 200 mg Topiramate 200mg tablets | 60 tablet P MS £57.60 DT + £47.57

Topamax (Janssen-Cilag Ltd)

Topiramate 25 mg Topamax 25mg tablets | 60 tablet P MS £11.29 DT + £6.32

Topiramate 50 mg Topamax 50mg tablets | 60 tablet P MS £31.69 DT + £9.33

Topiramate 100 mg Topamax 100mg tablets | 60 tablet P MS £56.76 DT + £14.83

Topiramate 200 mg Topamax 200mg tablets | 60 tablet P MS £110.23 DT + £47.57

www.getintopharma.com
### Vigabatrin

**INDICATIONS AND DOSE**
Adjuvantive treatment of focal seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics (under expert supervision)

- **BY MOUTH**
  - Child 1-23 months: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg)
  - Child 2-11 years: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g)
  - Child 12-17 years: Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily
  - Adult: Initially 1 g once daily, alternatively initially 1 g daily in 2 divided doses, then increased in steps of 500 mg every week, adjusted according to response; usual dose 2–3 g daily; maximum 3 g per day

- **BY RECTUM**
  - Child 1-23 months: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg)
  - Child 2-11 years: Initially 15–20 mg/kg twice daily (max. per dose 250 mg), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g)
  - Child 12-17 years: Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily

**SIDE-EFFECTS**

- **Elderly** Myoclonus, tonic and atonic seizures.
- **Visual** Deterioration after discontinuation cannot be excluded. Defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Patients and their carers should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion. Gradual withdrawal of vigabatrin should be considered.

**INTERACTIONS** → Appendix 1: antiepileptics

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Encephalopathic symptoms** Encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG can occur rarely - reduce dose or withdraw.
- **Visual field defects** About one-third of patients treated with vigabatrin have suffered visual field defects; counselling and careful monitoring for this side-effect are required.
- **PREGNANCY** See also Pregnancy in Epilepsy p. 305. Monitoring The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.
- **BREAST FEEDING** Present in milk—manufacturer advises avoid.

**RENAI IMPAIRMENT**
Dose adjustments → In adults Consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73 m².
- In children Consider reduced dose or increased dose interval if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Closely monitor neurological function.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use The contents of a sachet should be dissolved in water or a soft drink immediately before taking. Tablets may be crushed and dispersed in liquid.
- With rectal use Dissolve contents of sachet in small amount of water and administer rectally [unlicensed use]

**PATIENT AND CARER ADVICE** Patients and their carers should be warned to report any new visual symptoms that develop.

Medicines for Children leaflit: Vigabatrin for preventing seizures www.medicinesforchildren.org.uk/vigabatrin-preventing-seizures

**UNLICENSED USE** Granules not licensed for rectal use. Tablets not licensed to be crushed and dispersed in liquid. Vigabatrin doses in BNF publications may differ from those in product literature.

**CONTRA-INDICATIONS** Visual field defects

**CAUTIONS**

- Elderly history of behavioural problems • history of depression • history of psychosis
- General FURTHER INFORMATION Vigabatrin may worsen absence, myoclonic, tonic and atonic seizures.
- Visual field defects Vigabatrin is associated with visual field defects. The onset of symptoms varies from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Patients and their carers should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion. Gradual withdrawal of vigabatrin should be considered.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

- **Powder** CAUTIONARY AND ADVISORY LABELS 3, 8, 13
  - Sabril (Sanofi)
  - Vigabatrin 500 mg Sabril 500 mg oral powder sachets sugar-free 50 sachets [PDF] £24.60 DT + £24.60

- **Tablet** CAUTIONARY AND ADVISORY LABELS 3, 8
  - Sabril (Sanofi)
  - Vigabatrin 500 mg Sabril 500mg tablets 100 tablet [PDF] £44.41 DT = £44.41

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www.getintopharma.com
Zonisamide

20-Feb-2009

INDICATIONS AND DOSE

Monotherapy for treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy

BY MOUTH

Adult: Initially 100 mg once daily for 2 weeks, then increased in steps of 100 mg every 2 weeks, usual maintenance dose 300 mg once daily; maximum 500 mg per day

Adjunctive treatment for refractory focal seizures with or without secondary generalisation

BY MOUTH

Child 6-17 years (body-weight 20-54 kg): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days, usual maintenance 6-8 mg/kg once daily (max. per dose 500 mg once daily), dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

Child 6-17 years (body-weight 55 kg and above): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days, usual maintenance 300-500 mg once daily, dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

Adult: Initially 50 mg daily in 2 divided doses for 7 days, then increased to 100 mg daily in 2 divided doses, then increased in steps of 100 mg every 7 days, usual maintenance 300-500 mg daily in 1-2 divided doses, dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

Patient and carer advice

Appendix 1: antiepileptics

Side-effects

Common or very common
- Alopecia
- Anxiety
- Appetite decreased
- Ataxia
- Bradynephrenia
- Concentration impaired
- Confusion
- Constipation
- Depression
- Diarrhoea
- Dizziness
- Drowsiness
- Fatigue
- Fever
- Gastrointestinal discomfort
- Hypersensitivity
- Influenza like illness
- Insomnia
- Memory loss
- Mood altered
- Nausea
- Nystagmus
- Parasthesia
- Peripheral oedema
- Psychosis
- Rash (consider discontinuation)
- Skin reactions
- Speech disorder
- Tremor
- Urticaria
- Vision disorders
- Vomiting
- Weight decreased

Uncommon
- Behaviour abnormal
- Gallbladder disorders
- Hallucination
- Hypokalaemia
- Increased risk of infection
- Leucopenia
- Respiratory disorders
- Seizures
- Suicidal tendencies
- Thrombocytopenia

Rare or very rare
- Agranulocytosis
- Angle closure glaucoma
- Anhidrosis
- Bone marrow disorders
- Coma
- Dyspnorea
- Eye pain
- Heat stroke
- Hepatocellular injury
- Hydronephrosis
- Leucocytosis
- Lymphadenopathy

Metabolic acidosis
- Myasthenic syndrome
- Neuroleptic malignant syndrome
- Pancreatitis
- Renal failure
- Renal tubular acidosis
- Rhabdomyolysis
- Severe cutaneous adverse reactions (SCARs)
- Urine abnormal

Frequency not known
- Sudden unexplained death in epilepsy
- Allergy and cross-sensitivity
- Contra-indicated in sulphonamide hypersensitivity.

Antiepileptic hypersensitivity syndrome theoretically associated with zonisamide. See under Epilepsy p. 305 for more information.

Conception and contraception
- Manufacturer advises women of childbearing potential should use effective contraception during treatment and for one month after last dose—avoid in women of childbearing potential not using effective contraception unless clearly necessary and the potential benefit outweighs risk; patients should be fully informed of the risks related to the use of zonisamide during pregnancy.

Pregnancy
- Manufacturer advises use only if clearly necessary and the potential benefit outweighs risk—toxicity in animal studies; patients should be fully informed of the risks related to the use of zonisamide during pregnancy. See also Pregnancy in Epilepsy p. 305.

Monitoring
- The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

Breast feeding
- Manufacturer advises avoid for 4 weeks after last dose.

Hepatic impairment
- Avoid in severe impairment.

Dose adjustments
- Initially increase dose at 2-week intervals if mild or moderate impairment.

Renal impairment
- Dose adjustments
- Initially increase dose at 2-week intervals; discontinue if renal function deteriorates.

Treatment cessation
- Avoid abrupt withdrawal (consult product literature for recommended withdrawal regimens in children).

Prescribing and dispensing information
- Switching between formulations
- Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients and carer advice
- Children and their carers should be made aware of how to prevent and recognise overheating and dehydration.

Medicines for Children leaflet: Zonisamide for preventing seizures

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SMC No. 949/14

The Scottish Medicines Consortium has advised (March 2014) that zonisamide (Zonegran®) is accepted for restricted use within NHS Scotland as an adjunctive treatment of focal seizures, with or without secondary generalisation, in adolescents and children aged 6 years and above. It is restricted to use on advice from specialists in paediatric neurology or epilepsy.
Epilepsy and other seizure disorders

SPECIFIC SIDE-EFFECTS
- With oral use: Anxiety, hallucination, hypotension, megaloblastic anaemia, severe cutaneous adverse reactions (SCARs), thrombocytopenia
- With parental use: Agitation, anaemia, aplastic anaemia, Dupuytren’s contracture, hypocalcaemia, irritability, toxic epidermal necrolysis

Overdose: For details on the management of poisoning, see Active elimination techniques, under Emergency treatment of poisoning p. 1359.

ALLERGY AND CROSS-SENSITIVITY: Antiepileptic hypersensitivity syndrome associated with phenobarbital. See under Epilepsy p. 305 for more information.

PREGNANCY
Monitoring: The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING: Avoid if possible; drowsiness may occur.

HEPATIC IMPAIRMENT: Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

RENAL IMPAIRMENT: Use with caution.

MONITORING REQUIREMENTS
- Plasma-phenobarbital concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre); however, monitoring the plasma-drug concentration is less useful than with other drugs because tolerance occurs.

TREATMENT CESSATION: Avoid abrupt withdrawal (dependence with prolonged use).

DIRECTIONS FOR ADMINISTRATION
- With oral use: For administration by mouth, tablets may be crushed.
- With intravenous use in adults: Solution for injection must be diluted before intravenous administration.
- With intravenous use in children: For intravenous injection, dilute to a concentration of 20 mg/ml with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute).

PRESCRIBING AND DISPENSING INFORMATION
Some hospitals supply alcohol-free formulations of varying phenobarbital strengths.

The RCPCH and NPPG recommend that, when a liquid special of phenobarbital is required, the following strength is used: 50 mg/5 ml.

Switching between formulations: Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer’s product.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Phenobarbital for preventing seizures www.medicinesforchildren.org.uk/phenobarbital-preventing-seizures

MEDI CINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Tablet
CAUTIONARY AND ADVISORY LABELS 2, 8
- Phenobarbital (Non-proprietary)
  - Phenobarbital 15 mg Phenobarbital 15 mg tablets | 28 tablet (P) £24.95 DT + £16.71 (D)
  - Phenobarbital 30 mg Phenobarbital 30 mg tablets | 28 tablet (P) £5.99 DT + £0.69 (D)
  - Phenobarbital 60 mg Phenobarbital 60 mg tablets | 28 tablet (P) £7.99 DT + £6.67 (D)

Solution for injection
EXCIPIENTS: May contain Propylene glycol.
- Phenobarbital (Non-proprietary)
  - Phenobarbital sodium 30 mg per 1 ml Phenobarbital 30 mg/1 ml solution for injection ampoules | 10 ampoule (P) £98.42 DT + £98.42 (D)

Antiepileptics

BARBITURATES

Phenobarbital (Phenobarbitone)

INDICATIONS AND DOSE
All forms of epilepsy except typical absence seizures
- By mouth
  - Child 1 month–11 years: Initially 1–1.5 mg/kg twice daily, then increased in steps of 2 mg/kg as daily as required; maintenance 2.5–4 mg/kg 1–2 times a day
  - Child 12–17 years: 60–180 mg once daily
  - Adult: 60–180 mg once daily, dose to be taken at night

Status epilepticus
- By intravenous injection
  - Adult: 10 mg/kg (max. per dose 1 g), dose to be administered at a rate not more than 100 mg/minute, injection to be diluted 1 in 10 with water for injections
  - By slow intravenous injection

Neonate: Initially 20 mg/kg, dose to be administered at a rate no faster than 1 mg/kg/minute, then 2.5–5 mg/kg 1–2 times a day.

Child 1 month–11 years: Initially 20 mg/kg, dose to be administered at a rate no faster than 1 mg/kg/minute, then 2.5–5 mg/kg 1–2 times a day

Child 12–17 years: Initially 20 mg/kg (max. per dose 1 g), dose to be administered at a rate no faster than 1 mg/kg/minute, then 300 mg twice daily

DOSE EQUIVALENCE AND CONVERSION
- For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect.

CAUTIONS
- Avoid in Acute porphyrias p. 1058.
- Children: debilitated elderly: history of alcohol abuse: history of drug abuse: respiratory depression (avoid if severe)

CAUTIONS: FURTHER INFORMATION
Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

INTERATIONS
- Appendix 1: antiepileptics

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
Phenobarbital sodium 60 mg per 1 ml
Phenobarbital 60mg/1ml solution for injection ampoules 10 ampoule
£103.84 DT = £103.84
Phenobarbital sodium 200 mg per 1 ml
Phenobarbital 200mg/1ml solution for injection ampoules 10 ampoule
£84.66 DT = £84.66

Oral solution
CAUTIONARY AND ADVISORY LABELS 2, 8
• Phenobarbital (Non-proprietary)
• Phenobarbital 3 mg per 1 ml
  Phenobarbital 15mg/5ml elixir 500 ml
  £83.00–£83.01 DT = £83.01

Nervous system

ALLERGY AND CROSS-SENSITIVITY

INTERACTIONS

▶ Uncommon

INTERACTIONS

▶ Cautions

INTERACTIONS

▶ Avoid in Acute porphyrias p. 1058 • children • debilitated • elderly • history of alcohol abuse • history of drug abuse • respiratory depression (avoid if severe)

INTERACTIONS

▶ Cautions, further information

INTERACTIONS

▶ Common or very common

INTERACTIONS

▶ Uncommon

INTERACTIONS

▶ Rare or very rare

INTERACTIONS

▶ Frequency not known

INTERACTIONS

▶ Allergy and cross-sensitivity

INTERACTIONS

▶ Indications and dose

INDICATIONS AND DOSE

Epilepsy and other seizure disorders

Phenobarbital (Non-proprietary)

EXCIPIENTS: May contain Alcohol

2, 8

Oral solution

Primidone

INDICATIONS AND DOSE

All forms of epilepsy except typical absence seizures

▶ BY MOUTH

▶ Adult:

• Initially 125 mg daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, adjusted according to response; maintenance 125–250 mg twice daily

• Child 2–4 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, adjusted according to response; maintenance 250–375 mg twice daily

• Child 5–8 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, increased to 250 mg twice daily, then increased in steps of 250 mg every 3 days (max. per dose 750 mg twice daily), adjusted according to response

• Child 9–17 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, increased to 250 mg twice daily, then increased in steps of 250 mg every 3 days (max. per dose 750 mg twice daily)

Essential tremor

▶ BY MOUTH

• Adult: Initially 50 mg daily, then adjusted according to response to up to 750 mg daily, dose to be increased over 2–3 weeks

CAUTIONS

Avoid in Acute porphyrias p. 1058 • children • debilitated • elderly • history of alcohol abuse • history of drug abuse • respiratory depression (avoid if severe)

CAUTIONS, FURTHER INFORMATION

Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

INTERACTIONS

▶ Appendix 1: antiepileptics

SIDE-EFFECTS

▶ Common or very common

SIDE-EFFECTS

▶ Uncommon

SIDE-EFFECTS

▶ Rare or very rare

SIDE-EFFECTS

▶ Frequency not known

SIDE-EFFECTS

▶ Allergy and cross-sensitivity

SIDE-EFFECTS

▶ Indications and dose

ADJUNCT IN EPILEPSY

▶ Child 6–17 years: Initially 5 mg daily, dose to be increased if necessary at intervals of 5 days, maintenance 0.3–1 mg/kg daily, daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided; maximum 60 mg per day

▶ Adult: 20–30 mg daily, then increased if necessary up to 60 mg daily

ANXIETY (SHORT-TERM USE)

▶ By mouth

▶ Adult: 20–30 mg daily in divided doses, alternatively 20–30 mg once daily, dose to be taken at bedtime; increased if necessary up to 60 mg daily in divided doses, dose only increased in severe anxiety (in hospital patients), for debilitated patients, use elderly dose

▶ Elderly: 10–20 mg daily

UNLICENSED USE

▶ In children

Not licensed as monotherapy.

CONTRA-INDICATIONS

Chronic psychosis (in adults) • hyperekinesia • not for use alone to treat anxiety associated with depression (in adults) • obsessive states • phobic states • respiratory depression

CAUTIONS

Muscle weakness • organic brain changes
### Clonazepam

**INDICATIONS AND DOSE**

**All forms of epilepsy**

- **BY MOUTH**
  - Child 1–11 months: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 0.5–1 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary.
  - Child 1–4 years: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 1–3 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary.
  - Child 5–11 years: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 3–6 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary.
  - Child 12–17 years: Initially 1 mg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, dose usually taken at night; may be given in 3–4 divided doses if necessary.

**All forms of epilepsy / Myoclonus**

- **BY MOUTH**
  - Adult: Initially 1 mg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary.
  - Elderly: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary.

**Panic disorders (with or without agoraphobia) resistant to antidepressant therapy**

- **BY MOUTH**
  - Adult: 1–2 mg daily

**UNLICENSED USE** Clonazepam doses in BNF may differ from those in product literature. Use for panic disorders (with or without agoraphobia) resistant to antidepressant therapy is an unlicensed indication.

### Important Safety Information

**Safe Practice**

Clonazepam has been confused with clobazam; care must be taken to ensure the correct drug is prescribed and dispensed.

<table>
<thead>
<tr>
<th>CONTRA-INDICATIONS</th>
<th>Coma · current alcohol abuse · current drug abuse · respiratory depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAUTIONS</td>
<td>Acute porphyrias p. 1058 · airways obstruction · brain damage · cerebellar ataxia · depression · spinal ataxia · suicidal ideation</td>
</tr>
</tbody>
</table>

**CAUTIONS, FURTHER INFORMATION** The effectiveness of clonazepam may decrease significantly after weeks or months of continuous therapy.

**INTERACTIONS**

- Zacco (Thame Laboratories Ltd)
  - Clobazam 1 mg per 1 ml Zacco 5mg/5ml oral suspension sugar-free
  - 150 ml (POM) £82.00 DT = £90.00 (C04-D)
  - Clobazam 2 mg per 1 ml Zacco 10mg/5ml oral suspension sugar-free
  - 150 ml (POM) £87.00 DT = £95.00 (C04-D)

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>2, 8, 19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clobazam (non-proprietary)</strong></td>
<td>Frisium (Sanofi)</td>
</tr>
<tr>
<td>Clobazam 10 mg</td>
<td>Frisium 10mg tablets</td>
</tr>
<tr>
<td>30 tablet (POM)</td>
<td>£3.65 DT</td>
</tr>
<tr>
<td>£3.64 (C04-D)</td>
<td></td>
</tr>
</tbody>
</table>

**NHS restrictions**

Clobazam is not prescribable in NHS primary care except for the treatment of epilepsy; endorse prescription ‘SLS’.

**NATIONAL FUNDING / ACCESS DECISIONS**

**Renal impairment**

Dose adjustments Start with small doses in severe impairment.

**MONITORING REQUIREMENTS**

- In children Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected noncompliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should not be undertaken unless clinically indicated.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic clobazam product.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Clobazam for preventing seizures www.medicinesforchildren.org.uk/clobazam-preventing-seizures-0

<table>
<thead>
<tr>
<th>Oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAUTIONARY AND ADVISORY LABELS</td>
</tr>
<tr>
<td><strong>Clobazam (non-proprietary)</strong></td>
</tr>
<tr>
<td>Clobazam 1 mg per 1 ml Clobazam 5mg/5ml oral suspension sugar-free sugar-free</td>
</tr>
<tr>
<td>250 ml (Pom) £100.00 (C04-D)</td>
</tr>
<tr>
<td>Clobazam 2 mg per 1 ml Clobazam 10mg/5ml oral suspension sugar-free sugar-free</td>
</tr>
<tr>
<td>250 ml (Pom) £105.00 (C04-D)</td>
</tr>
<tr>
<td>Perizam (Rosemont Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Clobazam 1 mg per 1 ml Perizam 1mg/ml oral suspension sugar-free</td>
</tr>
<tr>
<td>Clobazam 2 mg per 1 ml Perizam 2mg/ml oral suspension sugar-free</td>
</tr>
<tr>
<td>Tapclob (Martindale Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Clobazam 1 mg per 1 ml Tapclob 5mg/5ml oral suspension sugar-free</td>
</tr>
<tr>
<td>250 ml (Pom) £100.00 (C04-D)</td>
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</tr>
</tbody>
</table>

### Breathing Difficulties in Children

**CAUTIONARY AND ADVISORY LABELS** 2, 5, 19

**INTERACTIONS**

- Appendix 1: clobazam

**SIDE-EFFECTS**

- Appetite decreased · consciousness impaired · constipation · drug abuse · dry mouth · fall · gait unsteady · libido loss · movement disorders · muscle spasms · nystagmus · respiratory disorder · severe cutaneous adverse reactions (SCARs) · skin reactions · speech impairment · weight increased

**BREAST FEEDING**

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**Monitoring**

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

**RENAL IMPAIRMENT**

Dose adjustments Start with small doses in severe impairment.

**MONITORING REQUIREMENTS**

- In children Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected noncompliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should not be undertaken unless clinically indicated.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic clobazam product.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Clobazam for preventing seizures www.medicinesforchildren.org.uk/clobazam-preventing-seizures-0

**NATIONAL FUNDING / ACCESS DECISIONS**

**Renal impairment**

Dose adjustments Start with small doses in severe impairment.

**Monitoring**

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

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2.1 Status epilepticus

Other drugs used for Status epilepticus: Diazepam, p. 343 - Fosphenytoin sodium, p. 314 - Phenoobarbital, p. 335 - Phenytoin, p. 323

ANTIEPILEPTICS > BARBITURATES

Thiopental sodium
(Thiopentone sodium)

- INDICATIONS AND DOSE
  Status epilepticus (only if other measures fail)
  ▶ BY SLOW INTRAVENOUS INJECTION
    Adult: 75–125 mg for 1 dose, to be administered as a 2.5% (25 mg/mL) solution

  Induction of anaesthesia
  ▶ BY SLOW INTRAVENOUS INJECTION
    Adult: Initially 100–150 mg, to be administered over 10–15 seconds usually as a 2.5% (25 mg/mL) solution, followed by 100–150 mg after 0.5–1 minute if required, dose to be given in fit and premedicated adults; debilitated patients or adults over 65 years may require a lower dose or increased administration time, alternatively initially up to 4 mg/kg (max. per dose 500 mg)

  Anaesthesia of short duration
  ▶ BY SLOW INTRAVENOUS INJECTION
    Adult: Initially 100–150 mg, to be administered over 10–15 seconds usually as a 2.5% (25 mg/mL) solution, followed by 100–150 mg after 0.5–1 minute if required, dose to be given in fit and premedicated adults; debilitated patients or adults over 65 years may require a lower dose or increased administration time, alternatively initially up to 4 mg/kg (max. per dose 500 mg)

  Reduction of raised intracranial pressure if ventilation controlled
  ▶ BY SLOW INTRAVENOUS INJECTION
    Adult: 1.5–3 mg/kg, repeated if necessary

- IMPORTANT SAFETY INFORMATION
  Thiopental sodium should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- CONTRA-INDICATIONS
  Acute porphyrias p. 1058 - myotonic dystrophy

- CAUTIONS
  Acute circulatory failure (shock) - avoid intravenous injection - cardiovascular disease - elderly - fixed cardiac output - hypovolaemia - reconstituted solution is highly alkaline (extravasation causes tissue necrosis and severe pain)

- INTERACTIONS
  → Appendix 1: thiopental

- SIDE-EFFECTS
  Common or very common
  Arrhythmia - myocardial contractility decreased

- Frequency not known
  Appetite decreased - circulatory collapse - cough - electrolyte imbalance - extravasation necrosis - hypotension - respiratory disorders - skin erosion - sneezing

- PREGNANCY
  May depress neonatal respiration when used during delivery.

- BREAST FEEDING
  Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

- HEPATIC IMPAIRMENT
  Manufacturer advises caution.

- Dose adjustments
  Manufacturer advises dose reduction.

- RENAL IMPAIRMENT
  Caution in severe impairment.

- PATIENT AND CARER ADVICE
  Driving and skilled tasks
  Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general
HYPNOTICS, SEDATIVES AND ANXIOLYTICS > BENZODIAZEPINES

Lorazepam

INDICATIONS AND DOSE

Short-term use in anxiety
> BY MOUTH
  - Adult: 1–4 mg daily in divided doses, for debilitated patients, use elderly dose
  - Elderly: 0.5–2 mg daily in divided doses

Short-term use in insomnia associated with anxiety
> BY MOUTH
  - Adult: 1–2 mg daily, to be taken at bedtime

Acute panic attacks
> BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION
  - Adult: 25–30 micrograms/kg every 6 hours if required; usual dose 1.5–2.5 mg every 6 hours if required, intravenous injection to be administered into a large vein, only use intramuscular route when oral and intravenous routes not possible

Conscious sedation for procedures
> BY MOUTH
  - Adult: 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 50 micrograms/kg, to be administered 30–45 minutes before operation
  - BY INTRAMUSCULAR INJECTION
  - Adult: 50 micrograms/kg, to be administered 60–90 minutes before operation

PREMEDICATION
> BY MOUTH
  - Adult: 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation
  - BY SLOW INTRAVENOUS INJECTION
  - Adult: 50 micrograms/kg, to be administered 30–45 minutes before operation
  - BY INTRAMUSCULAR INJECTION
  - Adult: 50 micrograms/kg, to be administered 60–90 minutes before operation

Status epilepticus | Febrile convulsions | Convulsions caused by poisoning
> BY SLOW INTRAVENOUS INJECTION
  - Child 1 month-11 years: 100 micrograms/kg (max. per dose 4 mg) for 1 dose, then 100 micrograms/kg after 10 minutes if required for 1 dose, to be administered into a large vein
  - Child 12-17 years: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein
  - Adult: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein

UNLICENSED USE

IMPORTANT SAFETY INFORMATION

ANAESTHESIA
Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

CONTRA-INDICATIONS
Avoid injections containing benzyl alcohol in neonates – chronic psychosis (in adults) – CNS depression – compromised airway – hyperkinesia – not for use alone to treat depression (or anxiety associated with depression) in adults – obsessional states – phobic states – respiratory depression

CAUTIONS
Muscle weakness – organic brain changes – parenteral administration

CAUTIONS, FURTHER INFORMATION
Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

Special precautions for parenteral administration When given parenterally, facilities for managing respiratory depression with mechanical ventilation must be available. Close observation required until full recovery from sedation.

INTERACTIONS
> Appendix 1: lorazepam

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Uncommon Allergic dermatitis – constipation – sexual dysfunction

Rare or very rare Agranulocytosis – hyponatraemia – pancytopenia – SIADH – thrombocytopenia

SPECIFIC SIDE-EFFECTS

Rare or very rare
> With oral use Saliva altered
> Frequency not known
> With parenteral use Leucopenia

BREAST FEEDING
Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

RENAI IMPAIRMENT
Dose adjustments Start with small doses in severe impairment.

DIRECTIONS FOR ADMINISTRATION
With intravenous use in children For intravenous injection, dilute with an equal volume of Sodium Chloride 0.9% (for neonates, dilute injection solution to a concentration of 100 micrograms/mL). Give over 3–5 minutes; max. rate 50 micrograms/kg over 3 minutes.

With intramuscular use in adults For intramuscular injection, solution for injection should be diluted with an equal volume of water for injections or sodium chloride 0.9% (but only use when oral and intravenous routes not possible).

With intravenous use in adults For slow intravenous injection, solution for injection should preferably be diluted with an equal volume of water for injections or sodium chloride 0.9%.

PATIENT AND CARER ADVICE
Driving and skilled tasks Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of undertaking
340  Epilepsy and other seizure disorders

Nervous system

Premedication

after administration. Responsible persons should be

 Conscious sedation for procedures

BY SLOW INTRAVENOUS INJECTION

Adult: Initially 2–2.5 mg, to be administered
5–10 minutes before procedure at a rate of
approximately 2 mg/minute, increased in steps of 1 mg
if required, usual total dose is 3.5–5 mg; maximum
7.5 mg per course

Elderly: Initially 0.5–1 mg, to be administered
5–10 minutes before procedure at a rate of
approximately 2 mg/minute, increased in steps of
0.5–1 mg if required; maximum 3.5 mg per course

Sedative in combined anaesthesia

Adult: 30–100 micrograms/kg, repeated if necessary,
alternatively (by continuous intravenous infusion)
30–100 micrograms/kg/hour

Elderly: Lower doses needed

Premedication

BY DEEP INTRAMUSCULAR INJECTION

Adult: 70–100 micrograms/kg, to be administered
20–60 minutes before induction, for debilitated
patients, use elderly dose

Benzodiazepines should only be administered for
anaesthesia by, or under the direct supervision of,
personnel experienced in their use, with adequate
training in anaesthesia and airway management.

PREScribing of Midazolam in Palliative CARE

The use of high-strength midazolam (5 mg/mL in 2 mL
and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules)
should be considered in palliative care and other
situations where a higher strength may be more
appropriate to administer the prescribed dose, and
where the risk of overdosage has been assessed. It is
advised that flumazenil is available when midazolam is
used, to reverse the effects if necessary.

CONTRA-indICATIONS  CNS depression • compromised
airway • severe respiratory depression

CAUTIONS  Cardiac disease • children (particularly if
cardiovascular impairment) • concentration of midazolam
in children under 15 kg not to exceed 1 mg/mL • debilitated
patients (reduce dose) in children • hypothermia •
hypovolaemia (risk of severe hypotension) · neonates · risk of airways obstruction and hypoventilation in children under 6 months (monitor respiratory rate and oxygen saturation) · vasoconstriction

**CAUTIONS, FURTHER INFORMATION**
- Recovery when used for sedation. Midazolam has a fast onset of action, recovery is faster than for other benzodiazepines such as diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing.
- **INTERACTIONS** → Appendix 1: midazolam
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common: Level of consciousness decreased · vomiting
    - Uncommon: Skin reactions
    - **Frequency not known**: Appetite increased · disinhitation (severe; with sedative and peri-operative use) (in children) · fall · saliva altered
  - **SPECIFIC SIDE-EFFECTS**
    - With buccal use: Thrombosis
    - With parenteral use: Angioedema · drug abuse · drug withdrawal seizure · embolism and thrombosis
  - **SIDE-EFFECTS, FURTHER INFORMATION**: Higher doses are associated with prolonged sedation and risk of hypoventilation. The co-administration of midazolam with other sedative, hypnotic, or CNS-depressant drugs results in increased sedation. Midazolam accumulates in adipose tissue, which can significantly prolong sedation, especially in patients with obesity, hepatic impairment or renal impairment.

- **Overdose**: There have been reports of overdosage when high strength midazolam has been used for conscious sedation. The use of high-strength midazolam (5mg/mL in 2mL and 10mL ampoules, or 2mg/mL in 5mL ampoules) should be restricted to general anaesthesia, intensive care, palliative care, or other situations where the risk has been assessed. It is advised that flumazenil is available when midazolam is used, to reverse the effects if necessary.

- **BREAST FEEDING**: Small amount present in milk—avoid breast-feeding for 24 hours after administration (although amount probably too small to be harmful after single doses).

- **HEPATIC IMPAIRMENT** For parenteral preparations: manufacturer advises caution in all degrees of impairment. **Dose adjustments**: For parenteral preparations: manufacturer advises consider dose reduction in all degrees of impairment.

- **RENAL IMPAIRMENT**: Use with caution in chronic renal failure.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in adults: For intravenous infusion (Hypnovel®), give continuously in Glucose 5% or Sodium chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Palliative care: For further information on the use of midazolam in palliative care, see www.medicinescomplete.com/#/content/palliative/benzodiazepines-and-z-drugs.
  - **PATIENT AND CARER ADVICE**: Patients or carers should be given advice on how and when to administer midazolam oromucosal solution.

Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of undertaking skilled tasks (e.g. driving) afterwards. For intravenous benzodiazepines the risk extends to at least 24 hours after administration.

Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

Medicines for Children leaflet: Midazolam for stopping seizures www.medicinesforchildren.org.uk/midazolam-stopping-seizures

- **EPISATUS OROMUCOSAL SOLUTION**

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (November 2017) that midazolam oromucosal solution (Epistatus®) is accepted for use within NHS Scotland for the treatment of prolonged, acute, convulsive seizures in patients aged 10 years to less than 18 years.

- **MEDICINAL FORMS**: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oromucosal solution, solution for injection, solution for infusion

**Solution for injection**

- **Midazolam (Non-proprietary)**
  - Midazolam (as Midazolam hydrochloride) 1 mg per 1 mL Midazolam 5mg/5mL solution for injection ampoules | 10 ampoule (Pom) £16.89 DT = £9.63 (C01)
  - Midazolam 2mg/2mL solution for injection ampoules | 10 ampoule (Pom) £4.50–6.00 DT = £5.00 (C03)
  - **Midazolam (as Midazolam hydrochloride) 2 mg per 1 mL Midazolam 10mg/5mL solution for injection ampoules | 10 ampoule (Pom) £6.75 DT = £6.86 (Hospital only) (C03)
  - 10 ampoule (Pom) £7.60 DT = £6.86 (C03)
  - **Midazolam (as Midazolam hydrochloride) 5 mg per 1 mL Midazolam 50mg/10mL solution for injection ampoules | 10 ampoule (Pom) £33.77 DT = £27.93 (C03)
  - Midazolam 10mg/2mL solution for injection ampoules | 10 ampoule (Pom) £16.55 DT = £16.13 (C03)
  - **Hypnovel (Roche Products Ltd)**
  - Midazolam (as Midazolam hydrochloride) 5 mg per 1 mL Hypnovel 10mg/2mL solution for injection ampoules | 10 ampoule (Pom) £7.11 DT = £6.13 (C03)

**Solution for infusion**

- **Midazolam (Non-proprietary)**
  - Midazolam (as Midazolam hydrochloride) 1 mg per 1 mL Midazolam 50mg/50mL solution for infusion vials | 1 vial (Pom) £3.56–11.00 (C01)
  - **Midazolam (as Midazolam hydrochloride) 2 mg per 1 mL Midazolam 100mg/50mL solution for infusion vials | 1 vial (Pom) £9.05–11.50 (C03)

**Oromucosal solution**

- **CAUTIONARY AND ADVISORY LABELS 2**
  - **EXCIPIENTS**: May contain Ethanol
  - **Buccolam** (Shire Pharmaceuticals Ltd)
  - **Midazolam (as Midazolam hydrochloride) 5 mg per 1 mL Buccolam 10mg/2mL oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £101.50 DT = £91.50 (C03)
  - Buccolam 7.5mg/1.5mL oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £83.00 DT = £80.00 (C03)
  - Buccolam 5mg/1mL oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £65.50 DT = £65.50 (C03)
  - Buccolam 2.5mg/0.5mL oromucosal solution pre-filled oral syringes sugar-free | 4 unit dose (Pom) £50.00 DT = £50.00 (C03)
  - **Epistatus (Veriton Pharma Ltd)**
  - **Midazolam (as Midazolam maleate) 10 mg per 1 mL Epistatus 10mg/1mL oromucosal solution pre-filled oral syringes sugar-free | 1 unit dose (Pom) £45.76 DT = £45.76 (C03)

3 Mental health disorders

3.1 Anxiety

Other drugs used for Anxiety

## Antidepressants > Serotonin Receptor Agonists

### Buspirone hydrochloride

**Indications and Dose**

- **Anxiety (short-term use)**
  - **By mouth**
  - **Adults:** 5 mg 2–3 times a day, increased if necessary up to 45 mg daily, dose to be increased at intervals of 2–3 days; usual dose 15–30 mg daily in divided doses

**Dose Adjustments Due to Interactions**
- Manufacturer advises reduce dose to 2.5 mg twice daily with concurrent use of potent inhibitors of CYP3A4.

### Contra-Indications

- Epilepsy

### Cautions

- Does not alleviate symptoms of benzodiazepine withdrawal

### Contraindications

- A patient taking a benzodiazepine still needs to have the benzodiazepine solution different from other medicines containing the same drug. Forms available

### Mediations and Forms

- Tablet
  - Buspirone hydrochloride (non-proprietary)
  - Buspirone hydrochloride 5 mg
    - 30 tablet(s) (£11.30 DT) x £3.70
  - Buspirone hydrochloride 10 mg
    - 30 tablet(s) (£15.62 DT) x £3.66

## Hypnotics, Sedatives and Anxiolytics > Benzodiazepines

### Benzodiazepines

#### Contra-Indications

- Acute pulmonary insufficiency
- Marked neuromuscular respiratory weakness
- Sleep apnoea syndrome
- Unstable myasthenia gravis

#### Cautions

- Avoid prolonged use (and abrupt withdrawal thereafter), debilitated patients (reduce dose) (in adults).

### Indications and Dose

- **Short-term use in anxiety**
  - **By mouth**
  - **Adults:** 250–500 micrograms 3 times a day, increased if necessary up to 3 mg daily, for debilitated patients, use elderly dose

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*www.getintopharma.com*
Chlordiazepoxide hydrochloride

29-Mar-2019

- **INDICATIONS AND DOSE**
  - **Short-term use in anxiety**
    - **BY MOUTH**
      - Adult: 10 mg 3 times a day, increased if necessary to 60–100 mg daily in divided doses, for debilitated patients, use elderly dose
      - Elderly: 5 mg 3 times a day, increased if necessary to 30–50 mg daily in divided doses
  - **Treatment of alcohol withdrawal in moderate dependence**
    - **BY MOUTH**
      - Adult: 10–30 mg 4 times a day, dose to be gradually reduced over 5–7 days, consult local protocols for titration regimens
  - **Treatment of alcohol withdrawal in severe dependence**
    - **BY MOUTH**
      - Adult: 10–50 mg 4 times a day and 10–40 mg as required for the first 2 days, dose to be gradually reduced over 7–10 days, consult local protocols for titration regimens; maximum 250 mg per day

- **CONTRA-INDICATIONS** Chronic psychosis, hyperkinesia, not for use alone to treat depression (or anxiety associated with depression) - obsessional states - phobic states - respiratory depression
- **CAUTIONS** Muscle weakness, organic brain changes
- **INTERACTIONS** → Appendix 1: alprazolam
- **SIDE-EFFECTS**
  - **Common or very common** Appetite decreased, concentration impaired, constipation, dermatitis, dry mouth, memory loss, movement disorders, sexual dysfunction, weight changes
  - **Uncommon** Menstruation irregular
  - **Frequency not known** Angioedema, autonomic dysfunction, hepatic disorders, hyperprolactinaemia, peripheral oedema, photosensitivity reaction, suicide, thinking abnormal

Diazepam

28-Jun-2018

- **INDICATIONS AND DOSE**
  - **Muscle spasm of varied aetiology**
    - **BY MOUTH**
      - Adult: 2–15 mg daily in divided doses, then increased if necessary to 60 mg daily, adjusted according to response, dose only increased in spastic conditions
      - **Acute muscle spasm**
        - **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRavenous INJECTION**
          - Adult: 10 mg, then 10 mg after 4 hours if required, intravenous injection to be administered into a large vein at a rate of no more than 5 mg/minute
      - **Tetanus**
        - **BY INTRavenous INJECTION**
          - Child: 100–300 micrograms/kg every 1–4 hours
          - Adult: 100–300 micrograms/kg every 1–4 hours
          - **BY INTRavenous INFUSION, OR BY NASODuodenAL TUBE**
            - Child: 3–10 mg/kg, adjusted according to response, to be given over 24 hours
            - Adult: 3–10 mg/kg, adjusted according to response, to be given over 24 hours
      - **Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm**
        - **BY MOUTH**
          - Child 1–11 months: Initially 250 micrograms/kg twice daily
          - Child 1–4 years: Initially 2.5 mg twice daily
          - Child 5–11 years: Initially 5 mg twice daily
          - Child 12–17 years: Initially 10 mg twice daily; maximum 40 mg per day; continued →
Anxiety
▶ BY MOUTH
- Adult: 2 mg 3 times a day, then increased if necessary to 15–30 mg daily in divided doses, for debilitated patients, use elderly dose
- Elderly: 1 mg 3 times a day, then increased if necessary to 7.5–15 mg daily in divided doses

Insomnia associated with anxiety
▶ BY MOUTH
- Adult: 5–15 mg daily, to be taken at bedtime

Severe acute anxiety | Control of acute panic attacks |
Acute alcohol withdrawal
▶ BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION
- Adult: 10 mg, then 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute

Acute drug-induced dystonic reactions
▶ BY INTRAVENOUS INJECTION
- Adult: 5–10 mg, then 5–10 mg after at least 10 minutes as required, to be administered into a large vein, at a rate of not more than 5 mg/minute

Acute anxiety and agitation
▶ BY MOUTH
- Adult: 500 micrograms/kg, then 500 micrograms/kg after 12 hours as required
- Elderly: 250 micrograms/kg, then 250 micrograms/kg after 12 hours as required

Premedication
▶ BY MOUTH
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

Sedation in dental procedures carried out in hospital
▶ BY MOUTH
- Adult: Up to 20 mg, to be given 1–2 hours before procedure

Conscious sedation for procedures, and in conjunction with local anaesthesia
▶ BY MOUTH
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for debilitated patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

Sedative cover for minor surgical and medical procedures
▶ BY INTRAVENOUS INJECTION
- Adult: 10–20 mg, to be administered into a large vein over 2–4 minutes, immediately before procedure

Status epilepticus | Febrile convulsions | Convulsions due to poisoning
▶ BY INTRAVENOUS INJECTION
- Neonate: 300–400 micrograms/kg, then 300–400 micrograms/kg after 10 minutes if required, to be given over 3–5 minutes.
- Child 1 month-1 year: 300–400 micrograms/kg (max. per dose 10 mg), then 300–400 micrograms/kg after 10 minutes if required, to be given over 3–5 minutes
- Child 12-17 years: 10 mg, then 10 mg after 10 minutes if required, to be given over 3–5 minutes
- Adult: 10 mg, then 10 mg after 10 minutes if required, administered at a rate of 1 mL (5 mg) per minute
PROFESSIONAL AND PUBLIC INFORMATION

Dental practitioners’ formulation
Diazepam Tablets may be prescribed.
Diazepam Oral Solution 2 mg/5 mL may be prescribed.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository

Tablet

CAUTIONARY AND ADVISORY LABELS 2, 19

Diazepam (Non-proprietary)
Diazepam 2 mg Diazepam 2mg tablets | 28 tablet (PO) £1.10 DT = £0.59 (C04-F)
Diazepam 5 mg Diazepam 5mg tablets | 28 tablet (PO) £1.12 DT = £0.61 (C04-F)
Diazepam 10 mg Diazepam 10mg tablets | 28 tablet (PO) £4.99 DT = £0.66 (C04-F)

Emulsion for injection

Diazemuls ( Accord Healthcare Ltd)
Diazepam 5 mg per 1 ml Diazemuls 10mg/2ml emulsion for injection ampoules | 10 ampoule (IV) £3.05 (C04-F)

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol, ethanol, propylene glycol
Diazepam (Non-proprietary)
Diazepam 5 mg per 1 ml Diazepam 10mg/2ml solution for injection ampoules | 10 ampoule (IV) £3.50-$7.20 DT = $5.50 (C04-F)

Oral suspension

CAUTIONARY AND ADVISORY LABELS 2, 19

Diazepam (Non-proprietary)
Diazepam 400 microgram per 1 ml Diazepam 2mg/5ml oral suspension | 100 ml (PO) £31.75 DT = £31.75 (C04-F)

Oral solution

CAUTIONARY AND ADVISORY LABELS 2, 19

Diazepam (Non-proprietary)
Diazepam 400 microgram per 1 ml Diazepam 2mg/5ml oral solution sugar free sugar-free | 100 ml (PO) £42.81-£43.91 DT = £42.81 (C04-F)

Enema

CAUTIONARY AND ADVISORY LABELS 2, 19

Diazepam (Non-proprietary)
Diazepam 2 mg per 1 ml Diazepam 5mg Rectubes | 5 tube (PO) £5.85 DT = £5.85 (C04-F)
Diazepam 5 mg per 1 ml Diazepam 5mg Rectubes | 5 tube (PO) £15.65 DT = £15.65 (C04-F)
Diazepam 5 mg per 1 ml Diazepam 5mg/2.5ml rectal solution tube | 5 tube (PO) £15.85 DT = £15.85 (C04-F)
Diazepam 4 mg per 1 ml Diazepam 10mg Rectubes | 5 tube (PO) £7.35 DT = £7.35 (C04-F)
Diazepam 10 mg per 1 ml Diazepam 10mg Rectubes | 5 tube (PO) £7.35 DT = £7.35 (C04-F)
Stesolid ( Accord Healthcare Ltd)
Diazepam 2 mg per 1 ml Stesolid 5mg rectal tube | 5 tube (PO) £6.89 DT = £5.85 (C04-F)
Diazepam 4 mg per 1 ml Stesolid 10mg rectal tube | 5 tube (PO) £8.78 DT = £7.35 (C04-F)

Oxazepam

INDICATIONS AND DOSE

Anxiety (short-term use)

BY MOUTH
Adult: 15–30 mg 3–4 times a day, for debilitated patients, use elderly dose
Elderly: 10–20 mg 3–4 times a day

Insomnia associated with anxiety

BY MOUTH
Adult: 15–25 mg once daily (max. per dose 50 mg), dose to be taken at bedtime

CONTRA-INDICATIONS
Chronic psychosis • hyperkinesis • not for use alone to treat depression (or anxiety associated with depression) • obsessional states • phobic states • respiratory depression

CAUTIONS
Muscle weakness • organic brain changes

www.getintopharma.com
Mental health disorders

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CAUTIONS, FURTHER INFORMATION

- Paradoxical effects: A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.
- INTERACTIONS: Appendix 1: oxazepam
- SIDE-EFFECTS: Fever, leucopenia, memory loss, oedema, salivary altered speech, slurred, syncope, urticaria
- BREAST FEEDING: Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.
- RENAL IMPAIRMENT: Dose adjustments: Start with small doses in severe impairment.
- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 2
- Oxazepam (Non-proprietary)
  - Oxazepam 10 mg: Oxazepam 10mg tablets | 28 tablet (Pkt) £13.73
  - Oxazepam 15 mg: Oxazepam 15mg tablets | 28 tablet (Pkt) £13.44
  - DT = £7.38 (04–1)

HYPNOTICS, SEDATIVES AND ANXIOLYTIKS

NON-BENZODIAZEPINE HYPNOTICS AND SEDATIVES

Meprobamate

INDICATIONS AND DOSE

Short-term use in anxiety—not recommended
- BY MOUTH
- Adult: 400 mg 3–4 times a day
- Elderly: Up to 200 mg 3–4 times a day

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: MEPROBAMATE: LICENCE TO BE CANCELLED (APRIL 2016)

Following an EU-wide review of meprobamate, the UK licence holder has ceased manufacturing and the licence is due to be cancelled by December 2016. No new stock will be released into the normal distribution chain after 31 December 2016, although existing stock placed on the market before that date is likely to be dispensed until the products approach their expiry date.

Prescribers should review the treatment of any patient who is currently receiving a meprobamate-containing medicine with a view to switching them to an alternative treatment, and not start any new patients on medicines that contain meprobamate.

CONTRA-INDICATIONS: Acute porphyrias p. 1058 • acute pulmonary insufficiency • respiratory depression

CAUTIONS: Abrupt withdrawal (may precipitate convulsions) • avoid prolonged use • debilitated • elderly • emotionally unstable personality (if taken over long periods) • increased risk of dependence • epilepsy (may induce seizures) • history of alcohol dependence • history of drug dependence • muscle weakness • respiratory disease

INTERACTIONS: Appendix 1: meprobamate

SIDE-EFFECTS: Agitation • agranulocytosis • anal inflammation • ataxia • blood disorder • bone marrow disorders • dizziness • drowsiness • hypersensitivity • hypotension • nausea • paraesthesia • purpura non-thrombocytopenic • skin reactions • Stevens-Johnson syndrome • stomatitis • thrombocytopenia • vomiting • withdrawal syndrome

PREGNANCY: Avoid if possible.

BREAST FEEDING: Avoid. Concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant.

HEPATIC IMPAIRMENT: Elimination may be prolonged in chronic impairment.

RENAI IMPAIRMENT: Increased cerebral sensitivity. Dose adjustments: Start with small doses in severe impairment.

PATIENT AND CARER ADVICE: Driving and skilled tasks: Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

LESS SUITABLE FOR PRESCRIBING: Meprobamate is less suitable for prescribing.

Meprobamate (Non-proprietary)

Tablet

CAUTIONARY AND ADVISORY LABELS 2
- Meprobamate (Non-proprietary)
  - Meprobamate 400 mg: Meprobamate 400mg tablets | 84 tablet (Pkt) £197.63 DT = £319.63 (04–1)

3.2 Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder

04-Aug-2018

Description of condition

Attention deficit hyperactivity disorder (ADHD) is a behavioural disorder characterised by hyperactivity, impulsivity and inattention, which can lead to functional impairment such as psychological, social, educational or occupational difficulties. While these symptoms tend to co-exist, some patients are predominantly hyperactive and impulsive, while others are principally inattentive. Symptoms typically appear in children aged 3–7 years, but may not be recognised until after 7 years of age, especially if hyperactivity is not present. ADHD is more commonly diagnosed in males than in females. ADHD is usually a persisting disorder and some children continue to have symptoms throughout adolescence and into adulthood, where inattentive symptoms tend to persist, and hyperactive-impulsive symptoms tend to recede over time. ADHD is also associated with an increased risk of disorders such as oppositional defiant disorder (ODD), conduct disorder, and possibly mood disorders such as depression, mania, and anxiety, as well as substance misuse.

Aims of treatment

The aims of treatment are to reduce functional impairment, severity of symptoms, and to improve quality of life.

Non-drug treatment

Patients should be advised about the importance of a balanced diet, good nutrition and regular exercise.

Environmental modifications are changes made to the physical environment that can help reduce the impact of ADHD symptoms on a person’s day-to-day life. The modifications should be specific to the person’s circumstances, and may involve changes to seating arrangements, lighting and noise, reducing distractions,
optimising work or education by having shorter periods of focus with movement breaks, and reinforcing verbal requests with written instructions. These changes should form part of the discussion at the time of diagnosis of ADHD and be trialled and reviewed for effectiveness before drug treatment is started.

ADHD focused psychological interventions which may involve elements of, or a complete course of cognitive behavioural therapy (CBT) may be effective in patients who have refused drug treatment, have difficulty with adherence, are intolerant of, or unresponsive to drug treatment. In patients who have benefited from drug treatment, but whose symptoms are still causing significant impairment in at least one area of function (such as interpersonal relationships, education and occupational attainment, and risk awareness), consider a combination of non-drug treatment with drug treatment.

### Drug treatment

**Drug treatment** should be initiated by a specialist trained in the diagnosis and management of ADHD. Following dose stabilisation, continuation and monitoring of drug treatment can be undertaken by the patient’s general practitioner under a shared care arrangement. Treatment should be started in patients with ADHD whose symptoms are still causing significant impairment in at least one area of function, despite environmental modifications. Patients with ADHD and anxiety disorder, tic disorder, or autism spectrum disorder should be offered the same treatment options as other patients with ADHD.

Lisdexamfetamine mesilate p. 351 or methylphenidate hydrochloride p. 348 are recommended as first-line treatment. If symptoms have not improved following a 6-week trial of either drug, switching to the alternative first-line treatment should be considered. Dexamfetamine sulphate p. 350 (unlicensed) can be tried if the patient is having a beneficial response to lisdexamfetamine mesilate but cannot tolerate its longer duration of effect.

Modified-release preparations of stimulants are preferred because of their pharmacokinetic profile, convenience, improved adherence, reduced risk of drug diversion (drugs being forwarded to others for non-prescription use or misuse), and the lack of need to be taken to work. Immediate-release preparations can be given when more flexible dosing regimens are required, or during initial dose titration. A combination of modified-release and immediate-release preparations taken at different times of the day can be used to extend the duration of effect. The magnitude, duration of effect, and side-effects of stimulants vary between patients.

In patients who are intolerant to both methylphenidate hydrochloride p. 348 and lisdexamfetamine mesilate, or who have not responded to separate 6-week trials of both drugs, treatment with the non-stimulant atomoxetine below can be considered.

Advice from, or referral to a tertiary specialist ADHD service should be considered if the patient is unresponsive to one or more stimulant drugs (e.g. methylphenidate hydrochloride p. 348 and lisdexamfetamine mesilate) and atomoxetine below. A specialist service should also be consulted for advice before starting treatment with guanfacine p. 352 (unlicensed), or an atypical antipsychotic in addition to stimulants in patients with ADHD and co-existing pervasive aggression, rages or irritability. If sustained orthostatic hypotension or fainting episodes occur with guanfacine p. 352 treatment, the dose should be reduced or an alternative treatment offered.

Other treatment options such as buproprion hydrochloride p. 498, modafinil p. 492, tricyclic antidepressants, and venlafaxine p. 368 (all unlicensed) have been used in the management of ADHD, but due to limited evidence their use is not recommended without specialist advice.
### Methylenidate hydrochloride

#### INDICATIONS AND DOSE

**Attention deficit hyperactivity disorder (initiated under specialist supervision)**

* By mouth using immediate-release medicines

  **Child 6–17 years:** Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose (up to a maximum of 90 mg daily) under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation

  **Adult:** Initially 5 mg 2–3 times a day, dose is increased if necessary at weekly intervals according to response, increased if necessary up to 100 mg daily in 2–3 divided doses, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation

**Narcolepsy**

* By mouth using immediate-release medicines

  **Adult:** 10–60 mg daily in divided doses; usual dose 20–30 mg daily in divided doses, dose to be taken before meals

#### DOSE EQUIVALENCE AND CONVERSION

- When switching from immediate-release preparations to modified-release preparations—consult product literature.

**CONCERTA® XL**

**Attention deficit hyperactivity disorder**

* By mouth

  **Child 6–17 years:** Initially 18 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response; increased if

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#### Methylenidate hydrochloride

**QT-interval prolongation**

- Structural cardiac abnormalities
- Susceptibility to angle-closure glaucoma
- Tachycardia

#### INTERACTIONS

Appendix 1: atomoxetine

#### SIDE-EFFECTS

- **Common or very common**
  - Anxiety
  - Appetite decreased
  - Arrhythmias
  - Asthenia
  - Chills
  - Constipation
  - Depression
  - Dizziness
  - Drowsiness
  - Dry mouth
  - Feeling jittery
  - Flatulence
  - Gastrointestinal discomfort
  - Genital pain
  - Headaches
  - Hyperhidrosis
  - Menstrual cycle irregularities
  - Mood altered
  - Mydriasis
  - Nausea
  - Palpitations
  - Periorbital oedema
  - Raynaud's phenomenon
  - Syncope
  - Vasoconstriction
  - Vasodilation
  - Vasovagal syncope
  - Venous thromboembolism
  - Vomiting
  - Weight decreased

- **Rare or very rare**
  - Abnormal vision
  - Depression
  - Diarrhoea
  - Dizziness
  - Dysphagia
  - Hypersensitivity
  - Intestinal obstruction
  - Mood lability
  - Myalgia
  - Myocardial infarction
  - Neuroleptic malignant syndrome
  - Neurotoxicity
  - Nystagmus
  - Overactive bladder
  - Pain
  - Paralytic ileus
  - Periorbital oedema
  - Pruritus
  - Raynaud's phenomenon
  - Seizures
  - Sinus tachycardia
  - Skin reactions
  - Sleep disorders
  - Taste
  - Tics
  - Tremor
  - Urinary disorders
  - Venous thromboembolism
  - Weight decreased

- **Uncommon**
  - Abnormal vision
  - Constipation
  - Depression
  - Dizziness
  - Drowsiness
  - Dysphagia
  - Dyspepsia
  - Flatulence
  - Genital pain
  - Headaches
  - Hyperhidrosis
  - Mood lability
  - Myalgia
  - Myocardial infarction
  - Nausea
  - Palpitations
  - Periorbital oedema
  - Raynaud's phenomenon
  - Syncope
  - Venous thromboembolism
  - Vomiting
  - Weight decreased

- **Frequency not known**
  - Sudden cardiac death

#### PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risks.

#### BREAST FEEDING

Avoid present in milk in animal studies.

#### HEPATIC IMPAIRMENT

- **Dose adjustments**
  - Manufacturer advises halve dose in moderate impairment and quarter dose in severe impairment.

- **Monitoring requirements**
  - Monitor for appearance or worsening of anxiety, depression or tics.
  - Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

#### PATIENT AND CARER ADVICE

- **Suicidal ideation**
  - Following reports of suicidal thoughts and behaviour, patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression.

- **Hepatic impairment**
  - Following rare reports of hepatic disorders, patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine, or jaundice.

Medicines for Children leaflet: Atomoxetine for attention deficit hyperactivity disorder (ADHD) [www.medicinesforchildren.org.uk/atomoxetine-attention-deficit-hyperactivity-disorder-adhd](http://www.medicinesforchildren.org.uk/atomoxetine-attention-deficit-hyperactivity-disorder-adhd)

#### NATIONAL FUNDING/ACCESS DECISIONS

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1107/15

The Scottish Medicines Consortium has advised (December 2015) that atomoxetine oral solution (Strattera®) is accepted for restricted use within NHS Scotland for the treatment of attention deficit hyperactivity disorder (ADHD) in children of 6 years and older, in adolescents and in adults. It is restricted to patients who are unable to swallow capsules.
Attention deficit hyperactivity disorder

**DOSE EQUIVALENCE AND CONVERSION**
- Total daily dose of 15 mg of standard-release formulation is considered equivalent to Concerta® XL 18 mg once daily.
- Total daily dose of 15 mg of standard-release formulation is considered equivalent to Delmosart® 18 mg once daily.
- Total daily dose of 15 mg of standard-release formulation is considered equivalent to Xaggitin® XL 18 mg once daily.
- Total daily dose of 15 mg of standard-release formulation is considered equivalent to Equisym® XL 18 mg once daily.

**EQUIVALENTS**
- Concerta® XL
- Delmosart® Prolonged-Release Tablet
- Xaggitin® XL
- Equisym®

**PRESCRIBING AND DISPENSING INFORMATION**
- Concerta® XL Contains of an immediate-release component (22% of the dose) and a modified-release component (78% of the dose).
- Equisym®

**SIDE-EFFECTS**
- Uncommon: Chest discomfort - constipation - dysphonia - fatigue - haematuria - hallucinations - muscle complaints - psychotic disorder - suicidal tendencies - tic - tremor - vision disorders
- Rare or very rare: Anaemia - angina pectoris - cardiac arrest - cerebrovascular insufficiency - confusion - gynaecomastia - hepatic coma - hyperfocus - hyperhidrosis - leucopenia - mydriasis - myocardial infarction - neuroleptic malignant syndrome - peripheral coldness - Raynaud’s phenomenon - seizures - sexual dysfunction - skin reactions - sudden cardiac death - thinking abnormal - thrombocytopenia
- Frequency not known: Delusions - drug dependence - hyperpyrexia - intracranial haemorrhage - logorrhea - pancytopenia - vasculitis
- Pregnancy: Limited experience—avoid unless potential benefit outweighs risk
- Breast feeding: Limited information available—avoid.

**DIRECTIONS FOR ADMINISTRATION**
- Medikinet® XL
- Medikinet®
- Equisym®

**TREATMENT CESSATION**
- Avoid abrupt withdrawal.

**MONITORING REQUIREMENTS**
- Monitor for psychiatric disorders.
- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**UNLICENSED USE**
- Doses over 60 mg daily not licensed; doses of Concerta® XL over 54 mg daily not licensed.
- Not licensed for use in narcolepsy. Not licensed for use in adults for attention deficit hyperactivity disorder.

**CONTRA-INDICATIONS**
- Anorexia nervosa - arrhythmias - cardiomyopathy - cardiovascular disease - cerebrovascular disorders - heart failure - hyperthyroidism - phaeochromocytoma - psychosis - severe depression - severe hypertension - structural cardiac abnormalities - suicidal ideation - uncontrolled bipolar disorder - vasculitis

**CAUTIONS**
- Agitation - alcohol dependence - anxiety - drug dependence - epilepsy (discontinue if increased seizure frequency) - family history of Tourette syndrome - susceptibility to angle-closure glaucoma - tics

**CONCERTA® XL, DELMOSART® PROLONGED-RELEASE TABLET**
- Dysphagia (dose form not appropriate) restricted gastro-intestinal lumen (dose form not appropriate)
- Xaggitin® XL Dysphagia (dose form not appropriate)

**INTERACTIONS**
- Appendix 1: methylphenidate

**Nervous System**

**DOSE EQUIVALENCE AND CONVERSION**
- Total daily dose of 15 mg of standard-release formulation is considered equivalent to Xaggitin® XL 18 mg once daily.

**Attention deficit hyperactivity disorder (under expert supervision)**
- **BY MOUTH**
  - Child 6-17 years: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day
  - Adult: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; maximum 100 mg per day

**Attention deficit hyperactivity disorder (under expert supervision)**
- **BY MOUTH**
  - Child 6-17 years: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals according to response; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day
  - Adult: Initially 10 mg once daily, dose to be taken in the morning before breakfast; adjusted at weekly intervals according to response; maximum 100 mg per day

**Attention deficit hyperactivity disorder**
- **BY MOUTH**
  - Child 6-17 years: Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day
  - Adult: Initially 10 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response, discontinue if no response after 1 month; maximum 54 mg per day

**Attention deficit hyperactivity disorder**
- **BY MOUTH**
  - Child 6-17 years: Initially 10 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response, discontinue if no response after 1 month; maximum 54 mg per day
  - Adult: Initially 18 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response, discontinue if no response after 1 month; maximum 54 mg per day

**Attention deficit hyperactivity disorder**
- **BY MOUTH**
  - Child 6-17 years: Initially 18 mg once daily, dose to be taken in the morning, then increased in steps of 18 mg every week if required, discontinue if no response after 1 month; maximum 54 mg per day
  - Adult: Initially 18 mg once daily, dose to be taken in the morning, then increased in steps of 18 mg every week if required, discontinue if no response after 1 month; maximum 54 mg per day

**Attention deficit hyperactivity disorder**
- **BY MOUTH**
  - Child 6-17 years: Initially 18 mg once daily, dose to be taken in the morning, then increased in steps of 18 mg every week if required, discontinue if no response after 1 month; maximum 108 mg per day
MEDICATIONS

**MEDICINAL FORMS**

- **MEDICATIONS**
  - Methylphenidate hydrochloride (Non-proprietary)
  - Methylphenidate hydrochloride 5 mg Tablets
  - Methylphenidate hydrochloride 10 mg Tablets
  - Methylphenidate hydrochloride 15 mg Tablets
  - Methylphenidate hydrochloride 20 mg Tablets
  - Methylphenidate hydrochloride 30 mg Tablets
  - Methylphenidate hydrochloride 40 mg Tablets
  - Methylphenidate hydrochloride 50 mg Tablets
  - Methylphenidate hydrochloride 60 mg Tablets
  - Methylphenidate hydrochloride 60 mg modified-release Tablets
  - Methylphenidate hydrochloride 75 mg Tablets
  - Methylphenidate hydrochloride 80 mg Tablets

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Methylphenidate for attention deficit hyperactivity disorder (ADHD) www.medicinesforchildren.org.uk/methylphenidate-attention-deficit-hyperactivity-disorder-adhd

Driving and skilled tasks - Drugs and Driving

Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

2015 legislation regarding driving whilst taking certain drugs, may also apply to methylphenidate, see Drugs and driving under Guidance on prescribing p. 1.

CONCERTA® XL	Consists of an immediate-release component (70% of the dose).

DELMOSART® PROLONGED-RELEASE TABLET	Manufacturer advises tablet membrane may pass through gastrointestinal tract unchanged.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Modified-release tablet**

Cautions and advisory labels 25

- Concerta XL (Janssen-Cilag Ltd)
  - Methylphenidate hydrochloride 18 mg	Concerta XL 18 mg tablets | 30 tablet | $31.19 DT | $31.19 (C03)
  - Methylphenidate hydrochloride 27 mg	Concerta XL 27 mg tablets | 30 tablet | $36.81 DT | $36.81 (C03)
  - Methylphenidate hydrochloride 36 mg	Concerta XL 36 mg tablets | 30 tablet | $42.45 DT | $42.45 (C03)
  - Methylphenidate hydrochloride 54 mg	Concerta XL 54 mg tablets | 30 tablet | $73.62 DT | $73.62 (C03)

- Delmosart (Actavis UK Ltd)
  - Methylphenidate hydrochloride 18 mg	Delmosart 18 mg modified-release tablets | 30 tablet | $31.19 DT | $31.19 (C03)
  - Methylphenidate hydrochloride 27 mg	Delmosart 27 mg modified-release tablets | 30 tablet | $36.81 DT | $36.81 (C03)
  - Methylphenidate hydrochloride 36 mg	Delmosart 36 mg modified-release tablets | 30 tablet | $42.45 DT | $42.45 (C03)
  - Methylphenidate hydrochloride 54 mg	Delmosart 54 mg modified-release tablets | 30 tablet | $73.62 DT | $73.62 (C03)

- Xaggitin XL (Ethypharm UK Ltd)
  - Methylphenidate hydrochloride 18 mg	Xaggitin XL 18 mg tablets | 30 tablet | $31.19 DT | $31.19 (C03)
  - Methylphenidate hydrochloride 27 mg	Xaggitin XL 27 mg tablets | 30 tablet | $36.81 DT | $36.81 (C03)
  - Methylphenidate hydrochloride 36 mg	Xaggitin XL 36 mg tablets | 30 tablet | $42.45 DT | $42.45 (C03)
  - Methylphenidate hydrochloride 54 mg	Xaggitin XL 54 mg tablets | 30 tablet | $73.62 DT | $73.62 (C03)

**Tablet**

- Methylphenidate hydrochloride (Non-proprietary)
  - Methylphenidate hydrochloride 5 mg	Methylphenidate 5 mg tablets | 30 tablet | $3.03 DT | $3.03 (C03)
  - Methylphenidate hydrochloride 10 mg	Methylphenidate 10 mg tablets | 30 tablet | $5.29 DT | $5.29 (C03)
  - Methylphenidate hydrochloride 20 mg	Methylphenidate 20 mg tablets | 30 tablet | $10.92 DT | $10.92 (C03)
  - Methylphenidate hydrochloride 30 mg	Methylphenidate 30 mg tablets | 30 tablet | $14.81 DT | $14.81 (C03)

- Medikinet (Flynn Pharma Ltd)
  - Methylphenidate hydrochloride 5 mg	Medikinet 5 mg tablets | 30 tablet | $3.03 DT | $3.03 (C03)
  - Methylphenidate hydrochloride 10 mg	Medikinet 10 mg tablets | 30 tablet | $5.29 DT | $5.29 (C03)
  - Methylphenidate hydrochloride 20 mg	Medikinet 20 mg tablets | 30 tablet | $10.92 DT | $10.92 (C03)

**Ritalin** (Novartis Pharmaceuticals UK Ltd)

- Methylphenidate hydrochloride 10 mg	Ritalin 10 mg tablets | 30 tablet | $6.68 DT | $3.57 (C03)

- Tranquilyn (Genesys Pharmaceuticals Ltd)

- Methylphenidate hydrochloride 5 mg	Tranquilyn 5 mg tablets | 30 tablet | $3.03 DT | $3.03 (C03)
  - Methylphenidate hydrochloride 10 mg	Tranquilyn 10 mg tablets | 30 tablet | $4.27 DT | $3.57 (C03)
  - Methylphenidate hydrochloride 20 mg	Tranquilyn 20 mg tablets | 30 tablet | $10.92 DT | $10.92 (C03)

**Modifed-release capsule**

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- Equasym XL (Shire Pharmaceuticals Ltd)
  - Methylphenidate hydrochloride 10 mg	Equasym XL 10 mg capsules | 30 capsule | $25.00 DT | $25.00 (C03)
  - Methylphenidate hydrochloride 20 mg	Equasym XL 20 mg capsules | 30 capsule | $30.00 DT | $30.00 (C03)
  - Methylphenidate hydrochloride 30 mg	Equasym XL 30 mg capsules | 30 capsule | $35.00 DT | $35.00 (C03)

- Medikinet XL (Flynn Pharma Ltd)

- Methylphenidate hydrochloride 5 mg	Medikinet XL 5 mg capsules | 30 capsule | $24.04 DT | $24.04 (C03)
  - Methylphenidate hydrochloride 10 mg	Medikinet XL 10 mg capsules | 30 capsule | $24.04 DT | $24.04 (C03)
  - Methylphenidate hydrochloride 20 mg	Medikinet XL 20 mg capsules | 30 capsule | $28.86 DT | $28.86 (C03)
  - Methylphenidate hydrochloride 30 mg	Medikinet XL 30 mg capsules | 30 capsule | $33.66 DT | $33.66 (C03)
  - Methylphenidate hydrochloride 40 mg	Medikinet XL 40 mg capsules | 30 capsule | $37.72 DT | $37.72 (C03)
  - Methylphenidate hydrochloride 50 mg	Medikinet XL 50 mg capsules | 30 capsule | $42.52 DT | $42.52 (C03)
  - Methylphenidate hydrochloride 60 mg	Medikinet XL 60 mg capsules | 30 capsule | $47.22 DT | $47.22 (C03)

**Dexamfetamine sulfate**

(Dexamphetamine sulfate)

**INDICATIONS AND DOSE**

Narcolepsy

- Adult: Initially 10 mg daily in divided doses, increased in steps of 10 mg every week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day
  - Elderly: Initially 5 mg daily in divided doses, increased in steps of 5 mg every week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

Refractory attention deficit hyperactivity disorder (initiated under specialist supervision)

- By mouth
  - Adult: Initially 2.5 mg 2–3 times a day, increased in steps of 5 mg once weekly if required; usual maximum 1 mg/kg daily, up to 20 mg daily (40 mg daily has been required in some children); maintenance dose to be given in 2–4 divided doses
  - Adult: Initially 5 mg twice daily, dose is increased at weekly intervals according to response, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

**UNLICENSED USE**

Not licensed for use in adults for refractory attention deficit hyperactivity disorder.

**CONTRA-INDICATIONS**

Advanced arteriosclerosis (in adults) - agitation states - cardiovascular disease - history of alcohol abuse - history of drug abuse - hyperexcitability - hypertyroidism - moderate hypertension - severe hypertension - structural cardiac abnormalities

**CAUTIONS**

Anorexia - bipolar disorder - history of epilepsy - discontinue if seizures occur - mild hypertension - psychosis - susceptibility to angle-closure glaucoma - tics - Tourette syndrome
Attention deficit hyperactivity disorder 351

- **Meditinal Forms** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release capsule, oral suspension, oral solution

- **Oral Solution**
  - Dexamfetamine sulfate (Non-proprietary) Dexamfetamine sulfate 1 mg per ml Dexamfetamine 5mg/5ml oral solution sugar free sugar-free | 150 ml (Pos) £24.44–£34.35 (CD)
  - sugar-free | 500 ml (Pos) £11.49 DT = £11.49 (CD)

- **Modified-release capsule**
  - Dexedrine Spansules (Imported (United States)) Dexedrine sulfate 5 mg Dexedrine 5mg Spansules | 100 capsule (Pos) £16.74 (CD)
  - Dexedrine sulfate 10 mg Dexedrine 10mg Spansules | 100 capsule (Pos) £16.74 (CD)
  - Dexedrine sulfate 15 mg Dexedrine 15mg Spansules | 100 capsule (Pos) £16.74 (CD)

- **Tablet**
  - Dexamfetamine sulfate (Non-proprietary) Dexamfetamine sulfate 5 mg Dexamfetamine 5mg tablets | 28 tablet (Pos) £24.75 DT = £24.62 (CD)
  - Amfexa (Pfynn Pharma Ltd) Dexamfetamine sulfate 5 mg Amfexa 5mg tablets | 30 tablet (Pos) £19.89 (CD)
  - Dexamfetamine sulfate 10 mg Amfexa 10mg tablets | 30 tablet (Pos) £39.78 DT = £39.78 (CD)
  - Dexamfetamine sulfate 20 mg Amfexa 20mg tablets | 30 tablet (Pos) £79.56 DT = £79.56 (CD)

**Lisdexamfetamine mesilate**

- **Drug Action** Lisdexamfetamine is a prodrug of dexamfetamine.

- **indications and Dose** Attention deficit hyperactivity disorder (initiated by a specialist)
  - **by Mouth**
    - Child 6–17 years: Initially 30 mg once daily, alternatively initially 20 mg once daily, increased in steps of 10–20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day
    - Adult: Initially 30 mg once daily, increased in steps of 20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day

- **Contra-indications** Advanced arteriosclerosis - agitated states - hyperthyroidism - moderate hypertension - severe hypertension - symptomatic cardiovascular disease

- **Caution** Bipolar disorder - history of cardiovascular disease - history of substance abuse - may lower seizure threshold (discontinue if seizures occur) - psychotic disorders - susceptibility to angle-closure glaucoma - tics - Tourette syndrome

- **Caution, Further Information** Cardiovascular disease Manufacturer advises caution in patients with underlying conditions that might be compromised by increases in blood pressure or heart rate; see also Contra-indications.

- **Interactions** Appendix 1: amphetamines

- **Side-effects**
  - **Common or very common** Abdominal pain - anxiety - appetite decreased - behavioural abnormal - constipation - diarrhoea - dizziness - dry mouth - dysphoria - fatigue - feeling jittery - headache - hyperdysidrosis (uncommon in children) - insomnia - mood altered - movement disorders (uncommon in children) - nausea - palpitations - sexual dysfunction (uncommon in children) - tachycardia - tremor - weight decreased
  - **Uncommon** Depression (very common in children) - drowsiness (very common in children) - fever (very
common in children) - logorrhoea - psychiatric disorders (very common in children) - skin reactions (very common in children) - taste altered - vision blurred - vomiting (very common in children)

- **Frequency not known** Angioedema - cardiomyopathy (uncommon in children) - drug dependence - hallucination (uncommon in children) - hepatitis - myasthenia (uncommon in children) - psychotic disorder - Raynaud's phenomenon (uncommon in children) - seizure - Stevens-Johnson syndrome

**Overdose** Amfetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. See Stimulants under Emergency Treatment of poisoning p. 1359.

- **PREGNANCY** Manufacturer advises monitor for aggressive behaviour or hostility during initial treatment.

**Dose adjustments**

Manufacturer advises avoid amfetamines, see Drugs and driving legislation regarding driving whilst taking certain controlled drugs, including amfetamines, see Drugs and driving under Guidance on prescribing p. 1

- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk.

- **RENAI IMPAIRMENT**

**Dose adjustments** Manufacturer advises max. dose 50 mg daily in severe impairment.

**Monitoring requirements**

- Manufacturer advises monitor for aggressive behaviour or hostility during initial treatment.
- Manufacturer advises monitor pulse, blood pressure, and for psychiatric symptoms before treatment initiation, following each dose adjustment, and at least every 6 months thereafter. Monitor weight in adults before treatment initiation and during treatment; in children, height and weight should be recorded before treatment initiation, and height, weight and appetite monitored at least every 6 months during treatment.

- **TREATMENT CESSION** Avoid abrupt withdrawal.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises swallow whole or mix contents of capsule with soft food such as yoghurt or in a glass of water or orange juice; contents should be dispersed completely and consumed immediately.

- **PATIENT AND CARER ADVICE** Patients and carers should be counselled on the administration of capsules.

- **Driving and skilled tasks** Drugs and Driving Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

- **For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including amfetamines, see Drugs and driving under Guidance on prescribing p. 1.**

- **NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (May 2013) that lisdexamfetamine dimesylate (Elvanse®) is accepted for use within NHS Scotland as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

- **In adults** The Scottish Medicines Consortium has advised (September 2015) that lisdexamfetamine dimesylate (Elvanse Adult®) is accepted for use within NHS Scotland as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in adults. Based on clinical judgment, patients should have ADHD of at least moderate severity.

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**All Wales Medicines Strategy Group (AWMSG) decisions**

The All Wales Medicines Strategy Group has advised (December 2013) that lisdexamfetamine dimesylate (Elvanse®) is recommended as an option for use within NHS Wales as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children aged six years and over when response to previous methylphenidate treatment is considered clinically inadequate. Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

- **In adults** The All Wales Medicines Strategy Group has advised (October 2015) that lisdexamfetamine dimesylate (Elvanse Adult®) is recommended as an option for use within NHS Wales as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in adults.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

Cautory and advisory labels 3, 25

- Elvanse (Shire Pharmaceuticals Ltd).

Lisdexamfetamine dimesylate 20 mg

| Elvanse 20mg capsules | 28 capsule (PPh) | £54.62 DT = £54.62 (DO) |
| Lisdexamfetamine dimesylate 30 mg | | |
| Elvanse Adult 30mg capsules | 28 capsule (PPh) | £58.24 DT = £58.24 (DO) |
| Lisdexamfetamine dimesylate 40 mg | | |
| Elvanse 40mg capsules | 28 capsule (PPh) | £62.82 DT = £62.82 (DO) |
| Lisdexamfetamine dimesylate 50 mg | | |
| Elvanse Adult 50mg capsules | 28 capsule (PPh) | £68.60 DT = £68.60 (DO) |
| Lisdexamfetamine dimesylate 60 mg | | |
| Elvanse 60mg capsules | 28 capsule (PPh) | £75.18 DT = £75.18 (DO) |
| Lisdexamfetamine dimesylate 70 mg | | |
| Elvanse 70mg capsules | 28 capsule (PPh) | £83.16 DT = £83.16 (DO) |
| Elvanse Adult 70mg capsules | 28 capsule (PPh) | £83.16 DT = £83.16 (DO) |

**SYMPATHOMIMETICS > ALPHA1-ADRENOCEPTOR AGONISTS**

Guanfacine

- **INDICATIONS AND DOSE** Attention deficit hyperactivity disorder in children for whom stimulants are not suitable, not tolerated or ineffective (initiated under specialist supervision)

  - **BY MOUTH**

    - Child 6-12 years (body-weight 25 kg and above): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 4 mg), for optimal weight-adjusted dose titrations, consult product literature

    - Child 13-17 years (body-weight 34–41.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 4 mg), for optimal weight-adjusted dose titrations, consult product literature

    - Child 13-17 years (body-weight 41.5–49.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 5 mg), for optimal weight-adjusted dose titrations, consult product literature

    - Child 13-17 years (body-weight 49.5–58.4 kg): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 6 mg), for
optimal weight-adjusted dose titrations, consult product literature

» Child 13–17 years (body-weight 58.5 kg and above): Initially 1 mg once daily; adjusted in steps of 1 mg every week if necessary and if tolerated; maintenance 0.05–0.12 mg/kg once daily (max. per dose 7 mg), for optimal weight-adjusted dose titrations, consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

» Manufacturer advises reduce dose by half with concurrent use of moderate and potent inhibitors of CYP3A4.

» Manufacturer advises increase dose up to max. 7 mg daily with concurrent use of potent inducers of CYP3A4—no specific recommendation made for children.

● CAUTIONS
  » Bradycardia (risk of torsade de pointes) - heart block (risk of torsade de pointes) - history of cardiovascular disease - history of QT-interval prolongation - hypokalaemia (risk of torsade de pointes)

● INTERACTIONS → Appendix 1: guanfacine

● SIDE-EFFECTS
  » Common or very common
    » Anxiety, appetite decreased, arrhythmias, asthenia, constipation, depression, diarrhoea, dizziness, drowsiness, dry mouth, gastrointestinal discomfort, headache, hypotension, mood altered, nausea, skin reactions, sleep disorders, urinary disorders, vomiting, weight increased
  » Uncommon
    » Asthma, atrioventricular block, chest pain, hallucination, loss of consciousness, pallor, seizure, syncope
  » Rare or very rare
    » Hypertension, hypertensive encephalopathy, malaise
  » Frequency not known
    » Erectile dysfunction

SIDE-EFFECTS, FURTHER INFORMATION

Somnolence and sedation may occur, predominantly during the first 2–3 weeks of treatment and with dose increases; manufacturer advises to consider dose reduction or discontinuation of treatment if symptoms are clinically significant or persistent.

Overdose

Features may include hypotension, initial hypertension, bradycardia, lethargy, and respiratory depression. Manufacturer advises that patients who develop lethargy should be observed for development of more serious toxicity for up to 24 hours.

» CONCEPTION AND CONCEPTION

Manufacturer recommends effective contraception in females of childbearing potential.

» PREGNANCY

Manufacturer advises avoid—toxicity in animal studies.

» BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

» HEPATIC IMPAIRMENT

Manufacturer advises caution (pharmacokinetics have not been assessed in paediatric patients with hepatic impairment).

» RENAL IMPAIRMENT

Manufacturer advises consider dose reduction.

» MONITORING REQUIREMENTS

Manufacturer advises to conduct a baseline evaluation to identify patients at risk of somnolence, sedation, hypotension, bradycardia, QT-prolongation, and arrhythmia; this should include assessment of cardiovascular status. Monitor for signs of these adverse effects weekly during dose titration and then every 3 months during the first year of treatment, and every 6 months thereafter. Monitor BMI prior to treatment and then every 3 months for the first year of treatment, and every 6 months thereafter. More frequent monitoring is advised following dose adjustments.

» Monitor blood pressure and pulse during dose downward titration and following discontinuation of treatment.

» TREATMENT CESSATION

Manufacturer advises avoid abrupt withdrawal; consider dose tapering to minimise potential withdrawal effects.

» DIRECTIONS FOR ADMINISTRATION

Manufacturer advises avoid administration with high fat meals (may increase absorption).

» PATIENT AND CARER ADVICE

Patients or carers should be counselled on administration of guanfacine modified-release tablets.

Missed doses

Manufacturer advises that patients and carers should inform their prescriber if more than one dose is missed; consider dose re-titration.

Driving and skilled tasks

Manufacturer advises patients and carers should be counselled about the effects on driving and performance of skilled tasks—increased risk of dizziness and syncope.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 2, 25

Intuniv (Shire Pharmaceuticals Ltd)

Guanfacine (as Guanfacine hydrochloride) 1 mg Intuniv 1mg modified-release tablets | 28 tablet £56.00 DT = £56.00
Guanfacine (as Guanfacine hydrochloride) 2 mg Intuniv 2mg modified-release tablets | 28 tablet £55.52 DT = £55.52
Guanfacine (as Guanfacine hydrochloride) 3 mg Intuniv 3mg modified-release tablets | 28 tablet £55.52 DT = £55.52
Guanfacine (as Guanfacine hydrochloride) 4 mg Intuniv 4mg modified-release tablets | 28 tablet £76.16 DT = £76.16

3.3 Bipolar disorder and mania

Mania and hypomania

Overview

Antimanic drugs are used to control acute attacks and to prevent recurrence of episodes of mania or hypomania. Long-term treatment of bipolar disorder should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse.

An antidepressant drug may also be required for the treatment of co-existing depression, but should be avoided in patients with rapid-cycling bipolar disorder, a recent history of hypomania, or with rapid mood fluctuations.

Benzodiazepines

Use of benzodiazepines (such as lorazepam p. 339) may be helpful in the initial stages of treatment for behavioral disturbance or agitation; they should not be used for long periods because of the risk of dependence.

Antipsychotic drugs

Antipsychotic drugs (normally olanzapine p. 398, quetiapine p. 401, or risperidone p. 402) are useful in acute episodes of mania and hypomania; if the response to antipsychotic drugs is inadequate, lithium or valproate may be added. An antipsychotic drug may be used concomitantly with lithium or valproate in the initial treatment of severe acute mania. See Important safety information, Conception and contraception, and Pregnancy in the valproic acid p. 354 and sodium valproate p. 327 monographs.

Olanzapine can be used for the long-term management of bipolar disorder in patients whose manic episode responded to olanzapine therapy. It can be given either as monotherapy, or in combination with lithium or valproate if...
the patient has frequent relapses or continuing functional impairment.

Asenapine p. 356, a second-generation antipsychotic, is licensed for the treatment of moderate to severe manic episodes associated with bipolar disorder.

When discontinuing antipsychotics, the dose should be reduced gradually over at least 4 weeks if the patient is continuing with other antimanic drugs; if the patient is not continuing with other antimanic drugs or if there is a history of manic relapse, a withdrawal period of up to 3 months should be considered.

**Carbamazepine**

Carbamazepine p. 311 may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients unresponsive to a combination of other prophylactic drugs; it is used in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine should not normally be increased if an acute episode of mania occurs.

**Valproate**

Valproate (valproic acid (as the semisodium salt) and sodium valproate) is used for the treatment of manic episodes associated with bipolar disorder. It must be started and supervised by a specialist experienced in managing bipolar disorder. Valproate (valproic acid and sodium valproate) is also used for the prophylaxis of bipolar disorder. Because of its high teratogenic risk, valproate must not be used in females of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and alternative treatments are ineffective or not tolerated. Valproic acid and sodium valproate must not be used during pregnancy in bipolar disorder. The benefit and risk of valproate therapy should be carefully reconsidered at regular treatment reviews. For further information, see Important safety information, Conception and contraception, and Pregnancy in the valproic acid and sodium valproate monographs.

In patients with frequent relapse or continuing functional impairment, consider switching therapy to lithium or olanzapine, or adding lithium or olanzapine to valproate. If a patient taking valproate experiences an acute episode of mania that is not ameliorated by increasing the valproate dose, consider concomitant therapy with olanzapine, quetiapine, or risperidone.

**Lithium**

Lithium salts are used in the prophylaxis and treatment of mania, hypomania and depression in bipolar disorder (manic-depressive disorder), and in the prophylaxis and treatment of recurrent unipolar depression. Lithium is also used as concomitant therapy with antidepressant medication in patients who have had an incomplete response to treatment for acute bipolar depression and to augment other antidepressants in patients with treatment-resistant depression [unlicensed indication]. It is also licensed for the treatment of aggressive or self-harming behaviour.

The decision to give prophylactic lithium requires specialist advice, and must be based on careful consideration of the likelihood of recurrence in the individual patient, and the benefit of treatment weighed against the risks. The full prophylactic effect of lithium may not occur for six to twelve months after the initiation of therapy. Olanzapine or valproate (given alone or as adjunctive therapy with lithium) are alternative prophylactic treatments in patients who experience frequent relapses or continued functional impairment.

## Other drugs used for Bipolar disorder and mania


### ANTIEPILEPTICS

#### Valproic acid

**INDICATIONS AND DOSE**

**Treatment of manic episodes associated with bipolar disorder**

- **BY MOUTH**
  - Adult: Initially 750 mg daily in 2–3 divided doses, then increased to 1–2 g daily, adjusted according to response, doses greater than 45 mg/kg daily require careful monitoring.

#### Migraine prophylaxis

- **BY MOUTH**
  - Adult: Initially 250 mg twice daily, then increased if necessary to 1 g daily in divided doses

#### DOSE EQUIVALENCE AND CONVERSION

- Semisodium valproate comprises equimolar amounts of sodium valproate and valproic acid.

#### Epilepsy

- **BY MOUTH**
  - Adult: Initially 600 mg daily in 2–4 divided doses, increased in steps of 150–300 mg every 3 days; usual maintenance 1–2 g daily in 2–4 divided doses, max. 2.5 g daily in 2–4 divided doses

#### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE: VALPROATE MEDICATIONS: CONTRA-INDICATED IN WOMEN AND GIRLS OF CHILDBEARING POTENTIAL UNLESS CONDITIONS OF PREGNANCY PREVENTION PROGRAMME ARE MET (APRIL 2018)**

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to neurodevelopmental disorders (approx. 30–40% risk) and congenital malformations (approx. 10% risk). Valproate must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met (see Conception and contraception) and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist.

Use of valproate in pregnancy is contra-indicated for migraine prophylaxis [unlicensed] and bipolar disorder; it must only be considered for epilepsy if there is no suitable alternative treatment (see Pregnancy). Women and girls (and their carers) must be fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy; supporting materials have been provided to use in the implementation of the Pregnancy Prevention Programme (see Prescribing and dispensing information). The MHRA advises that:

- GPs must recall all women and girls who may be of childbearing potential, provide the Patient Guide, check they have been reviewed by a specialist in the last year and are on highly effective contraception;

- Specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme, re-evaluate treatment as required, and provide the Pregnancy Prevention Programme Patient Guide.
Liver toxicity

CAUTIONS

- Pharmacists must ensure valproate medicines are dispensed in whole packs whenever possible—all packs dispensed to women and girls of childbearing potential should have a warning label either on the carton or via a sticker. They must also discuss risks in pregnancy with female patients each time valproate medicines are dispensed, ensure they have the Patient Guide and have seen their GP or specialist to discuss their treatment and the need for contraception.

MHRA/CHM ADVICE: VALPROATE MEDICINES: ARE YOU ACTING IN COMPLIANCE WITH THE PREGNANCY PREVENTION MEASURES? (DECEMBER 2018)

The MHRA advises that all healthcare professionals must continue to identify and review all female patients on valproate, including when used outside licensed indications (off-label use) and provide them with the patient information materials every time they attend appointments or receive their medicines.

Guidance for psychiatrists on the withdrawal of, and alternatives to, valproate in women of child-bearing potential who have a psychiatric illness is available from the Royal College of Psychiatrists.

MHRA/CHM ADVICE: VALPROATE MEDICINES AND SERIOUS HARM IN PREGNANCY: NEW ANNUAL RISK ACKNOWLEDGEMENT FORM AND CLINICAL GUIDANCE FROM PROFESSIONAL BODIES TO SUPPORT COMPLIANCE WITH THE PREGNANCY PREVENTION PROGRAMME (APRIL 2019)

The Annual Risk Acknowledgement Form has been updated and should be used for all future reviews of female patients on valproate. Specialists should comply with guidance given on the form if they consider the patient is not at risk of pregnancy, including the need for review in case her risk status changes.

Guidance has been published to support healthcare professionals with the use of valproate. These include a summary by NICE of their guidance and safety advice, pan-college guidance by national healthcare bodies, and paediatric guidance by the British Paediatric Neurology Association and the Royal College of Paediatrics and Child Health.

CONTRA-INDICATIONS

- Acute porphyrias p. 1058 - known or suspected mitochondrial disorders (higher rate of acute liver failure and liver-related deaths) - personal or family history of severe hepatic dysfunction

SAFETY

- Systemic lupus erythematosus

CAUTIONS, FURTHER INFORMATION

- Liver toxicity: Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

INTERACTIONS

- Appendix 1: antiepileptics

SIDE-EFFECTS


SIDE-EFFECTS, FURTHER INFORMATION

- Hepatic dysfunction

Withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control.

- Pancreatitis

Discontinue treatment if symptoms of pancreatitis develop.

CONCEPTION AND CONTRACEPTION

- The MHRA advises that all women and girls of childbearing potential being treated with valproate medicines must be supported on a Pregnancy Prevention Programme—pregnancy should be excluded before treatment initiation and highly effective contraception must be used during treatment.

- PREGNANCY

- For migraine prophylaxis [unlicensed] and bipolar disorder, the MHRA advises that valproate must not be used. For epilepsy, the MHRA advises valproate must not be used unless there is no suitable alternative treatment; in such cases, access to counselling about the risks should be provided (see Healthcare Professional Guide for more information) and a Risk Acknowledgement Form signed by both specialist and patient. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Neonatal bleeding (related to hypofibrinemia). Neonatal hepatotoxicity also reported. See also Pregnancy in Epilepsy p. 305.

MONITORING

- Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy.

- The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- BREAST FEEDING

- Present in milk—risk of haematological disorders in breast-fed newborns and infants.

- HEPATIC IMPAIRMENT

- Manufacturer advises avoid.

- RENAL IMPAIRMENT

- Dose adjustments Reduce dose.

- MONITORING REQUIREMENTS

- Monitor closely if dose greater than 45 mg/kg daily.

- Monitor liver function before therapy and during first 6 months especially in patients most at risk.

- Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.

- EFFECT ON LABORATORY TESTS

- False-positive urine tests for ketones.

- TREATMENT CESSATION

- In bipolar disorder, avoid abrupt withdrawal; if treatment with valproate is stopped, reduce the dose gradually over at least 4 weeks.

- PRESCRIBING AND DISPENSING INFORMATION

- The Pregnancy Prevention Programme is supported by the following materials provided by the manufacturer: Patient Guide, Guide for Healthcare Professionals, Risk Acknowledgement Form, and for pharmacists, Patient Cards and Stickers with warning symbols; the MHRA has also produced a patient information sheet providing advice for women and girls taking valproate medicines.

CONVULEX® Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic oral valproic acid product.
PATIENT AND CARER ADVICE
Valproate use by women and girls. The MHRA advises women and girls should not stop taking valproate without first discussing it with their doctor.

Blood or hepatic disorders. Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop.

Pancreatitis. Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop.

Pregnancy Protection Programme. Pharmacists must ensure that female patients have a patient card—see also Important safety information.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution gastro-resistant capsule.

Gastro-resistant capsule

CAUTIONARY AND ADVISORY LABELS 8, 10, 21, 25

- Convulex (Pfizer Ltd)▼
  - Valproic acid 150 mg Convulex 150mg gastro-resistant capsules | 100 capsule POM £3.68 DT = £3.68
  - Valproic acid 300 mg Convulex 300mg gastro-resistant capsules | 100 capsule POM £7.35 DT = £7.35
  - Valproic acid 500 mg Convulex 500mg gastro-resistant capsules | 100 capsule POM £11.25 DT = £11.25

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 10, 21, 25

- Depakote (Sanofi)▼
  - Valproic acid (as Valproate semisodium) 250 mg Depakote 250mg gastro-resistant tablets | 30 tablet POM £3.69 | 90 tablet POM £9.08 DT = £9.08
  - Valproic acid (as Valproate semisodium) 500 mg Depakote 500mg gastro-resistant tablets | 30 tablet POM £11.37 | 90 tablet POM £34.11 DT = £34.11

ANTIPSYCHOTICS > SECOND-GENERATION

Asenapine

INDICATIONS AND DOSE
Monotherapy for the treatment of moderate to severe manic episodes associated with bipolar disorder

- BY MOUTH
  - Adult: Initially 10 mg twice daily, reduced to 5 mg twice daily, adjusted according to response

Combination therapy for the treatment of moderate to severe manic episodes associated with bipolar disorder

- BY MOUTH
  - Adult: Initially 5 mg twice daily, increased if necessary to 10 mg twice daily, adjusted according to response

CAUTIONS
Dementia with Lewy Bodies

INTERACTIONS → Appendix 1: asenapine

SIDE-EFFECTS
- Common or very common: Anxity, appetite increased, fatigue, muscle rigidity, nausea, oral disorders, taste altered
- Uncommon: Bundle branch block, dysarthria, dysphagia, hyperglycaemia, sexual dysfunction, syncope
- Rare or very rare: Accommodation disorder, rhadomyolysis

PREGNANCY
Use only if potential benefit outweighs risk—toxicity in animal studies.

BREAST FEEDING
Avoid—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises caution in moderate impairment; avoid in severe impairment (risk of increased exposure).

RENAL IMPAIRMENT
Use with caution if eGFR less than 15 mL/minute/1.73 m²—no information available.

PATIENT AND CARER ADVICE
Patient or carer should be given advice on how to administer asenapine sublingual tablet.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Sublingual tablet

CAUTIONARY AND ADVISORY LABELS 2, 26

- Sycrest (Lundbeck Ltd)
  - Asenapine (as Asenapine maleate) 5 mg Sycrest 5mg sublingual tablets sugar-free | 60 tablet POM DT £102.60 DT + £102.60
  - Asenapine (as Asenapine maleate) 10 mg 20 mg sublingual tablets sugar-free | 60 tablet POM DT £102.60 DT + £102.60

ANTIPSYCHOTICS > LITHIUM SALTS

Lithium salts

CONTRA-INDICATIONS
Addison’s disease, cardiac insufficiency, dehydration, family history of Brugada syndrome, low sodium diets, personal history of Brugada syndrome, rhythm disorder, untreated hyperthyroidism

CAUTIONS
Avoid abrupt withdrawal, cardiac disease, concurrent ECT (may lower seizure threshold), diuretic treatment (risk of toxicity), elderly (reduce dose), epilepsy (may lower seizure threshold), myasthenia gravis, psoriasis (risk of exacerbation), QT interval prolongation, review dose as necessary in diarrhoea, review dose as necessary in intercurrent infection (especially if sweating profusely), review dose as necessary in vomiting, surgery.

CAUTIONS, FURTHER INFORMATION
- Long-term use: Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid function every 6 months (more often if there is evidence of deterioration).

The need for continued therapy should be assessed regularly and patients should be maintained on lithium after 3–5 years only if benefit persists.

SIDE-EFFECTS
- Rare or very rare: Nephropathy
- Frequency not known: Abdominal discomfort, alopecia, angioedema, appetite decreased, arrhythmias, atrioventricular block, cardiomyopathy, cerebellar syndrome, circulatory collapse, coma, delirium, diarrhoea, dizziness, dry mouth, electrolyte imbalance, encephalopathy, foliniculitis, gastritis, goitre, hyperglycaemia, hyperparathyroidism, hypersalivation, hypotension, hypothyroidism, idiopathic intracrinal hypertension, leucocytosis, memory loss, movement disorders, muscle weakness, myasthenia gravis, nausea, neoplasms, nystagmus, peripheral neuropathy, peripheral oedema, polyuria, QT interval prolongation, reflexes abnormal, renal disorders, renal impairment, rhadomyolysis, seizure, sexual dysfunction, skin reactions, skin ulcer, speech impairment, taste altered, thyrotoxicosis, tremor, vertigo, vision disorders, vomiting, weight increased

SIDE-EFFECTS, FURTHER INFORMATION
Overdose: Signs of intoxication require withdrawal of treatment and include increasing gastro-intestinal disturbances (vomiting, diarrhoea), visual disturbances, polyuria, muscle weakness, fine tremor increasing to coarse tremor, CNS disturbances (confusion and drowsiness increasing to lack of coordination, restlessness, stupor); abnormal reflexes, myoclonus, incontinence, hypernatraemia. With severe overdose seizures, cardiac arrhythmias (including sinoatrial block, bradycardia and first-degree heart block),
blood pressure changes, circulatory failure, renal failure, coma and sudden death reported.

For details on the management of poisoning, see Lithium, under Emergency treatment of poisoning p. 1359.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment for women of child bearing potential.

- **PREGNANCY** Avoid if possible, particularly in the first trimester (risk of teratogenicity, including cardiac abnormalities).

- **Dose adjustments** Dose requirements increased during the second and third trimesters (but on delivery return abruptly to normal).

- **Monitoring** Close monitoring of serum-lithium concentration advised in pregnancy (risk of toxicity in neonate).

- **BREAST FEEDING** Present in milk and risk of toxicity in infant—avoid.

- **RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

- **Monitoring requirements** Serum concentrations. Lithium salts have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring serum-lithium concentrations are available.

A target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms. It is important to determine the optimum range for each individual patient. Routine serum-lithium monitoring should be performed weekly after initiation and after each dose change until concentrations are stable, then every 3 months thereafter.

Additional serum-lithium measurements should be made if a patient develops significant intercurrent disease or if there is a significant change in a patient’s sodium or fluid intake.

- **Manufacturer advises to assess renal, cardiac, and thyroid function before treatment initiation.** An ECG is recommended in patients with cardiovascular disease or risk factors for it. Body-weight or BMI, serum electrolytes, and a full blood count should also be measured before treatment initiation.

- **Monitor body-weight or BMI, serum electrolytes, eGFR, and thyroid function every 6 months during treatment, and more often if there is evidence of impaired renal or thyroid function, or raised calcium levels.** Manufacturer also advises to monitor cardiac function regularly.

- **Treatment Cessation** While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Patients and their carers should be warned of the risk of relapse if lithium is discontinued abruptly. If lithium is stopped or is to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate.

- **Patient and carer advice** Patients should be advised to report signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance). Maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake.

Lithium treatment packs A lithium treatment pack should be given to patients on initiation of treatment with lithium. The pack consists of a patient information booklet, lithium alert card, and a record book for tracking serum-lithium concentration. Packs may be purchased from 3M 0845 610 1112 nhsforms@mmm.uk.com

Driving and skilled tasks May impair performance of skilled tasks (e.g. driving, operating machinery).
Lithium carbonate (Non-proprietary)
Lithium carbonate 250 mg Lithium carbonate 250mg tablets | 100 tablet £87.00 DT = £87.00

INDICATIONS AND DOSE
Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

BY MOUTH
Adult: Initially 450–675 mg twice daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Elderly: Initially 225 mg twice daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

DOSE EQUIVALENCE AND CONVERSION
Preparations vary widely in bioavailability; changing the preparation requires the same precautions as initiation of treatment.

LI-LIQUID
Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

BY MOUTH
Adult (body-weight up to 50 kg): Initially 509 mg daily in 2 divided doses, dose adjusted according to serum-lithium concentration

Adult (body-weight 50 kg and above): Initially 0.4–1.2 g once daily, alternatively initially 0.4–1.2 g daily in 2 divided doses, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Elderly: Initially 200–400 mg daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

DOSE EQUIVALENCE AND CONVERSION
Fox Li-Liquid®: Lithium citrate tetrahydrate 509 mg is equivalent to lithium carbonate 200 mg.

PRIADEL® LIQUID
Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

BY MOUTH
Adult (body-weight up to 50 kg): Initially 520 mg twice daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Adult (body-weight 50 kg and above): Initially 1.04–3.12 g daily in 2 divided doses, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Elderly: Initially 520 mg twice daily, dose adjusted according to serum-lithium concentration, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

INTERACTIONS
Appendix 1: lithium

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 10, 25
Lithium carbonate 400 mg Camcolit 400 modified-release tablets | 100 tablet £48.18 DT = £4.02

www.getintopharma.com
Antidepressant drugs

Overview
Antidepressant drugs are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as loss of appetite and sleep disturbance; improvement in sleep is usually the first benefit of therapy. Ideally, patients with moderate to severe depression should be treated with psychological therapy in addition to drug therapy. Antidepressant drugs are also effective for dysthymia (lower grade chronic depression typically of at least 2 years duration). Antidepressant drugs should not be used routinely in mild depression, and psychological therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or in those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in patients with a history of moderate or severe depression.

Choice
The major classes of antidepressant drugs include the tricyclic and related antidepressants, the selective serotonin re-uptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). A number of antidepressant drugs cannot be accommodated easily into this classification.

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient’s requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. Since there may be an interval of 2 weeks before the antidepressant action takes place, electroconvulsive treatment may be required in severe depression when delay is hazardous or intolerable. During the first few weeks of treatment, there is an increased potential for agitation, anxiety, and suicidal ideation.

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. In patients with unstable angina or who have had a recent myocardial infarction, sertraline p. 367 has been shown to be safe.

Tricyclic antidepressants have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects; toxicity in overdose is also a problem. SSRIs are less sedating and have fewer antimuscarinic and cardio toxic effects than tricyclic antidepressants.

MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists.

Although anxiety is often present in depressive illness (and may be the presenting symptom), the use of an antipsychotic or an anxiolytic may mask the true diagnosis. Anxiolytics or antipsychotic drugs should therefore be used with caution in depression but they are useful adjuncts in agitated patients. Augmenting antidepressants with antipsychotics under specialist supervision may also be necessary in patients who have depression with psychotic symptoms.

St John’s wort (Hypericum perforatum) is a popular herbal remedy on sale to the public for treating mild depression. It should not be prescribed or recommended for depression because St John’s wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs, including conventional antidepressants, have been identified. Furthermore, the amount of active ingredient varies between different preparations of St John’s wort and switching from one to another can change the degree of enzyme induction. If a patient stops taking St John’s wort, the concentration of interacting drugs may increase, leading to toxicity.

Management
Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2–4 weeks (elderly patients may take longer to respond).

Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly), or for at least 12 months in patients receiving treatment for generalised anxiety disorder (as the likelihood of relapse is high). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.

Hyponatraemia and antidepressant therapy
Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressants. Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

Suicidal behaviour and antidepressant therapy
The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

Serotonin syndrome
Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity. Onset of symptoms, which range from mild to lifethreatening, can occur within hours or days following the initiation, dose escalation, or overdose of a serotonergic drug, the addition of a new serotonergic drug, or the replacement of one serotonergic drug by another without allowing a long enough washout period in-between, particularly when the first drug is an irreversible MAOI or a drug with a long half-life. Severe toxicity, which is a medical emergency, usually occurs with a combination of serotonergic drugs, one of which is generally an MAOI.

The characteristic symptoms of serotonin syndrome fall into 3 main areas, although features from each group may not be seen in all patients—neuromuscular hyperactivity (such as tremor, hyperreflexia, clonus, myoclonus, rigidity), autonomic dysfunction (tachycardia, blood pressure changes, hyperthermia, diaphoresis, shivering, diarrhoea), and altered mental state (agitation, confusion, mania).
Mental health disorders

Treatment consists of withdrawal of the serotonergic medication and supportive care; specialist advice should be sought.

Failure to respond
Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or mirtazapine p. 372. Other second-line choices include lofepramine p. 377, moclobemide p. 362, and reboxetine p. 363. Other tricyclic antidepressants and venlafaxine p. 368 should be considered for more severe forms of depression; irreversible MAOIs should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or use of an augmenting agent (such as lithium, aripiprazole p. 395 [unlicensed], olanzapine p. 398 [unlicensed], quetiapine p. 401, or risperidone p. 402 [unlicensed]), but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.

Anxiety disorders and obsessive-compulsive disorder
Management of acute anxiety generally involves the use of a benzodiazepine or buspirole hydrochloride p. 342. For chronic anxiety (of longer than 4 weeks’ duration) it may be appropriate to use an antidepressant. Combined therapy with a benzodiazepine may be required until the antidepressant takes effect. Patients with generalised anxiety disorder, a form of chronic anxiety, should be offered psychological treatment before initiating an antidepressant. If drug treatment is needed, an SSRI such as escitalopram p. 365, paroxetine p. 366, or sertraline p. 367 [unlicensed], can be used. Duloxetine p. 367 and venlafaxine p. 368 (serotonin and noradrenaline reuptake inhibitors) are also recommended for the treatment of generalised anxiety disorder; if the patient cannot tolerate SSRIs or serotonin and noradrenaline reuptake inhibitors (or if treatment has failed to control symptoms), pregabalin p. 324 can be considered.

Panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobic states such as social anxiety disorder are treated with SSRIs. Clomipramine hydrochloride p. 373 or imipramine hydrochloride p. 376 can be used second-line in panic disorder [unlicensed]; clomipramine hydrochloride can also be used second-line for obsessive-compulsive disorder. Moclobemide p. 362 is licensed for the treatment of social anxiety disorder.

Tricyclic and related antidepressant drugs
Choice
Tricyclic and related antidepressants block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, clomipramine hydrochloride is more selective for serotonergic transmission, and imipramine hydrochloride is more selective for noradrenergic transmission. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties and those that are less sedating. Agitated and anxious patients tend to respond best to the sedative compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones. Those with sedative properties include amitriptyline hydrochloride p. 372, clomipramine hydrochloride, dosulepin hydrochloride p. 374, doxepin p. 375, mianserin hydrochloride p. 371, trazodone hydrochloride p. 370, and trimipramine p. 378. Those with less sedative properties include imipramine hydrochloride, lofepramine p. 377, and nortriptyline p. 378.

Tricyclic and related antidepressants also have varying degrees of antimuscarinic side-effects and cardiotoxicity in overdose, which may be important in individual patients. Lofepramine has a lower incidence of side-effects and is less dangerous in overdose but is infrequently associated with hepatic toxicity. Imipramine hydrochloride is also well established, but has more marked antimuscarinic side-effects than other tricyclic and related antidepressants. Amitriptyline hydrochloride and dosulepin hydrochloride are effective but they are particularly dangerous in overdose and are not recommended for the treatment of depression; dosulepin hydrochloride should be initiated by a specialist.

Dosage
About 10 to 20% of patients fail to respond to tricyclic and related antidepressant drugs and inadequate dosage may account for some of these failures. It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. In most patients the long half-life of tricyclic antidepressant drugs allows once-daily administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Some tricyclic antidepressants are used in the management of panic and other anxiety disorders. Some tricyclic antidepressants may also have a role in some forms of neuralgia and in nocturnal enuresis in children.

Children and adolescents
Studies have shown that tricyclic antidepressants are not effective for treating depression in children.

Monoamine-oxidase inhibitors
Monoamine-oxidase inhibitors are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions and the fact that it is easier to prescribe MAOIs when tricyclic antidepressants have been unsuccessful than vice versa.

Tranylcypromine p. 362 has a greater stimulant action than phenelzine p. 362 or isocarboxazid p. 362 and is more likely to cause a hypertensive crisis. Isocarboxazid and phenelzine are more likely to cause hepatotoxicity than tranylcypromine.

Moclobemide should be reserved as a second line treatment.

Phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to the sedative compounds. Some tricyclic antidepressants and related antidepressants (for example, amitriptyline, doxepin, imipramine) may be more effective than MAOIs and such patients may be better treated with them.

Other antidepressants should not be started for at least 2 weeks if starting clomipramine or imipramine. Conversely, an MAOI should not be started until:

- at least 2 weeks after a previous MAOI has been stopped (then started at a reduced dose)
- at least 7–14 days after a tricyclic or related antidepressant (3 weeks in the case of clomipramine or imipramine) has been stopped
- at least a week after an SSRI or related antidepressant (at least 5 weeks in the case of fluoxetine) has been stopped

Other antidepressant drugs
The thioxanthene fluoxetine p. 385 (Fluanxol®) has antidepressant properties when given by mouth in low doses. Fluoxetine is also used for the treatment of psychoses.

Vortioxetine p. 380, an antidepressant thought to directly modulate serotonergic receptor activity and inhibit the re-uptake of serotonin, is recommended in patients whose condition has responded inadequately to 2 antidepressants within the current episode.
Tryptophan is licensed for use in treatment-resistant depression, used as monotherapy and as an adjunct to other antidepressant drugs; it should be initiated by hospital specialists.

### Other drugs used for Depression
Lithium carbonate, p. 357
- Lithium citrate, p. 358

#### MONITORING REQUIREMENTS

- **RENAL IMPAIRMENT**
- **BREAST FEEDING**
- **PREGNANCY**

#### SIDE-EFFECTS

- **CONTRA-INDICATIONS**
- **DRUG ACTION**
- **INTERACTIONS**
- **SIDE-EFFECTS**
- **UNCOMMON**
- **RARE or very rare**
- **SIDE-EFFECTS, FURTHER INFORMATION**
- **PREGNANCY**
- **HEPATIC IMPAIRMENT**
- **RENAI IMPAIRMENT**
- **MONITORING REQUIREMENTS**
- **PATIENT AND CARER ADVICE**

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**Antidepressants** ➔ **Melatonin Receptor Agonists**

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<th>Agomelatine</th>
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**Drug action**: A melatonin receptor agonist and a selective serotonin-receptor antagonist; it does not affect the uptake of serotonin, noradrenaline, or dopamine.

**Indications and Dose**

- **Major depression**
  - Adult: 25 mg daily, dose to be taken at bedtime. Dose to be increased if necessary after 2 weeks, increased if necessary to 50 mg daily, dose to be taken at bedtime.

**Contra-Indications**: Dementia, patients over 75 years of age.

**Caution**: Alcoholism, bipolar disorder, diabetes, excessive alcohol consumption, hypomania, mania, non-alcoholic fatty liver disease, obesity.

**Interactions**: Appendix 1: agomelatine

**Side-Effects**

- Common or very common: Abdominal pain, anxiety, back pain, constipation, diarrhoea, dizziness, drowsiness, fatigue, headaches, nausea, sleep disorders, vomiting, weight changes.
- Uncommon: Aggression, confusion, hyperhidrosis, mood altered, movement disorders, paraesthesia, skin reactions, suicidal tendencies, tinnitus, vision blurred.
- Rare or very rare: Angioedema, face oedema, hallucination, hepatic disorders, urinary retention.

**Side-Effects, Further Information**: The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

**Pregnancy**: Manufacturer advises avoid.

**Breast Feeding**: Avoid—present in milk in animal studies.

**Hepatic Impairment**: Manufacturer advises caution if transaminases are elevated; avoid in hepatic impairment or if transaminases exceed 3 times the upper limit of normal.

**Renal Impairment**: Caution in moderate to severe impairment.

**Monitoring Requirements**: Test liver function before treatment and after 3, 6, 12 and 24 weeks of treatment, and then regularly thereafter when clinically indicated (restart monitoring schedule if dose increased); discontinue if serum transaminases exceed 3 times the upper limit of reference range or symptoms of liver disorder.

**Patient and Carer Advice**: Hepatotoxicity. Patients should be told how to recognise signs of liver disorder, and advised to seek immediate medical attention if symptoms such as dark urine, light coloured stools, jaundice, bruising, fatigue, abdominal pain, or pruritus develop.

Patients should be given a booklet with more information on the risk of hepatic side-effects.

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**Monoamine-oxidase inhibitors**

**Drug action**: MAOIs inhibit monamine oxidase, thereby causing an accumulation of amine neurotransmitters.

**Contra-Indications**: Cerebrovascular disease, not indicated in manic phase, phaeochromocytoma.

**Caution**: Acute liver disease, p. 1058—avoid in agitated patients; blood disorders, cardiovascular disease; concurrent electroconvulsive therapy, diabetes mellitus, elderly (great caution), epilepsy, severe hypertensive reactions to certain drugs and foods, surgery.

**Side-Effects**: Akathisia, anxiety, appetite increased, arrhythmia, asthenia, behaviour abnormal, blood disorder, confusion, constipation, dizziness, drowsiness, dry mouth, dysuria, hallucination, headache, hyperhidrosis, insomnia, jaundice, nausea, paraesthesia, peripheral neuritis, postural hypotension, more common in elderly—reflexes increased, skin reactions, suicidal tendencies, tremor, vision blurred, vomiting, weight increased.

**Side-Effects, Further Information**: Risk of postural hypotension and hypertensive responses. Discontinue if palpitations or frequent headaches occur.

**Pregnancy**: Increased risk of neonatal malformations—manufacturer advises avoid unless there are compelling reasons.

**Hepatic Impairment**: In general, manufacturers advise avoid.

**Monitoring Requirements**: Monitor blood pressure (risk of postural hypotension and hypertensive responses).

**Treatment Cessation**: Withdrawal. If possible avoid abrupt withdrawal.

MAOIs are associated with withdrawal symptoms on cessation of therapy. Symptoms include agitation, irritability, ataxia, movement disorders, insomnia, drowsiness, vivid dreams, cognitive impairment, and slowed speech. Withdrawal symptoms occasionally experienced when discontinuing MAOIs include hallucinations and paranoid delusions. If possible MAOIs should be withdrawn slowly.

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

**Patient and Carer Advice**: Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or ‘going off’. This is especially important with meat, fish, poultry or offal; game should be avoided. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Patients should also be advised to avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.

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**Medicinal forms**

- **Tablet**
  - Agomelatine (Non-proprietary)
    - Agomelatine 25 mg Agomelatine 25mg tablets | 28 tablet £27.00–£30.00 DT £30.00
    - Valdoxan (Servier Laboratories Ltd)
      - Agomelatine 25 mg Valdoxan 25mg tablets | 28 tablet £30.00 DT £30.00

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www.getintopharma.com
Driving and skilled tasks  Drowsiness may affect performance of skilled tasks (e.g. driving).

**ANTIDEPRESSANTS › MONOAMINE-OXIDASE A AND B INHIBITORS, IRREVERSIBLE**

### Isocarboxazid  
30-Mar-2017

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially 30 mg daily until improvement occurs, initial dose may be given in single or divided doses, dose may be increased if necessary after 4 weeks, increased to 60 mg daily for 4–6 weeks, dose to be increased under close supervision only, then reduced to 10–20 mg daily, usual maintenance dose, but up to 40 mg daily may be required.
  - Elderly: 5–10 mg daily

**INTERACTIONS**  → Appendix 1: monoamine-oxidase A and B inhibitors, irreversible

**SIDE-EFFECTS**  Granulocytopenia - peripheral oedema - sexual dysfunction

**BREAST FEEDING**  Avoid.

**RENAL IMPAIRMENT**  Use with caution.

**LESS SUITABLE FOR PRESCRIBING**  Less suitable for prescribing.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension. There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS  3, 10

- **Isocarboxazid (Non-proprietary)**
  - Isocarboxazid 10 mg  Isocarboxazid 10mg tablets  | 56 tablet  [PO][M]  £239.52 DT = £228.64

### Phenelzine

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially 15 mg 3 times a day, response is usually seen within first week; dose may be increased if necessary after 2 weeks if response is not evident, increased if necessary to 15 mg 4 times a day, doses up to 30 mg three times a day may be used in hospital patients; response may not become apparent for up to 4 weeks; once satisfactory response has been achieved, reduce dose gradually to lowest suitable maintenance dose (15 mg on alternate days may be adequate)

**INTERACTIONS**  → Appendix 1: monoamine-oxidase A and B inhibitors, irreversible


**BREAST FEEDING**  Avoid—no information available.

**LESS SUITABLE FOR PRESCRIBING**  Less suitable for prescribing.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS  3, 10

- **Nardil (Kyowa Kirin Ltd)**
  - Phenelzine (as Phenelzine sulfate) 15 mg  Nardil 15mg tablets  | 100 tablet  [PO][M]  £22.50 DT = £22.50

### Tranylcypromine

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially 10 mg twice daily, dose to be taken at a time no later than 3 p.m., dose may be increased if necessary after 1 week, increased if necessary to 10 mg daily, dose to be taken in the morning and 20 mg daily, dose to be taken in the afternoon, doses above 30 mg daily, under close supervision only; maintenance 10 mg daily

**CONTRA-INDICATIONS**  Congestive heart failure - history of hepatic disease - hyperthyroidism

**INTERACTIONS**  → Appendix 1: monoamine-oxidase A and B inhibitors, irreversible

**SIDE-EFFECTS**

- Rare or very rare  Hepatocellular injury
- Frequency not known  Chest pain - diarrhoea - drug dependence - extrasytrole - flushing - hypertension - hypomania - mydriasis - pain - pallor - photophobia - sleep disorder - throbbing headache

**BREAST FEEDING**  Present in milk in animal studies.

**LESS SUITABLE FOR PRESCRIBING**  Less suitable for prescribing.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS  3, 10

- **Tranylcypromine (Non-proprietary)**
  - Tranylcypromine (as Tranylcypromine sulfate) 10 mg  Tranylcypromine 10mg tablets  | 28 tablet  [PO][M]  £311.18 DT = £287.07

### ANTIDEPRESSANTS › MONOAMINE-OXIDASE A INHIBITORS, REVERSIBLE

**Moclobemide**

**DRUG ACTION**  Moclobemide is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA).

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: Initially 300 mg daily in divided doses, adjusted according to response; usual dose 150–600 mg daily, dose to be taken after food

**SOCIAL ANXIETY DISORDER**

- **BY MOUTH**
  - Adult: Initially 300 mg daily for 3 days, then increased to 600 mg daily in 2 divided doses continued for 8–12 weeks to assess efficacy

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises reduce dose to half or one-third of the usual dose with concurrent use of cimetidine.

**CONTRA-INDICATIONS**  Acute confusional states - phaeochromocytoma

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CAUTIONS Avoid in agitated or excited patients (or give with sedative for up to 2–3 weeks) may provoke manic episodes in bipolar disorders • thyrotoxicosis

INTERACTIONS • Appendix 1: moclobemide

SIDE-EFFECTS

Common or very common Anxiety • constipation • diarrhoea • dizziness • dry mouth • headache • hypotension • irritability • nausea • paraesthesia • skin reactions • sleep disorder • vomiting

Uncommon Asthenia • confusion • flushing • oedema • suicidal tendencies • taste altered • visual impairment

Rare or very rare Appetite decreased • delusions • hyponatraemia • serotonin syndrome

PREGNANCY Safety in pregnancy has not been established—manufacturer advises avoid unless there are compelling reasons.

BREAST FEEDING Amount too small to be harmful, but patient information leaflet advises avoid.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (risk of decreased metabolism). Dose adjustments Manufacturer advises dose reduction to half or one-third of the daily dose in severe impairment,

TREATMENT CESSATION Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

PATIENT AND CARER ADVICE Moclobemide is claimed to cause less potentiation of the pressor effect of tyramine than the traditional (irreversible) MAOIs, but patients should avoid consuming large amounts of tyramine-rich food (such as mature cheese, yeast extracts and fermented soya bean products).

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet CAUTIONARY AND ADVISORY LABELS 10, 21

Moclobemide (Non-proprietary)

Moclobemide 150 mg Moclobemide 150mg tablets 30 tablet £22.12 DT + £22.10

Moclobemide 300 mg Moclobemide 300mg tablets 30 tablet £15.00 DT + £13.99

Manerix (Mera Pharmaceuticals Ltd)

Moclobemide 150 mg Manerix 150mg tablets 30 tablet £9.33 DT + £22.10

Moclobemide 300 mg Manerix 300mg tablets 30 tablet £13.99 DT + £13.99

ANTIDEPRESSANTS • NORADRENERGIC REUPTAKE INHIBITORS

Reboxetine

DRUG ACTION Reboxetine is a selective inhibitor of noradrenaline re-uptake.

INDICATIONS AND DOSE

Major depression

BY MOUTH

Adult: 4 mg twice daily for 3–4 weeks, then increased if necessary to 10 mg daily in divided doses; maximum 12 mg per day

CAUTIONS Bipolar disorder • history of cardiovascular disease • history of epilepsy • prostatic hypertrophy • susceptibility to angle-closure glaucoma • urinary retention

INTERACTIONS • Appendix 1: reboxetine

SIDE-EFFECTS

Common or very common Accommodation disorder • akathisia • anxiety • appetite decreased • chills • constipation • dizziness • dry mouth • headache • hyperhidrosis • hypertension • hypotension • insomnia • nausea • palpitations • paraesthesia • sexual dysfunction • skin reactions • tachycardia • taste altered • urinary disorders • urinary tract infection • vasodilation • vomiting

Uncommon Mydriasis • vertigo

Rare or very rare Glaucoma

Frequency not known Aggression • hallucination • hyponatraemia • irritability • peripheral coldness • potassium depletion (long term use) • Raynaud’s phenomenon • suicidal tendencies • testicular pain

PREGNANCY Use only if potential benefit outweighs risk— limited information available.

BREAST FEEDING Small amount present in milk—use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT Manufacturer advises caution (risk of increased exposure). Dose adjustments Manufacturer advises initial dose reduction to 2 mg twice daily, increased according to tolerance.

RENAL IMPAIRMENT Dose adjustments Initial dose 2 mg twice daily, increased according to tolerance.

TREATMENT CESSATION Caution—avoid abrupt withdrawal.

PATIENT AND CARER ADVICE Driving and skilled tasks Counselling advised.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

Edronax (Pfizer Ltd) Reboxetine (as Reboxetine mesilate) 4 mg Edronax 4mg tablets 18 DT £18.91

60 tablet £9.91

ANTIDEPRESSANTS • SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin re-uptake inhibitors

DRUG ACTION Selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT).

CONTRA-INDICATIONS Poorly controlled epilepsy • SSRIs should not be used if the patient enters a manic phase.

CAUTIONS Cardiac disease • concurrent electroconvulsive therapy • diabetes mellitus • epilepsy (discontinue if convulsions develop) • history of bleeding disorders (especially gastro-intestinal bleeding) • history of mania • susceptibility to angle-closure glaucoma

SIDE-EFFECTS

Common or very common Anxiety • appetite abnormal • arthralgia • asthenia • concentration impaired • confusion • constipation • depersonalisation • diarrhoea • dizziness • drowsiness • dry mouth • fever • gastrointestinal discomfort • haemorrhage • headache • hyperhidrosis • malaise • memory loss • menstrual cycle irregularities • myalgia • mydriasis • nausea (dose-related) • palpitations • paraesthesia • QT interval prolongation • sexual dysfunction • skin reactions • sleep disorders • taste altered • tinnitus • tremor • urinary disorders • visual impairment • vomiting • weight changes • yawning

Uncommon Alopecia • angioedema • behaviour abnormal • hallucination • mania • movement disorders

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photosensitivity reaction - postural hypotension - seizure - suicidal tendencies - syncope

- Rare or very rare: Galactorrhoea - hepatitis - hyperprolactinaemia - hypotrichia - serotonin syndrome - severe cutaneous adverse reactions (SCARs) - SIADH - thrombocytopenia

- Frequency not known: Withdrawal syndrome

SIDE-EFFECTS, FURTHER INFORMATION

Overdose

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nyctagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

For details on the management of poisoning, see Selective serotonin re-uptake inhibitors, under Emergency treatment of poisoning p. 1359.

- PREGNANCY: Manufacturers advise avoid during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when taken during early pregnancy. If used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported.

- RENAL IMPAIRMENT: In general, manufacturers advise caution (prolonged half-life).

- TREATMENT CESSATION: Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; palpitation and visual disturbances can occur less commonly. The dose should be tapered over at least a few weeks to avoid these effects. For some patients, it may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist.

- Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more.

- PATIENT AND CARER ADVICE: Driving and skilled tasks: May also impair performance of skilled tasks (e.g. driving, operating machinery).

- CONTRA-INDICATIONS: QT-interval prolongation

- CAUTIONS: Susceptibility to QT-interval prolongation

- INTERACTIONS: Appendix 1: SSRIs

- SIDE-EFFECTS: Common or very common: Acute angle closure glaucoma - apathy - flatulence - hypersalivation - migraine - rhinitis

- Rare or very rare: Cough - generalised tonic-clonic seizure

- Frequency not known: Hypokalaemia

- BREAST FEEDING: Present in milk—with use caution.

- HEPATIC IMPAIRMENT

- Dose adjustments: For tablets, manufacturer advises initial dose of 10 mg daily for the first two weeks in mild to moderate impairment—dose may be increased to max. 20 mg daily; use with extra caution and careful dose titration in severe impairment.

- For oral drops, manufacturer advises initial dose of 8 mg daily for the first two weeks in mild to moderate impairment—dose may be increased to max. 16 mg daily; use with extra caution and careful dose titration in severe impairment.

- RENAL IMPAIRMENT: No information available for eGFR less than 20 mL/minute/1.73 m².

- TREATMENT CESSATION: The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

- DIRECTIONS FOR ADMINISTRATION: Cipramil® oral drops should be mixed with water, orange juice, or apple juice before taking.

- PATIENT AND CARER ADVICE: Counselling on administration of oral drops is advised. Driving and skilled tasks: Patients should be advised of the effects of citalopram on driving and skilled tasks.

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

Oral drops

- EXCIPIENTS: May contain Alcohol

- Cipramil (Lundbeck Ltd)

- Citalopram (as Citalopram hydrobromide) 10 mg Cipramil tablets 28 tablet [PO] £0.00 DT + £0.88

- Citalopram (as Citalopram hydrobromide) 20 mg Cipramil tablets 28 tablet [PO] £0.00 DT + £0.88

- Citalopram (as Citalopram hydrobromide) 40 mg Cipramil tablets 28 tablet [PO] £0.12 DT + £0.96

- Cipramil (Lundbeck Ltd)

- Citalopram (as Citalopram hydrobromide) 20 mg Cipramil tablets 28 tablet [PO] £3.95 DT + £0.88

- Citalopram (as Citalopram hydrobromide) 40 mg Cipramil tablets 28 tablet [PO] £2.96 DT + £0.88

Citalopram (as Citalopram hydrobromide) 20 mg Cipramil tablets 28 tablet [PO] £0.96 DT + £0.88
Escitalopram

**DRUG ACTION** Escitalopram is the active enantiomer of citalopram.

**INDICATIONS AND DOSE**

- **Depressive illness**
  - Generalised anxiety disorder
  - Obsessive-compulsive disorder

  - **BY MOUTH**
    - Adult: 10 mg once daily; increased if necessary up to 20 mg daily
    - Elderly: Initially 5 mg once daily; maximum 10 mg per day

- **Panic disorder**
  - **BY MOUTH**
    - Adult: Initially 5 mg once daily for 7 days, then increased to 10 mg daily; maximum 20 mg per day
    - Elderly: Initially 2.5 mg once daily; maximum 10 mg per day

- **Social anxiety disorder**
  - **BY MOUTH**
    - Adult: Initially 10 mg once daily for 2–4 weeks, dose to be adjusted after 2–4 weeks of treatment; usual dose 5–20 mg daily

**CONTRA-INDICATIONS** QT-interval prolongation

**CAUTIONS** Susceptibility to QT-interval prolongation

**INTERACTIONS** → Appendix 1: SSRIs

**SIDE-EFFECTS**

- Common or very common
  - Sinusitis

- Uncommon
  - Oedema

**BREAST FEEDING** Present in breast milk; avoid.

**HEPATIC IMPAIRMENT**

- **Dose adjustments** Manufacturer advises initially 5 mg once daily for 2 weeks in mild to moderate impairment, thereafter increased to 10 mg once daily according to response; titrate dose with extra caution in severe impairment.

- **RENAL IMPAIRMENT** Caution if eGFR less than 30 ml/minute/1.73m².

- **TREATMENT CESSATION** The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

**DIRECTIONS FOR ADMINISTRATION** Oral drops can be mixed with water, orange juice, or apple juice before taking.

**PATIENT AND CARER ADVICE** Counselling on administration of oral drops advised. Driving and skilled tasks Patients should be counselled about the effects on driving.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Oral drops**

- **Cipralex** (Lundbeck Ltd)
  - Escitalopram (as Escitalopram oxalate) 20 mg per 1 ml

**Tablet**

- **Escitalopram (Non-proprietary)**
  - Escitalopram (as Escitalopram oxalate) 5 mg
  - Escitalopram 5mg tablets | 28 tablet (POD) £8.97 DT + £0.91
  - Escitalopram (as Escitalopram oxalate) 10 mg
  - Escitalopram 10mg tablets | 28 tablet (POD) £14.91 DT + £1.13

- **Cipralex** (Lundbeck Ltd)
  - Escitalopram (as Escitalopram oxalate) 5 mg
  - Cipralex 5mg tablets | 28 tablet (POD) £8.97 DT + £0.91
  - Escitalopram (as Escitalopram oxalate) 10 mg
  - Cipralex 10mg tablets | 28 tablet (POD) £14.91 DT + £1.13

Fluoxetine

**INDICATIONS AND DOSE**

- **Major depression**
  - **BY MOUTH**
    - Adult: Initially 20 mg daily, dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter, daily dose may be administered as a single or divided dose; maximum 60 mg per day
    - Elderly: Initially 20 mg daily, dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter, daily dose may be administered as a single or divided dose, usual maximum dose is 40 mg daily but doses up to 60 mg daily can be used

- **Bulimia nervosa**
  - **BY MOUTH**
    - Adult: 60 mg daily, daily dose may be administered as a single or divided dose
    - Elderly: Up to 40 mg daily, daily dose may be administered as a single or divided dose, usual maximum dose is 40 mg daily but doses up to 60 mg daily can be used

- **Obsessive-compulsive disorder**
  - **BY MOUTH**
    - Adult: 20 mg daily, increased if necessary up to 60 mg daily, daily dose may be administered as a single or divided dose, dose to be increased gradually, review treatment if inadequate response after 10 weeks; maximum 60 mg per day
    - Elderly: 20 mg daily, increased if necessary up to 40 mg daily, daily dose may be administered as a single or divided dose, dose to be increased gradually, review treatment if inadequate response after 10 weeks, usual maximum dose is 40 mg daily but doses up to 60 mg daily can be used

- **Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen)**
  - **BY MOUTH**
    - Adult: 20 mg once daily

**PHARMACOKINETICS**

- Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage).

**UNLICENSED USE**

- Fluoxetine is used for menopausal symptoms, but it is not licensed for this indication.

**INTERACTIONS** → Appendix 1: SSRIs

**SIDE-EFFECTS**

- **Common or very common**
  - Chills · feeling abnormal · postmenopausal haemorrhage · uterine disorder · vasodilation · vision blurred

- **Uncommon**
  - Cold sweat · dysphagia · dyspnoea · hypotension · mood altered · muscle twitching · self-injurious behaviour · temperature sensation altered · thinking abnormal

- **Rare or very rare**
  - Buccoglossal syndrome · leucopenia · neutropenia · esophageal pain · pharyngitis · respiratory disorders · serum sickness · speech disorder · vasculitis

- **Frequency not known**
  - Bone fracture

**BREAST FEEDING** Present in milk—avoid.

**HEPATIC IMPAIRMENT**

- **Dose adjustments** Manufacturer advises dose reduction or increasing dose interval.

**DIRECTIONS FOR ADMINISTRATION** Dispersible tablets can be dispersed in water for administration or swallowed whole with plenty of water.

**PATIENT AND CARER ADVICE** Patients and carers should be counselled on the administration of dispersible tablets.
Driving and skilled tasks Patients should be counselled about the effects on driving and skilled tasks.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- Fluoxetine (Non-proprietary)
  - Fluoxetine (as Fluoxetine hydrochloride) 10 mg: 30 tablet (£44.00 DT = £44.00)

**Dispersible tablet**
- Olena (Fluoxetine hydrochloride) 10 mg: 28 tablet (£3.44 DT = £3.44)

**Oral solution**
- Fluoxetine (Non-proprietary)
  - Fluoxetine (as Fluoxetine hydrochloride) 4 mg per 1 ml: 20mg/5ml oral solution | 70 ml (£12.75 DT = £2.93)
  - Fluoxetine (as Fluoxetine hydrochloride) 20 mg: 20mg/5ml oral solution sugar-free | 70 ml (£12.95 DT = £2.95)
  - Prozac (Eli Lilly and Company Ltd)

**Capsule**
- Fluoxetine (Non-proprietary)
  - Fluoxetine (as Fluoxetine hydrochloride) 10 mg: 30 capsule (£57.34 DT = £44.68)
  - Fluoxetine (as Fluoxetine hydrochloride) 20 mg: 30 capsule (£2.51 DT = £0.93)
  - Faverin (Schering-Plough Ltd)

**Fluoxetine maleate**
- Fluoxetine maleate 100 mg: 30 capsule (£64.00 DT = £2.10)
  - Fluoxetine maleate 50 mg: 30 capsule (£54.36 DT = £1.83)
  - Oxactin (Discovery Pharmaceutical Ltd)

**Fluoxetine**
- Fluoxetine (as Fluoxetine hydrochloride) 20 mg: 30 capsule (£0.72 DT = £0.93)
  - Prozac (Eli Lilly and Company Ltd)

**Interactions**
- Appendix 1: SSRIs
- Appendix 1: SSRI

**Side-effects**
- Rare or very rare: Hepatic function abnormal (discontinue)
- Frequency not known: Bone fracture - glaucoma - neuroleptic malignant-like syndrome - withdrawal syndrome neonatal

**Breast feeding** Present in milk — avoid.

**HEPATIC IMPAIRMENT**
- Dose adjustments: Manufacturer advises low initial dose.

**RENAL IMPAIRMENT**
- Dose adjustments: Start with low dose.

**TREATMENT CESSATION** The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

**Patient and carer advice**
- Driving and skilled tasks: Patients should be counselled about the effects on driving and skilled tasks.

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- Fluoxetine maleate (Non-proprietary)
  - Fluoxetine maleate 50 mg: 60 tablet (£20.98 DT = £17.54)
  - Fluoxetine maleate 100 mg: 30 tablet (£20.98 DT = £17.69)
  - Faverin (Mylan)

**Capsule**
- Fluoxetine maleate 50 mg: 30 tablet (£11.10 DT = £17.54)

**Paroxetine**
- **Indications and Dose**
  - Major depression | Social anxiety disorder | Post-traumatic stress disorder | Generalised anxiety disorder
  - **By mouth**
    - Adult: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 50 mg per day
    - Elderly: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 40 mg per day

**Obsessive-compulsive disorder**
- **By mouth**
  - Adult: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day
  - Elderly: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day

**Panic disorder**
- **By mouth**
  - Adult: Initially 10 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day

**Menopausal symptoms, particularly hot flushes, in women with breast cancer (except those taking tamoxifen)**
- **By mouth**
  - Adult: 10 mg once daily

**Unlicensed use** Paroxetine is used for menopausal symptoms, but it is not licensed for this indication.

**Caution** Achlorhydria - high gastric pH

**Caution** Achlorhydria or high gastric pH Causes reduced absorption of the oral suspension.

**Interactions**
- Appendix 1: SSRIs

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Sertraline

19-Mar-2018

Sertraline (as Sertraline hydrochloride) 10 mg
Paroxetine (as Paroxetine hydrochloride) 20 mg
Paroxetine (as Paroxetine hydrochloride) 30 mg
Paroxetine (as Paroxetine hydrochloride) 40 mg
Paroxetine (as Paroxetine hydrochloride) 20 mg
Paroxetine (as Paroxetine hydrochloride) 30 mg
Paroxetine (as Paroxetine hydrochloride) 40 mg
Paroxetine (as Paroxetine hydrochloride) 20 mg
Paroxetine (as Paroxetine hydrochloride) 30 mg
Paroxetine (as Paroxetine hydrochloride) 40 mg

INDICATIONS AND DOSE

Depressive illness
- Adult: Initially 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maintenance 50 mg daily; maximum 200 mg per day

Obsessive-compulsive disorder
- Adult: Initially 50 mg daily, then increased in steps of 50 mg at intervals of at least 1 week if required; maximum 200 mg per day

Panic disorder | Post-traumatic stress disorder | Social anxiety disorder
- Adult: Initially 25 mg daily for 1 week, then increased to 50 daily, then increased in steps of 50 mg at intervals of at least 1 week if required, increase only if response is partial and if drug is tolerated; maximum 200 mg per day

INTERACTIONS
- Appendix 1: SSRIs

SIDE-EFFECTS
- Common or very common: Chest pain, depression, gastrointestinal disorders, increased risk of infection, neumosuscular dysfunction, vasodilation
- Uncommon: Back pain, buping, chills, cold sweat, dysphagia, dyspnea, ear pain, euphoric mood, hypertention, hypothyroidism, migraine, muscle complaints, muscle weakness, oedema, oral disorders, osteoarthritiis, peripheral oedema, respiratory disorders, sensation abnormal, speech disorder, thinking abnormal, thirst
- Rare or very rare: Balanoposthitis, bone disorder, cardiac disorder, coma, conversion disorder, diabetes mellitus, drug dependence, dysphonia, eye disorders, gait abnormal, genital discharge, glaucoma, hair texture abnormal, hepatic disorders, hiccups, hypercholesterolaemia, hypoglycaemia, injury, lymphadenopathy, myocardial infarction, neoplasm, oliguria, peripheral ischaemia, psychotic disorder, vasodilation procedure, vision disorders, vulvovaginal atrophy
- Frequency not known: Cerebrovascular insufficiency, gynaecomastia, hyperglycaemia, leucopenia, neuroleptic malignant syndrome, pancreatitis

BREAST FEEDING
- Not known to be harmful but consider discontinuing breast-feeding.

HEPATIC IMPAIRMENT
- Manufacturer advises avoid in severe impairment (no information available).

RENAL IMPAIRMENT
- Use with caution.

TREATMENT CESSATION
- The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

PATIENT AND CARER ADVICE
- Driving and skilled tasks: Patients should be counselled about the effects on driving.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Oral suspension

CAUTIONARY AND ADVISORY LABELS
- 5, 21

Sertraline (as Sertraline hydrochloride) 50 mg/10 ml liquid sugar-free | 150 ml (Pfizer) £3.12 DT = £9.12

Tablet

CAUTIONARY AND ADVISORY LABELS
- 21

Paroxetine (as Paroxetine hydrochloride) 10 mg Paroxetine 10mg tablets | 28 tablet (Pfizer) £1.03 DT = £5.69
Paroxetine (as Paroxetine hydrochloride) 20 mg Paroxetine 20mg tablets | 30 tablet (Pfizer) £1.17 DT = £5.12
Paroxetine (as Paroxetine hydrochloride) 30 mg Paroxetine 30mg tablets | 30 tablet (Pfizer) £1.26 DT = £6.79
Paroxetine (as Paroxetine hydrochloride) 40 mg Paroxetine 40mg tablets | 28 tablet (Pfizer) £1.39 DT = £6.03 DT = £17.03 | 30 tablet (Pfizer) £18.25-25.07
Sertraline (as Sertraline hydrochloride) 10 mg Seroxat 10mg tablets | 28 tablet (Pfizer) £1.42 DT = £5.69
Sertraline (as Sertraline hydrochloride) 20 mg Seroxat 20mg tablets | 30 tablet (Pfizer) £1.52 DT = £6.12
Sertraline (as Sertraline hydrochloride) 30 mg Seroxat 30mg tablets | 30 tablet (Pfizer) £2.74 DT = £7.79
Generalised mental health disorders

368 Mental health disorders

### Generalised anxiety disorder

- **BY MOUTH**
- Adult: Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day

### Diabetic neuropathy

- **BY MOUTH**
- Adult: 60 mg once daily, discontinue if inadequate response after 2 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day

### Moderate to severe stress urinary incontinence

- **BY MOUTH**
- Adult (female): 40 mg twice daily, patient should be assessed for benefit and tolerability after 2–4 weeks, alternatively initially 20 mg twice daily for 2 weeks, this can minimise side effects, then increased to 40 mg twice daily, the patient should be assessed for benefit and tolerability after 2–4 weeks.

#### CAUTIONS
- Bleeding disorders - cardiac disease - elderly - history of seizures - hypertension (avoid if uncontrolled) - raised intra-ocular pressure - susceptibility to angle-closure glaucoma

#### INTERACTIONS
- Appendix 1: duloxetine

#### SIDE-EFFECTS
- Common or very common
  - Anxiety, appetite decreased - constipation - diarrhoea - dizziness - drowsiness - dry mouth - fall - fatigue - flushing - gastrointestinal discomfort - gastrointestinal disorders - headache - muscle complaints - nausea - pain - palpitations - paraesthesia - sexual dysfunction - skin reactions - sleep disorders - sweat changes - tinnitus - tremor - urinary disorders - vision disorders - vomiting - weight changes - yawning
- Uncommon
- Rare or very rare

#### PREGNANCY
- Toxicity in animal studies—avoid in patients with stress urinary incontinence; in other conditions use only if potential benefit outweighs risk. Risk of neonatal withdrawal symptoms if used near term.

#### BREAST FEEDING
- Present in milk—manufacturer advises avoid.

#### HEPATIC IMPAIRMENT
- Manufacturer advises avoid.

#### RENAL IMPAIRMENT
- Avoid if eGFR less than 30/minute/1.73 m²

#### TREATMENT CESSATION
- Nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances, and tremor are the most common features of abrupt withdrawal or marked reduction of the dose; dose should be reduced over at least 1–2 weeks.

#### NATIONAL FUNDING/ACCESS DECISIONS
- Cymbalta®

**Scottish Medicines Consortium (SMC) decisions**

- With oral use for Diabetic neuropathy The Scottish Medicines Consortium has advised (September 2006) that duloxetine (Cymbalta®) should be restricted for use by specialists when other treatments for diabetic peripheral neuropathic pain are unsuitable or inadequate.

#### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

1. **Gastro-resistant capsule**
   - **Duloxetine (Non-proprietary)**
   - Duloxetine (as Duloxetine hydrochloride) 20 mg: Duloxetine 20 mg gastro-resistant capsules | 28 capsule (DT = £3.53)
   - Duloxetine (as Duloxetine hydrochloride) 30 mg: Duloxetine 30 mg gastro-resistant capsules | 28 capsule (DT = £3.53)
   - Duloxetine (as Duloxetine hydrochloride) 40 mg: Duloxetine 40 mg gastro-resistant capsules | 56 capsule (DT = £5.40)
   - Duloxetine (as Duloxetine hydrochloride) 60 mg: Duloxetine 60 mg gastro-resistant capsules | 28 capsule (DT = £2.37)

2. **Cymbalta® (Eli Lilly and Company Ltd)**
   - Duloxetine (as Duloxetine hydrochloride) 30 mg: Cymbalta 30 mg gastro-resistant capsules | 28 capsule (DT = £1.68)
   - Duloxetine (as Duloxetine hydrochloride) 60 mg: Cymbalta 60 mg gastro-resistant capsules | 28 capsule (DT = £2.37)

3. **Depalta® (Disposable Medical Equipment Ltd)**
   - Duloxetine (as Duloxetine hydrochloride) 30 mg: Depalta 30 mg gastro-resistant capsules | 28 capsule (DT = £1.68)
   - Duloxetine (as Duloxetine hydrochloride) 60 mg: Depalta 60 mg gastro-resistant capsules | 28 capsule (DT = £2.37)

4. **Duciltia® (Aristo Pharma Ltd)**
   - Duloxetine (as Duloxetine hydrochloride) 30 mg: Duciltia 30 mg gastro-resistant capsules | 28 capsule (DT = £1.68)
   - Duloxetine (as Duloxetine hydrochloride) 60 mg: Duciltia 60 mg gastro-resistant capsules | 28 capsule (DT = £2.37)

5. **Dutor® (Torrent Pharma (UK) Ltd)**
   - Duloxetine (as Duloxetine hydrochloride) 20 mg: Dutor 20 mg gastro-resistant capsules | 28 capsule (DT = £3.53)
   - Duloxetine (as Duloxetine hydrochloride) 30 mg: Dutor 30 mg gastro-resistant capsules | 28 capsule (DT = £1.68)
   - Duloxetine (as Duloxetine hydrochloride) 40 mg: Dutor 40 mg gastro-resistant capsules | 28 capsule (DT = £2.37)

6. **Yentreve® (Eli Lilly and Company Ltd)**
   - Duloxetine (as Duloxetine hydrochloride) 20 mg: Yentreve 20 mg gastro-resistant capsules | 28 capsule (DT = £3.53)
   - Duloxetine (as Duloxetine hydrochloride) 40 mg: Yentreve 40 mg gastro-resistant capsules | 56 capsule (DT = £5.40)

### Venlafaxine

- **DRUG ACTION** A serotonin and noradrenaline re-uptake inhibitor.

1. **INDICATIONS AND DOSE**

#### Major depression

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 75 mg daily in 2 divided doses, then increased if necessary up to 375 mg daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Initially 75 mg once daily, increased if necessary up to 375 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day

#### Generalised anxiety disorder

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 75 mg once daily, increased if necessary up to 225 mg once daily, dose to be increased at intervals of at least 2 weeks; maximum 225 mg per day

#### Social anxiety disorder

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 75 mg once daily, there is no evidence of greater efficacy at higher doses, increased if necessary up to 225 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks; maximum 225 mg per day

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Menopausal symptoms, particularly hot flushes, in women with breast cancer

- **UNLICENSED USE** Venlafaxine is used for menopausal symptoms, but it is not licensed for this indication.
- **CONTRA-INDICATIONS** Conditions associated with high risk of cardiac arrhythmia - uncontrolled hypertension
- **CAUTIONS** Diabetes - heart disease (monitor blood pressure) - history of bleeding disorders - history of epilepsy - history or family history of mania - susceptibility to angle-closure glaucoma
- **INTERACTIONS** → Appendix 1: venlafaxine
- **SIDE-EFFECTS**
  - **Common or very common** Anxiety - appetite decreased - arrhythmias - asthenia - chills - confusion - constipation - depersonalisation - diarrhea - diziness - dry mouth - dysphoria - headache - hot flush - hypertension - menstrual cycle irregularities - movement disorders - muscle tone increased - mydriasis - nausea - palpitations - paroxysmal sympathetic hyperhidrosis - parasomnia - personality disorders - sleep disorders - sweat changes - taste altered - tinnitus - tremor - urinary disorders - vision disorders - vomiting - weight changes - yawning
  - **Uncommon** Alopecia - angioedema - apathy - behaviour abnormal - derealisation - haemorrhage - hallucination - hypotension - mood altered - photosensitivity reaction - syncope
- **Rare or very rare** Agranulocytosis - angle closure glaucoma - bone marrow disorders - delirium - hepatitis - hyponatraemia - neuroleptic malignant syndrome - neutropenia - pancreatitis - QT interval prolongation - respiratory disorders - rhabdomyolysis - seizure - serotonin syndrome - severe cutaneous adverse reactions (SCARs) - SIADH - thrombocytopenia
- **FREQUENCY NOT KNOWN** Suicidal tendencies - vertigo - withdrawal syndrome
- **PREGNANCY** Avoid unless potential benefit outweighs risk - toxicity in animal studies. Risk of withdrawal effects in neonate.
- **BREAST FEEDING** Present in milk - avoid.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution (inter-individual variability in clearance; limited information available in severe impairment).
- **Dose adjustments** Manufacturer advises consider dose reduction of 50% in mild to moderate impairment and of more than 50% in severe impairment.
- **RENAL IMPAIRMENT** Use with caution.
- **TREATMENT CESSION** Associated with a higher risk of withdrawal effects compared with other antidepressants. Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, tremor, sleep disturbances, and sweating are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks.
- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** May affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Modiﬁed-release tablet**

- **CAUTIONARY AND ADVISORY LABELS** 3, 21, 25
  - **Sunveniz XL** (Sun Pharmaceutical Industries Europe B.V.)
    - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Sunveniz XL
      - 75 mg tablets | 30 tablet [PST] £11.10 DT = £2.60
      - 75 mg tablets | 150 tablet [PST] £18.64 DT = £3.90
  - **Venladas XL** (Dexcel-Pharma Ltd)
    - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venladas XL
      - 75 mg tablets | 28 tablet [PST] £11.70 DT = £2.43
      - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venladas XL
        - 150 mg tablets | 28 tablet [PST] £18.70 DT = £4.24

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 3
  - **Venlafaxine (Non-proprietary)**
    - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venlafaxine
      - 75 mg tablets | 30 tablet [PST] £6.60 DT = £1.60
    - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venlafaxine
      - 150 mg tablets | 30 tablet [PST] £13.30 DT = £3.30
    - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venlafaxine
      - 75 mg tablets | 56 tablet [PST] £6.00 DT = £3.40
    - **ViePax XL** (Dexcel-Pharma Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg ViePax XL
        - 75 mg tablets | 28 tablet [PST] £2.60
      - Venlafaxine (as Venlafaxine hydrochloride) 150 mg ViePax XL
        - 150 mg tablets | 28 tablet [PST] £3.90
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg ViePax XL
        - 75 mg tablets | 56 tablet [PST] £5.13 DT = £3.40

**Modified-release capsule**

- **CAUTIONARY AND ADVISORY LABELS** 3, 21, 25
  - **Venlafaxine (Non-proprietary)**
    - Venlafaxine (as Venlafaxine hydrochloride) 225 mg Venlafaxine
      - 225 mg modified-release capsules | 30 capsule [PST] £44.75
    - **Alvena XL** (Consiient Health Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Alvena XL
        - 75 mg capsules | 28 capsule [PST] £13.12 DT = £2.60
    - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Alvena XL
      - 150 mg capsules | 28 capsule [PST] £31.88 DT = £3.90
    - **Apclaven XL** (Torrent Pharma (UK) Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Apclaven XL
        - 75 mg capsules | 28 capsule [PST] £8.25 DT = £2.25
    - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Apclaven XL
      - 150 mg capsules | 28 capsule [PST] £15.00 DT = £3.90
    - **Depofex XL** (Chiesi Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Depofex XL
        - 75 mg capsules | 28 capsule [PST] £10.40 DT = £2.60
    - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Depofex XL
      - 150 mg capsules | 28 capsule [PST] £17.00 DT = £3.90
    - **Eferox XL** (Pfizer Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Eferox XL
        - 75 mg capsules | 28 capsule [PST] £12.08 DT = £2.60
    - Venlafaxine (as Venlafaxine hydrochloride) 150 mg Eferox XL
      - 150 mg capsules | 28 capsule [PST] £36.81 DT = £3.90
    - Venlafaxine (as Venlafaxine hydrochloride) 225 mg Eferox XL
      - 225 mg capsules | 28 capsule [PST] £47.11 DT = £4.71
    - **Majovex XL** (Bristol Laboratories Ltd)
      - Venlafaxine (as Venlafaxine hydrochloride) 75 mg Majovex XL
        - 75 mg capsules | 28 capsule [PST] £5.25 DT = £0.25
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Majoven XL 75mg capsules | 28 capsule (Pkt) £2.08 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Majoven XL 150mg capsules | 28 capsule (Pkt) £3.81 DT = £3.90
• Politid XL (Actsavis UK Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Politid XL 75mg capsules | 28 capsule (Pkt) £23.41 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Politid XL 150mg capsules | 28 capsule (Pkt) £39.03 DT = £3.90
• Tonpular XL (Wockhardt UK Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Tonpular XL 75mg capsules | 28 capsule (Pkt) £7.00 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Tonpular XL 150mg capsules | 28 capsule (Pkt) £12.00 DT = £3.90
• Venaxx XL (Advanz Pharma)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venaxx XL 75mg capsules | 28 capsule (Pkt) £10.40 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venaxx XL 150mg capsules | 28 capsule (Pkt) £17.40 DT = £3.90
• Vencarm XL (Aspire Pharma Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg Vencarm XL 37.5mg capsules | 28 capsule (Pkt) £3.30 DT = £5.25
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Vencarm XL 75mg capsules | 28 capsule (Pkt) £5.29 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Vencarm XL 150mg capsules | 28 capsule (Pkt) £5.89 DT = £3.90
Venlafaxine (as Venlafaxine hydrochloride) 225 mg Vencarm XL 225mg capsules | 28 capsule (Pkt) £19.90 DT = £47.11
• Venlable XL (Cayo Pharma Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg Venlable XL 37.5mg capsules | 28 capsule (Pkt) £5.25 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venlable XL 75mg capsules | 28 capsule (Pkt) £5.75 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venlable XL 150mg capsules | 28 capsule (Pkt) £9.95 DT = £3.90
• Venlason XL (Sovereign Medical Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venlason XL 75mg capsules | 28 capsule (Pkt) £2.45 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venlason XL 150mg capsules | 28 capsule (Pkt) £3.75 DT = £3.90
• Vennir XL (Morningside Healthcare Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Vensir XL 75mg capsules | 28 capsule (Pkt) £2.60 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Vensir XL 150mg capsules | 28 capsule (Pkt) £3.90 DT = £3.90
Venlafaxine (as Venlafaxine hydrochloride) 225 mg Vensir XL 225mg capsules | 28 capsule (Pkt) £21.90 DT = £47.11
• Venzip XL (Milpharm Ltd)
Venlafaxine (as Venlafaxine hydrochloride) 75 mg Venzip XL 75mg capsules | 28 capsule (Pkt) £2.08 DT = £2.60
Venlafaxine (as Venlafaxine hydrochloride) 150 mg Venzip XL 150mg capsules | 28 capsule (Pkt) £3.81 DT = £3.90

ANTIDEPRESSANTS > SEROTONIN UPTAKE INHIBITORS

Trazodone hydrochloride

INDICATIONS AND DOSE
Depressive illness (particularly where sedation is required)

BY MOUTH
Adult: Initially 150 mg daily in divided doses, dose to be taken after food, alternatively initially 150 mg once daily, dose to be taken at bedtime, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only
Elderly: Initially 100 mg daily in divided doses, dose to be taken after food, alternatively initially 100 mg once daily, dose to be taken at bedtime, increased if necessary to 300 mg daily; increased if necessary to 600 mg daily in divided doses, higher dose for use in hospital patients only

Anxiety

BY MOUTH
Adult: 75 mg daily, increased if necessary to 300 mg daily

CONTRA-INDICATIONS Arhythmias; during the manic phase of bipolar disorder; heart block; immediate recovery period after myocardial infarction

CAUTIONS Cardiovascular disease; chronic constipation; diabetes; epilepsy; history of bipolar disorder; history of psychosis; hyperthyroidism (risk of arrhythmias); increased intra-ocular pressure; patients with a significant risk of suicide; phaeochromocytoma (risk of arrhythmias); prostatic hypertrophy; susceptibility to angle-closure glaucoma; urinary retention

CAUTIONS, FURTHER INFORMATION Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

INTERACTIONS Appendix 1: trazodone

SIDE-EFFECTS Agitation; agranulocytosis; alertness decreased; anaemia; anxiety; apathy; appetite abnormal; arrhythmias; arthralgia; asthenia; blood disorder; chest pain; confusion; constipation; delirium; delusions; diarrhoea; dizziness; drowsiness; dry mouth; dyspnoea; eosinophilia; fever; gastroenteritis; gastrointestinal discomfort; hallucination; headache; hepatic disorders; hyperhidrosis; hypersalivation; hypertension; hypogonadism; influenza like illness; jaundice (discontinue); leucopenia; libido decreased; mania; memory loss; movement disorders; myalgia; nasal congestion; nausea; neuroleptic malignant syndrome; oedema; pain; palpitations; paraesthesia; paralytic ileus; postural hypotension; priapism (discontinue); QT interval prolongation; seizure; serotonin syndrome; SIADH; skin reactions; sleep disorders; suicidal tendencies; syncope; taste altered; thrombocytopenia; tremor; urinary disorder; vertigo; vision blurred; vomiting; weight decreased; withdrawal syndrome

SIDE-EFFECTS, FURTHER INFORMATION The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

Overdose The tricyclic-related antidepressant drugs may be associated with a lower risk of cardiotoxicity in overdose.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1359.

PREGNANCY Avoid during first trimester—limited information available. Monitor infant for signs of withdrawal if used until delivery.

BREAST FEEDING The amount secreted into breast milk is too small to be harmful.

HEPATIC IMPAIRMENT Manufacturer advises caution, particularly in severe impairment (increased risk of side-effects).

RENAL IMPAIRMENT Use with caution in severe impairment.

TREATMENT CESSATION Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is
increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricylic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).
  - Effects of alcohol enhanced.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS** 3, 21
  - **Trazodone hydrochloride (Non-proprietary)**
    - **Trazodone hydrochloride 10 mg per 1 ml** Tracodone 50mg/5ml oral solution sugar free sugar-free | 120 ml (POM) £37.09–£80.00 DT + £37.09
    - **Trazodone hydrochloride 20 mg per 1 ml** Trazodone 100mg/5ml oral solution sugar free sugar-free | 120 ml (POM) £55.00–£195.60 DT + £175.30

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 3, 21
    - **Trazodone hydrochloride (Non-proprietary)**
      - **Trazodone hydrochloride 150 mg** Tracodone 150mg tablets | 28 tablet (POM) £34.00 DT + £4.69
    - **Molipaxin (Zentiva)**
      - **Trazodone hydrochloride 150 mg** Molipaxin 150mg tablets | 28 tablet (POM) £16.08 DT + £4.69

- **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 2, 21
    - **Trazodone hydrochloride 50 mg** Tracodone 50mg capsules | 84 capsule (POM) £35.00 DT + £5.22
    - **Trazodone hydrochloride 100 mg** Tracodone 100mg capsules | 56 capsule (POM) £41.00 DT + £5.69
    - **Molipaxin (Zentiva)**
      - **Trazodone hydrochloride 50 mg** Molipaxin 50mg capsules | 84 capsule (POM) £23.92 DT + £5.22
      - **Trazodone hydrochloride 100 mg** Molipaxin 100mg capsules | 56 capsule (POM) £28.14 DT + £5.69

**Antidepressants**

- **Tetracyclic Antidepressants**

  - **Mianserin hydrochloride**

    - **INDICATIONS AND DOSE**
      - **Depressive illness (particularly where sedation is required)**
        - **By mouth**
          - **Adult:** Initially 30–40 mg daily in divided doses, alternatively initially 30–40 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg
          - **Elderly:** Initially 30 mg daily in divided doses, alternatively initially 30 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg

    - **Contra-Indications**
      - Acute porphyrias p. 1058 • arrhythmias • during the manic phase of bipolar disorder • heart block • immediate recovery period after myocardial infarction

    - **CAUTIONS**
      - Cardiovascular disease • chronic constipation • diabetes • epilepsy • history of bipolar disorder • history of psychosis • hyperthyroidism (risk of arrhythmias) • increased intra-ocular pressure • patients with a significant risk of suicide • phaeochromocytoma (risk of arrhythmias) • prostatic hypertrophy • susceptibility to angle-closure glaucoma • urinary retention

Caution: Further information

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS**
  - Acid-base balance

- **SIDE-EFFECTS**
  - Agranulocytosis • arthritis • bone marrow disorders • breast abnormalities • diziness • granulocytopenia • gynaecomastia • hepatic disorders • hyperhidrosis • hyponatraemia • joint disorders • lactation in absence of pregnancy • leucopenia • mood altered • neuromuscular irritability • oedema • paranoid delusions • postural hypotension • psychosis • rash • seizure • sexual dysfunction • suicidal tendencies • tremor • withdrawal syndrome

Caution: Further information

The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose**

The tricyclic-related antidepressant drugs may be associated with a lower risk of cardioexcitotoxicity in overdosage.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypoesthesia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1359.

- **Pregnancy**

  - Avoid.

- **Breastfeeding**

  - The amount secreted into breast milk is too small to be harmful.

- **Hepatic Impairment**

  - Manufacturer advises caution; avoid in severe impairment.

- **Renal Impairment**

  - Dose adjustments Caution in renal impairment.

- **Monitoring Requirements**

  - A full blood count is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis, or other signs of infection develop.

  - **Treatment Cessation**

    - Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

  - **Prescribing and Dispensing Information** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

  - **Patient and Carer Advice**

    - **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

    - Effects of alcohol enhanced.

www.getintopharma.com
Nervous system

PATIENT AND CARER ADVICE

TREATMENT CESSATION

RENAL IMPAIRMENT
BREAST FEEDING

SIDE-EFFECTS

PATIENT AND CARER ADVICE

Side effects

Patients should be advised to report any side effect.

Blood Disorders Patients should be advised to report any fever, sore throat, stomatitis or other signs of infection during treatment. Blood count should be performed and the drug stopped immediately if blood dyscrasia suspected.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 2, 25

Mianserin hydrochloride (Non-proprietary)

Mianserin hydrochloride 10 mg Mianserin 10mg tablets
28 tablet (PO) £14.75 DT + £13.58
Mianserin hydrochloride 30 mg Mianserin 30mg tablets
28 tablet (PO) £33.45 DT + £30.82

Mirtazapine

DRUG ACTION Mirtazapine is a presynaptic alpha₂-adrenoreceptor antagonist which increases central noradrenergic and serotonergic neurotransmission.

INDICATIONS AND DOSE

Major depression

BY MOUTH

Adult: Initially 15–30 mg daily for 2–4 weeks, dose to be taken at bedtime, then adjusted according to response to up to 45 mg once daily, alternatively up to 45 mg daily in 2 divided doses

Caution

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 2, 25

Mirtazapine (Non-proprietary)

Mirtazapine 15 mg Mirtazapine 15mg tablets 28 tablet (PO) £4.60 DT + £1.23
Mirtazapine 30 mg Mirtazapine 30mg tablets 28 tablet (PO) £4.50 DT + £1.07
Mirtazapine 45 mg Mirtazapine 45mg tablets 28 tablet (PO) £4.95 DT + £1.36

Oral solution

CAUTIONARY AND ADVISORY LABELS 2

Mirtazapine (Non-proprietary)

Mirtazapine 15 mg per 1 ml Mirtazapine 15mg/ml oral solution sugar free sugar-free 66 ml (PO) £43.51 DT + £48.51

Orodispersible tablet

CAUTIONARY AND ADVISORY LABELS 2

EXCIPIENTS: May contain Aspartame

Mirtazapine (Non-proprietary)

Mirtazapine 15 mg Mirtazapine 15mg orodispersible tablets 30 tablet (PO) £15.19 DT + £1.83
Mirtazapine 30 mg Mirtazapine 30mg orodispersible tablets 30 tablet (PO) £15.19 DT + £2.00
Mirtazapine 45 mg Mirtazapine 45mg orodispersible tablets 30 tablet (PO) £15.19 DT + £2.07

Zispin SolTab (Merck Sharp & Dohme Ltd)

Mirtazapine 15 mg Zispin SolTab 15mg orodispersible tablets 30 tablet (PO) £15.06 DT + £1.83
Mirtazapine 30 mg Zispin SolTab 30mg orodispersible tablets 30 tablet (PO) £15.06 DT + £2.00
Mirtazapine 45 mg Zispin SolTab 45mg orodispersible tablets 30 tablet (PO) £15.06 DT + £2.07

ANTIDEPRESSANTS TRICYCLIC

Antidepressants

Amitriptyline hydrochloride

INDICATIONS AND DOSE

Abdominal pain or discomfort (in patients who have not responded to laxatives, loperamide, or antispasmodics)

BY MOUTH

Adult: Initially 5–10 mg daily, to be taken at night; increased in steps of 10 mg at least every 2 weeks as required; maximum 30 mg per day

Major depressive disorder [not recommended—increased risk of fatality in overdose]

BY MOUTH

Adult: Initially 50 mg daily in 2 divided doses, then increased in steps of 25 mg once daily on alternate days if required, maximum 150 mg daily in 2 divided doses

Major depressive disorder in patients with cardiovascular disease [not recommended—increased risk of fatality in overdose]

BY MOUTH

Adult: Initially 10–25 mg daily, increased if necessary up to 100–150 mg daily in 2 divided doses, dose increases dependent on individual patient response and tolerability—doses above 100 mg should be used with caution

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Neuropathic pain | Migraine prophylaxis | Chronic tension-type headache prophylaxis

- **BY MOUTH**
- **Adult:** Initially 10–25 mg daily, dose to be taken in the evening, then increased, if tolerated, in steps of 10–25 mg every 3–7 days in 1–2 divided doses; usual dose 25–75 mg daily, dose to be taken in the evening, doses above 100 mg should be used with caution (doses above 75 mg should be used with caution in the elderly and in patients with cardiovascular disease); maximum per dose 75 mg

- **UNLICENSED USE** Not licensed for use in abdominal pain or discomfort in patients who have not responded to laxatives, loperamide, or antispasmodics
- **CONTRA-INDICATIONS** Arrhythmias - during manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction
- **CAUTIONS** Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS** → Appendix 1: tricyclic antidepressants

**SIDE-EFFECTS**

- **Common or very common** Anticholinergic syndrome · drowsiness · QT interval prolongation
- **Frequency not known** Agranulocytosis · alopecia · anxiety · appetite abnormal · arrhythmias · asthma · bone marrow depression · breast enlargement · cardiac conduction disorders · coma · concentration impaired · confusion · constipation · delirium · delusions · diarrhea · diziness · dry mouth · dysarthria · eosinophilia · epigastric distress · face oedema · galactorrhoea · gynaecomastia · hallucination · headache · hepatic disorders · hyperhidrosis · hyperepyrexia · hypertension · hypoponataemia · hypotension · leucopenia · mood altered · movement disorders · mydriasis · myocardial infarction · nausea · neuroleptic malignant syndrome · oral disorders · palpitations · paralytic ileus · peripheral neuropathy · photosensitivity reaction · seizure · sensation abnormal · sexual dysfunction · SIADH · skin reactions · sleep disorders · stroke · sudden cardiac death · suicidal tendencies · syncpe · taste altered · testicular swelling · thrombocytopenia · tinnitus · tremor · urinary disorders · urinary tract dilatation · vision disorders · vomiting · weight changes · withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Overdosage with amitriptyline is associated with a relatively high rate of fatality. Symptoms of overdosage may include dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning, see Tricyclic and related antidepressants, under Emergency treatment of poisoning p. 1359.

**PREGNANCY** Use only if potential benefit outweighs risk.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Manufacturer advises use with caution in mild-to-moderate impairment; avoid in severe impairment.
- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE** Driving and skilled tasks Drowsiness may affect the performance of skilled tasks (e.g. driving).

- Effects of alcohol enhanced.

**LESS SUITABLE FOR PRESCRIBING** Amitriptyline hydrochloride is less suitable for prescribing, see Tricyclic and related antidepressant drugs in Antidepressant drugs p. 359.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

| CAUTIONARY AND ADVISORY LABELS 2 |
| Amtriptyline hydrochloride (Non-proprietary) |
| Amtriptyline hydrochloride 2 mg per 1 ml | Amitriptyline 10mg/5ml oral solution sugar free sugar-free | 150 ml | £131.90 DT = £131.90 |
| Amtriptyline hydrochloride 5 mg per 1 ml | Amitriptyline 25mg/5ml oral solution sugar free sugar-free | 150 ml | £18.00 DT = £18.00 |
| Amtriptyline hydrochloride 10 mg per 1 ml | Amitriptyline 50mg/5ml oral solution sugar free sugar-free | 150 ml | £24.00 DT = £19.20 |

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 2 |
| Amtriptyline hydrochloride (Non-proprietary) |
| Amtriptyline hydrochloride 10 mg | Amitriptyline 10mg tablets | 28 tablet | £1.50 DT = 0.87 |
| Amtriptyline hydrochloride 25 mg | Amitriptyline 25mg tablets | 28 tablet | £1.75 DT = 0.72 |
| Amtriptyline hydrochloride 50 mg | Amitriptyline 50mg tablets | 28 tablet | £5.99 DT = 2.04 |

**Clomipramine hydrochloride** 02-Jul-2018

- **INDICATIONS AND DOSE**
  - **Depressive illness**
    - **BY MOUTH**
      - **Adult:** Initially 10 mg daily, then increased if necessary to 30–150 mg daily in divided doses, dose to be increased gradually, alternatively increased if necessary to 30–150 mg once daily, dose to be taken at bedtime; maximum 250 mg per day
      - **Elderly:** Initially 10 mg daily, then increased to 30–75 mg daily, dose to be increased carefully over approximately 10 days
  - **Phobic and obsessional states**
    - **BY MOUTH**
      - **Adult:** Initially 25 mg daily, then increased to 100–150 mg daily, dose to be increased gradually over 2 weeks; maximum 250 mg per day
Mental health disorders

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 - arrhythmias - during the manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intraocular pressure - patients with a significant risk of suicide - pheochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

- **CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

- **INTERACTIONS** 
  - Appendix 1: tricyclic antidepressants

- **SIDE-EFFECTS**
  - Uncommon: Psychosis - seizure
  - Rare or very rare: Agranulocytosis - alopecia - cardiac conduction disorders - eosinophilia - glaucoma - hepatic disorders - hyperpyrexia - leucopenia - neuroleptic malignant syndrome - oedema - Q-T interval prolongation - respiratory disorders - thrombocytopenia - vaginal haemorrhage
  - Frequency not known: Rhabdomyolysis - serotonin syndrome - suicidal tendencies - withdrawal syndrome

- **SIDE-EFFECTS, FURTHER INFORMATION** The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop.

  The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 3 days). Consider using a lower starting dose in elderly patients.

- **OVERDOSE** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1399.

- **PREGNANCY** Neonatal withdrawal symptoms reported if used during third trimester.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution; avoid in severe impairment (risk of hypertensive crisis).

- **MONITORING REQUIREMENTS** Manufacturer advises monitor cardiac and hepatic function during long-term use.

- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

- **PATIENT AND CARER ADVICE** Driving and skilled tasks: Drowsiness may affect the performance of skilled tasks (e.g. driving).

  Effects of alcohol enhanced.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release tablet, oral suspension, oral solution

**Capsule**

- Clomipramine hydrochloride (Non-proprietary)
  - Clomipramine hydrochloride 10 mg
    - 28 capsule £6.72 OT £1.47
  - Clomipramine hydrochloride 25 mg
    - 28 capsule £9.36 OT £1.62
  - Clomipramine hydrochloride 50 mg
    - 28 capsule £11.76 OT £3.66

**Dosulepin hydrochloride**

- **INDICATIONS AND DOSE** Depressive illness, particularly where sedation is required (not recommended — increased risk of fatality in overdose) (initiated by a specialist)

  - **BY MOUTH**

    - Adult: Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use)

    - Elderly: Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 75–150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use)

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 - arrhythmias - during the manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intraocular pressure - patients with a significant risk of suicide - pheochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

- **CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.
Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS** → Appendix 1: tricyclic antidepressants

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects are reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Overdose with dosulepin is associated with a relatively high rate of fatality.

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning.

- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
- **TREATMENT CESSION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 3 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge. (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

A maximum prescription equivalent to 2 weeks’ supply of 75 mg daily should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dose adjustment, and until improvement occurs.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).
  - Effects of alcohol enhanced.
- **LESS SUITABLE FOR PRESCRIBING** Dosulepin hydrochloride is less suitable for prescribing, see Tricyclic and related antidepressant drugs in Antidepressant drugs p. 359.

**INDICATIONS AND DOSE** Depressive illness (particularly where sedation is required)

- **BY MOUTH**
  - Adult: Initially 75 mg daily in divided doses, alternatively 75 mg once daily, adjusted according to response, dose to taken at bedtime; maintenance 25–300 mg daily, doses above 100 mg given in 3 divided doses
  - Elderly: Start with lower doses and adjust according to response

**CONTRA-INDICATIONS** Acute porphyrias p. 1058 - arrhythmias - during manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

**CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperpyrexia (risk of arrhythmias) - increased intra-ocular pressure - patients with significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

- Elderly Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS** → Appendix 1: tricyclic antidepressants

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose.
effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1359.

- **PREGNANCY** Use with caution—limited information available.
- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful. Accumulation of metabolite may cause sedation and respiratory depression in neonate.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment. Dose adjustments Manufacturer advises consider dose reduction in mild to moderate impairment.
- **RENAI IMPAIRMENT** Use with caution.
- **TREATMENT CESSION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

**Capsule**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of (Non-proprietary)</td>
</tr>
<tr>
<td>Doxepin (as Doxepin hydrochloride) 25 mg</td>
</tr>
<tr>
<td>Dose of (as Doxepin hydrochloride) 50 mg</td>
</tr>
</tbody>
</table>

**Imipramine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Depressive illness**
    - **BY MOUTH**
      - Adult: Initially up to 75 mg daily in divided doses, then increased to 150–200 mg daily, up to 150 mg may be given as a single dose at bedtime, dose to be increased gradually.
      - Elderly: Initially 10 mg daily, increased to 30–50 mg daily, dose to be increased gradually.
    - **Depressive illness in hospital patients**
      - **BY MOUTH**
        - Adult: Initially up to 75 mg daily in divided doses, dose to be increased gradually, increased to up to 300 mg daily in divided doses

- **SIDE-EFFECTS**
  - **INTERACTIONS** 
    - tricyclic antidepressants
  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Contra-indications** Immediate recovery period after myocardial infarction (in adults). Acute porphyria p. 1058 - arrhythmia - during the manic phase of bipolar disorder - heart block

- **CAUTIONS**
  - Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure (in adults) - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy (in adults) - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS**
  - Appendix 1: tricyclic antidepressants

**SIDE-EFFECTS**

- **Common or very common** Anxiety - appetite decreased - arrhythmias - ashen skin - cardiac conduction disorders - confusion - delirium - depression - dizziness - drowsiness - epilepsy - hallucination - headache - hepatic disorders - hypotension - mood altered - nausea - palpitations - paraesthesia - sexual dysfunction - skin reactions - sleep disorder - tremor - vomiting - weight changes

- **Rare or very rare** Anticholinergic syndrome - cardiovascular effects - drug fever - hypotension - increased risk of fracture - neurological effects - paranoid delusions exacerbated - psychiatric disorder - suicidal tendencies - tinnitus - urinary disorder - withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1359.

- **PREGNANCY** Colic, tachycardia, dyspnoea, irritability, muscle spasms, respiratory depression and withdrawal
symptoms reported in neonates when used in the third trimester.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
- **RENAL IMPAIRMENT** Use with caution in severe impairment.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Imipramine for various conditions [www.medicinesforchildren.org.uk/imipramine-various-conditions](http://www.medicinesforchildren.org.uk/imipramine-various-conditions)

**Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

Effects of alcohol enhanced.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS** 2
- **Imipramine hydrochloride (Non-proprietary)**
  - Imipramine hydrochloride 5 mg per 1 ml: Imipramine 25mg/5ml oral solution sugar free sugar-free | 150 ml (PO) £45.00 DT = £45.00

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 2
- **Imipramine hydrochloride (Non-proprietary)**
  - Imipramine hydrochloride 10 mg: Imipramine 10mg tablets | 28 tablet (PO) £0.81 DT = £0.80
  - Imipramine hydrochloride 25 mg: Imipramine 25mg tablets | 28 tablet (PO) £0.83 DT = £0.83

### Lofepramine

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: 140–210 mg daily in divided doses
  - Elderly: May respond to lower doses

**CONTRA-INDICATIONS** Acute porphyrias p. 1058, arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

**CAUTIONS** Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS** → Appendix I: tricyclic antidepressants

**SIDE-EFFECTS** Accommodation disorder · agitation · agranulocytosis · arhythmias · bone marrow disorders · cardiac conduction disorder · confusion · constipation · coordination abnormal · dizziness · drowsiness · dry mouth · eosinophilia · face oedema · galactorrhoea · glaucoma · granulocytopenia · gynaecomastia · hallucination · headache · heart failure aggravated · hepatic disorders · hyperhidrosis (on discontinuation) · hypnataemia · hypotension · increased risk of fracture · leucopenia · malaise · mood altered · mucositis · nausea · paraesthesia · paranoid delusions · photosensitivity reaction · psychosis · respiratory depression · seizure · sexual dysfunction · SIADH · skin haemorrhage · skin reactions · sleep disorder · suicidal tendencies · taste altered · testicular disorders · thrombocytopenia · tinnitus · tremor · urinary disorders · vomiting · withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Lofepramine is associated with the lowest risk of fatality in overdose, in comparison with other tricyclic antidepressant drugs. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 3359.

**PREGNANCY** Neonatal withdrawal symptoms and respiratory depression reported if used during third trimester.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid in severe impairment.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Imipramine for various conditions [www.medicinesforchildren.org.uk/imipramine-various-conditions](http://www.medicinesforchildren.org.uk/imipramine-various-conditions)

**Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

Effects of alcohol enhanced.

**INDICATIONS AND DOSE**

**Depressive illness**

- **BY MOUTH**
  - Adult: 140–210 mg daily in divided doses
  - Elderly: May respond to lower doses

**CONTRA-INDICATIONS** Acute porphyrias p. 1058, arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

**CAUTIONS** Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS** → Appendix I: tricyclic antidepressants

**SIDE-EFFECTS** Accommodation disorder · agitation · agranulocytosis · arhythmias · bone marrow disorders · cardiac conduction disorder · confusion · constipation · coordination abnormal · dizziness · drowsiness · dry mouth · eosinophilia · face oedema · galactorrhoea · glaucoma · granulocytopenia · gynaecomastia · hallucination · headache · heart failure aggravated · hepatic disorders · hyperhidrosis (on discontinuation) · hypnataemia · hypotension · increased risk of fracture · leucopenia · malaise · mood altered · mucositis · nausea · paraesthesia · paranoid delusions · photosensitivity reaction · psychosis · respiratory depression · seizure · sexual dysfunction · SIADH · skin haemorrhage · skin reactions · sleep disorder · suicidal tendencies · taste altered · testicular disorders · thrombocytopenia · tinnitus · tremor · urinary disorders · vomiting · withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

**Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Lofepramine is associated with the lowest risk of fatality in overdose, in comparison with other tricyclic antidepressant drugs. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 3359.

**PREGNANCY** Neonatal withdrawal symptoms and respiratory depression reported if used during third trimester.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid in severe impairment.

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Imipramine for various conditions [www.medicinesforchildren.org.uk/imipramine-various-conditions](http://www.medicinesforchildren.org.uk/imipramine-various-conditions)

**Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

Effects of alcohol enhanced.
Nervous system

SIDE-EFFECTS

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Contraindications

Unlicensed use

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Oral suspension

Lofepramine (as Lofepramine hydrochloride) 14 mg per 1 ml Lofepramine 70mg/Sml oral suspension sugar free sugar-free | 150 ml PDP £30.00 DT £30.00

Tablet

Lofepramine (as Lofepramine hydrochloride) 70 mg Lofepramine 70mg tablets | SE tablet PDP £39.97 DT £117.41

Nortriptyline

INDICATIONS AND DOSE

Depressive illness

BY MOUTH

Adult: To be initiated at a low dose, then increased if necessary to 75–100 mg daily in divided doses, alternatively increased if necessary to 75–100 mg once daily; maximum 150 mg per day

Elderly: To be initiated at a low dose, then increased if necessary to 30–50 mg daily in divided doses

Neuropathic pain

BY MOUTH

Adult: Initially 10 mg once daily, to be taken at night, increased if necessary to 75 mg daily, dose to be increased gradually; higher doses to be given under specialist supervision

Unlicensed use

Not licensed for use in neuropathic pain.

Contra-indications

Arrhythmias during the manic phase of bipolar disorder; heart block; immediate recovery period after myocardial infarction

Cautions

Cardiovascular disease; chronic constipation; diabetes; epilepsy; history of bipolar disorder; history of psychosis; hyperthyroidism (risk of arrhythmias); increased intra-ocular pressure; patients with a significant risk of suicide; phaeochromocytoma (risk of arrhythmias); prostatic hypertrophy; susceptibility to angle-closure glaucoma; urinary retention

Cautions, further information

Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

Interactions

Appendix 1: tricyclic antidepressants

Side-effects

Agranulocytosis; alopecia; anxiety; appetite decreased; arrhythmias; asthenia; atroventricular block; bone marrow disorders; breast enlargement; confusion; constipation; delusions; diarrhoea; dizziness; drowsiness; drug cross-reactivity; drug fever; dry mouth; eosinophilia; fever; flushing; galactorrhoea; gastrointestinal discomfort; gynaecomastia; hallucination; headache; hepatic disorders; hyperhidrosis; hypertension; hypomania; hypotension; increased risk of fracture; increased risk of infection; malaise; movement disorders; mydriasis; myocardial infarction; nausea; oedema; oral disorders; palpitations; paralytic ileus; peripheral neuropathy; photophobia; photosensitivity reaction; psychosis exacerbated; seizure; sensation abnormal; sexual dysfunction; SIADH; skin reactions; sleep disorders; stroke; suicidal tendencies; taste altered; testicular swelling; thrombocytopenia; tinnitus; tremor; urinary disorders; urinary tract dilation; vision disorders; vomiting; weight changes

Side-effects, further information

The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

Overdose

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning p. 1359.

Pregnancy

Use only if potential benefit outweighs risk.

Breast feeding

The amount secreted into breast milk is too small to be harmful.

Hepatic impairment

Manufacturer advises avoid in severe impairment.

Monitoring requirements

Manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily, but evidence of practical value uncertain.

Treatment cessation

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

Prescribing and dispensing information

Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

Patient and carer advice

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

Nortriptyline (as Nortriptyline hydrochloride) 10 mg Nortriptyline 10mg tablets | 30 tablet PDP £5.87–£11.79 | 100 tablet PDP £68.41 DT = £4.29

Nortriptyline (as Nortriptyline hydrochloride) 25 mg Nortriptyline 25mg tablets | 30 tablet PDP £6.81–£12.43 | 100 tablet PDP £41.44 DT = £8.77

Nortriptyline (as Nortriptyline hydrochloride) 50 mg Nortriptyline 50mg tablets | 30 tablet PDP £24.86 DT = £24.86

Trimipramine

INDICATIONS AND DOSE

Depressive illness (particularly where sedation required)

BY MOUTH

Adult: Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–300 mg daily

Elderly: Initially 10–25 mg 3 times a day, maintenance 75–150 mg daily

Contra-indications

Acute porphyrias p. 1058; arrhythmias during the manic phase of bipolar disorder

www.getintopharma.com
heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease • chronic constipation • diabetes • epilepsy • history of bipolar disorder • history of psychosis • hyperthyroidism (risk of arrhythmias) • increased intra-ocular pressure • patients with a significant risk of suicide • phaeochromocytoma (risk of arrhythmias) • prostatic hypertrophy • susceptibility to angle-closure glaucoma • urinary retention

**CAUTIONS, FURTHER INFORMATION** Treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS** → Appendix 1: tricyclic antidepressants

- **SIDE-EFFECTS** Accumodation disorder • agitation • agranulocytosis • anticholinergic syndrome • arrhythmias • bone fracture • bone marrow depression • constipation • drowsiness • dry mouth • glyceryl trinitrate • hypoglycaemia • hyperhidrosis • hypotension • jaundice • lactic acidosis • mood altered • paranoid delusions • peripheral neuropathy • rash • respiratory depression • seizure • sexual dysfunction • suicidal tendencies • tremor • urinary retention • withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** The risk of side-effects is reduced by titrating slowly to the minimum effective dose (every 2–3 days). Consider using a lower starting dose in elderly patients.

- **Overdose** Tricyclic and related antidepressants cause dry mouth, constipation, varying degree of hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergencies treatment of poisoning p. 1359.

- **PREGNANCY** Use only if potential benefit outweighs risks.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment.

- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose.

- **PATIENT AND CARER ADVICE**
  - *Driving and skilled tasks* Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 2 | Tramiprimine (as Tramiprimine maleate) 10 mg Tramiprimine 10mg tablets | 28 tablet | £19.18 DT = £17.95 |

**Capsule**

| CAUTIONARY AND ADVISORY LABELS 2 | Trimipramine (Non-proprietary) Tramiprimine (as Trimipramine maleate) 25 mg | Tramiprimine 25mg tablets | 28 tablet | £20.44 DT = £19.00 |

**Other Antidepressants**

**Tryptophan**

(L-Tryptophan)

- **DRUG ACTION** Tryptophan is an essential dietary amino acid, and is a precursor of serotonin; it re-establishes the inhibitory action of serotonin on the amygdaloid nuclei, thereby reducing feelings of anxiety and depression.

- **INDICATIONS AND DOSE** Treatment-resistant depression (used alone or as adjunct to other antidepressant drugs) (initiated under direction of hospital consultant)

  - **BY MOUTH**
    - Adult: 3 g 3 times a day; maximum 6 g per day

- **CONTRA-INDICATIONS** History of eosinophilia myalgia syndrome following use of tryptophan

- **INTERACTIONS** → Appendix 1: tryptophan

- **SIDE-EFFECTS** Asthenia • dizziness • drowsiness • eosinophilia myalgia syndrome • headache • myalgia • myopathy • nausea • oedema • suicidal tendencies

  - **SIDE-EFFECTS, FURTHER INFORMATION** If patients experience any symptoms of eosinophilia myalgia syndrome (EMS), manufacturer advises to withhold treatment until possibility of EMS is excluded.

- **PREGNANCY** Manufacturer advises caution—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS** Manufacturer advises close monitoring for signs of suicidal thoughts, particularly in patients at high risk and during early treatment and dose changes.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and carers should be advised to seek medical advice immediately if any clinical worsening, suicidal thoughts, or unusual behaviour develops.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

**Capsule**

- **Optimax** (Intrapharm Laboratories Ltd) Tryptophan 500 mg Optimax 500mg capsules | 84 capsule | £42.00
**Vortioxetine**

**INDICATIONS AND DOSE**

- **Major depression**
  - Adult: Initially 10 mg once daily; adjusted according to response to 5–20 mg once daily
  - Elderly: Initially 5 mg once daily; increased if necessary up to 20 mg once daily

- **SIDE-EFFECTS**
  - **Common or very common** Abnormal dreams · constipation · diarrhoea · dizziness · nausea · pruritus · vomiting
  - **Uncommon** Flushing · night sweats
  - **Frequency not known** Hyponatraemia · neuroleptic malignant syndrome (discontinue if patient entering manic phase) · history of seizures · unstable epilepsy

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies. If used during the later stages of pregnancy, there is a risk of neonatal withdrawal symptoms and persistent pulmonary hypertension in the newborn.

- **BREAST FEEDING**
  - There is limited information available on breast feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment (no information available).

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution in severe impairment — limited information available.

- **TREATMENT CESSION**
  - Manufacturer advises treatment can be stopped abruptly, without need for gradual dose reduction.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Manufacturing advises patients and carers should be counselled on the effects on driving and performance of skilled tasks, especially when starting treatment or changing the dose.

- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Vortioxetine for treating major depressive episodes (November 2015) NICE TA367

Vortioxetine (Brintellix®) is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode.

Patients currently receiving vortioxetine whose disease does not meet the above criteria should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta367

**INTERACTIONS**

- **Frequency not known** Side-effects · serotonin (anxiolytic-like effects).

- **INTERACTIONS** → Appendix 1: vortioxetine

**CAUTIONS**

- Bleeding disorders · cirrhosis of the liver (risk of hyponatraemia) · elderly (risk of hyponatraemia) · history of mania (discontinue if patient entering manic phase) · history of seizures · unstable epilepsy

**MEDICINAL FORMS**

- **Tablet**
  - Brintellix (Lundbeck Ltd)
    - Vortioxetine (as Vortioxetine hydrobromide) 5 mg
      - 28 tablet (P) £27.72 OT = £27.72
    - Vortioxetine (as Vortioxetine hydrobromide) 10 mg
      - 28 tablet (P) £27.72 OT = £27.72
    - Vortioxetine (as Vortioxetine hydrobromide) 20 mg
      - 28 tablet (P) £27.72 OT = £27.72

**3.5 Inappropriate sexual behaviour**

**ANTIPSYCHOTICS > FIRST-GENERATION**

**Benperidol**

- **INDICATIONS AND DOSE**
  - Control of deviant antisocial sexual behaviour
    - **BY MOUTH**
      - Adult: 0.25–1.5 mg daily in divided doses, adjusted according to response, for debilitated patients, use elderly dose
      - Elderly: Initially 0.125–0.75 mg daily in divided doses, adjusted according to response

- **CONTRA-INDICATIONS**
  - CNS depression · comatose states · phaeochromocytoma

- **CAUTIONS**
  - Risk factors for stroke

- **INTERACTIONS** → Appendix 1: benperidol

- **SIDE-EFFECTS**
  - Appetite decreased · blood disorder · cardiac arrest · confusion · depression · dyspepsia · headache · hepatic disorders · hyperhidrosis · hypersalivation · hypertension · muscle rigidity · nausea · oculogyric crisis · oedema · oligomenorrhoea · paradoxical drug reaction · pruritus · psychiatric disorder · temperature regulation disorders · weight change

- **PREGNANCY**
  - Extrapyramidal effects and withdrawal syndrome have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy. Following maternal use of antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary.

- **BREAST FEEDING**
  - There is limited information available on the short- and long-term effects of antipsychotic drugs on the breast-fed infant. Animal studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution.

- **RENAL IMPAIRMENT**
  - **Dose adjustments** Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises regular blood counts and liver function tests during long-term treatment.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The proprietary name Benquil® has been used for benperidol tablets.

www.getintopharma.com
Psychoses and schizophrenia

3.6 Psychoses and schizophrenia


discussion and related disorders

Advice of Royal College of Psychiatrists on doses of antipsychotic drugs above BNF upper limit

Unless otherwise stated, doses in the BNF are licensed doses—any higher dose is therefore unlicensed

Consider alternative approaches including adjuvant therapy and newer or second-generation antipsychotic drugs such as clozapine.

Bear in mind risk factors, including obesity; particular caution is indicated in older patients, especially those over 70.

Consider potential for drug interactions—see interactions: Appendix 1 (antipsychotics).

Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse cardiac abnormality develops.

Increase dose slowly and not more often than once weekly.

Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.

Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important: When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be lower than the corresponding oral dose (owing to absence of first-pass effect), particularly if the patient is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for each route and should not imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least daily.

Antipsychotic drugs

Antipsychotic drugs are also known as ‘neuroleptics’ and (misleadingly) as ‘major tranquilisers’.

In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia

The aim of treatment is to alleviate the suffering of the patient (and carer) and to improve social and cognitive functioning. Many patients require life-long treatment with antipsychotic medication. Antipsychotic drugs relieve positive psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse; they are usually less effective on negative symptoms such as apathy and social withdrawal. In many patients, negative symptoms persist between episodes of treated positive symptoms, but earlier treatment of psychotic illness may protect against the development of negative symptoms over time. Patients with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a patient with a definitive diagnosis of schizophrenia is usually required after the first episode of illness in order to prevent relapses. Doses that are effective in acute episodes should generally be continued as prophylaxis.

First-generation antipsychotic drugs

The first-generation antipsychotic drugs act predominantly by blocking dopamine D₂ receptors in the brain. First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin. The phenothiazine derivatives can be divided into 3 main groups:

Group 1: chlorpromazine hydrochloride p. 384, levomepromazine p. 441, and promazine hydrochloride p. 406, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.

Group 2: pericyazine p. 388, generally characterised by moderate sedative effects, but fewer extrapyramidal side-effects than groups 1 or 3.

Group 3: fluphenazine decanoate p. 392, perphenazine, prochlorperazine p. 389, and trifluoperazine p. 390, generally characterised by fewer sedative and antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Butyrophenones (benperidol p. 380 and haloperidol p. 386) resemble the group 3 phenothiazines in their clinical properties. Thioxanthenes (flupentixol p. 385 and zuclopenthixol p. 391) have moderate sedative, antimuscarinic effects, and extrapyramidal effects.

Diphenylbutylpiperidines (pimozide p. 388) and the substituted benzamides (sulpiride p. 390) have reduced sedative, antimuscarinic, and extrapyramidal effects.

Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (sometimes referred to as ‘atypical antipsychotic drugs’) act on a range of receptors in comparison to first-generation antipsychotic drugs and have more distinct clinical profiles, particularly with regard to side-effects.

Prescribing for the elderly

The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack (see Dementia p. 300). Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather.

It is recommended that:

Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.

Initial doses of antipsychotic drugs in elderly patients should be reduced (to half the adult dose or less), taking into account factors such as the patient’s weight, comorbidity, and concomitant medication.

Treatment should be reviewed regularly.

Prescribing of antipsychotic drugs in patients with learning disabilities

When prescribing for patients with learning disabilities who are prescribed antipsychotic drugs and who are not experiencing psychotic symptoms, the following considerations should be taken into account:

A reduction in dose or the discontinuation of long-term antipsychotic treatment;

Review of the patient’s condition after dose reduction or discontinuation of an antipsychotic drug;
• referral to a psychiatrist experienced in working with patients who have learning disabilities and mental health problems;
• annual documentation of the reasons for continuing a prescription if the antipsychotic is not reduced in dose or discontinued.

Side-effects of antipsychotic drugs
Side-effects caused by antipsychotic drugs are common and contribute significantly to non-adherence to therapy.

Extrapyramidal symptoms
Extrapyramidal symptoms occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol and haloperidol), and the first-generation depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:
• parkinsonian symptoms (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
• dystonia (abnormal face and body movements) and dyskinesia, which occur more commonly in children or young adults and appear after only a few doses;
• akathisia (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated;
• tardive dyskinesia (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

Parkinsonian symptoms remit if the drug is withdrawn and may be suppressed by the administration of antimuscarinic drugs. However, routine administration of such drugs is not justified because not all patients are affected and they may unmask or worsen tardive dyskinesia.

Tardive dyskinesia is the most serious manifestation of extrapyramidal symptoms; it is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. In children, tardive dyskinesia is more likely to occur when the antipsychotic drug is withdrawn. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermicular movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

Hyperprolactinaemia
Most antipsychotic drugs, both first- and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Aripiprazole reduces prolactin because it is a dopamine-receptor partial agonist. Risperidone, amisulpride, and first-generation antipsychotic drugs are most likely to cause symptomatic hyperprolactinaemia. The clinical symptoms of hyperprolactinaemia include sexual dysfunction, reduced bone mineral density, menstrual disturbances, breast enlargement, and galactorrhea.

Sexual dysfunction
Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medication; physical illness, psychiatric illness, and substance misuse are contributing factors. Antipsychotic-induced sexual dysfunction is caused by more than one mechanism. Reduced dopamine transmission and hyperprolactinaemia decrease libido; antimuscarinic effects can cause disorders of arousal; and alpha-1-adrenoceptor antagonists are associated with erection and ejaculation problems in men. Risperidone and haloperidol commonly cause sexual dysfunction. If sexual dysfunction is thought to be antipsychotic-induced, dose reduction or switching medication should be considered.

Cardiovascular side-effects
Antipsychotic drugs have been associated with cardiovascular side-effects such as tachycardia, arrhythmias, and hypotension. QT-interval prolongation is a particular concern with pimozide and haloperidol. There is also a higher probability of QT-interval prolongation in patients using any intravenous antipsychotic drug, or any antipsychotic drug or combination of antipsychotic drugs with doses exceeding the recommended maximum. Cases of sudden death have occurred.

Hyperglycaemia and weight gain
Hyperglycaemia, and sometimes diabetes, can occur with antipsychotic drugs, particularly clozapine, olanzapine, quetiapine, and risperidone. All antipsychotic drugs may cause weight gain, but the risk and extent varies. Clozapine and olanzapine commonly cause weight gain.

Hypotension and interference with temperature regulation
Hypotension and interference with temperature regulation are dose-related side-effects that are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly. Clozapine, chlorpromazine, lurasidone, and quetiapine can cause postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some patients.

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of all antipsychotic drugs. Discontinuation of the antipsychotic drug is essential because there is no proven effective treatment, but bromocriptine and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

Blood dyscrasias
Perform blood counts if unexplained infection or fever develops.

Choice
There is little meaningful difference in efficacy between each of the antipsychotic drugs (other than clozapine p. 396), and response and tolerability to each antipsychotic drug varies markedly. There is no first-line antipsychotic drug which is suitable for all patients. Choice of antipsychotic medication is influenced by the patient’s medication history, the degree of sedation required (although tolerance to this usually develops), and consideration of individual patient factors such as risk of extrapyramidal side-effects, weight gain, impaired glucose tolerance, QT-interval prolongation, or the presence of negative symptoms.

Negative symptoms
Second-generation antipsychotic drugs may be better at treating the negative symptoms of schizophrenia.

Extrapyramidal side-effects
Second-generation antipsychotic drugs should be prescribed if extrapyramidal side-effects are a particular concern. Of these, aripiprazole p. 395, clozapine, olanzapine p. 398, and quetiapine p. 401 are least likely to cause extrapyramidal side-effects. Although amisulpride p. 394 is a dopamine-receptor antagonist, extrapyramidal side-effects are less common than with the first-generation antipsychotic drugs because amisulpride selectively blocks mesolimbic dopamine receptors, and extrapyramidal symptoms are caused by blockade of the striatal dopamine pathway.

QT interval
Aripiprazole has negligible effect on the QT interval. Other antipsychotic drugs with a reduced tendency to prolong QT interval include amisulpride, clozapine, fluoxetine p. 385,
Diabetes
Schizophrenia is associated with insulin resistance and diabetes; the risk of diabetes is increased in patients with schizophrenia who take antipsychotic drugs. First-generation antipsychotic drugs are less likely to cause diabetes than second-generation antipsychotic drugs, and of the first-generation antipsychotic drugs, fluphenazine decanoate and haloperidol p. 386 are lowest risk. Aminopropazine and pimiprazole have the lowest risk of diabetes of the second-generation antipsychotic drugs. Aminopropazine, aripiprazole, haloperidol, sulpiride, and trifluoperazine p. 390 are least likely to cause weight gain.

Sexual dysfunction and prolactin
The antipsychotic drugs with the lowest risk of sexual dysfunction are aripiprazole and quetiapine. Olanzapine may be considered if sexual dysfunction is judged to be secondary to hyperprolactinaemia. Hyperprolactinaemia is usually not clinically significant with aripiprazole, clozapine, olanzapine, and quetiapine treatment. When changing from other antipsychotic drugs, a reduction in prolactin concentration may increase fertility.

Patients should receive an antipsychotic drug for 4–6 weeks before it is deemed ineffective. Prescribing more than one antipsychotic drug at a time should be avoided except in exceptional circumstances (e.g. clozapine augmentation or when changing medication during titration) because of the increased risk of adverse effects such as extrapyramidal symptoms, QT-interval prolongation, and sudden cardiac death.

Clozapine is licensed for the treatment of schizophrenia in patients unresponsive to, or intolerant of, other antipsychotic drugs. Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks. If symptoms do not respond adequately to an optimised dose of clozapine, plasma-clozapine concentration should be checked before adding a second antipsychotic drug to augment clozapine; allow 8–10 weeks’ treatment to assess response. Patients must be registered with a clozapine patient monitoring service.

Monitoring
Full blood count, urea and electrolytes, and liver function test monitoring is required at the start of therapy with antipsychotic drugs, and then annually thereafter.

Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly.

Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly.

Before initiating antipsychotic drugs, an ECG may be required, particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardiovascular disease, or if the patient is being admitted as an inpatient.

Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs.

Other uses
Some antipsychotic drugs can be used for the treatment of nausea and vomiting, choreas, and motor tics. Chlorpromazine hydrochloride p. 384 and haloperidol p. 386 can be used for intractable hiccup. Benperidol p. 380 is used in deviant antisocial sexual behaviour but its value is not established.

Psychomotor agitation should be investigated for an underlying cause; it can be managed with low doses of chlorpromazine hydrochloride or haloperidol used for short periods. Antipsychotic drugs can be used with caution for the short-term treatment of severe agitation and restlessness in the elderly.

Equivalent doses of oral antipsychotics
These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication. Equivalent daily dose of antipsychotic drug:

- Chlorpromazine 100 mg
- Clozapine 50 mg
- Haloperidol 2–3 mg
- Pimozide 2 mg
- Risperidone 0.5–1 mg
- Sulpiride 200 mg
- Trifluoperazine 5 mg

Important: These equivalences must not be extrapolated beyond the maximum dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate.

Dosage
After an initial period of stabilisation, in most patients, the total daily oral dose can be given as a single dose. The Royal College of Psychiatrists has published advice on doses of antipsychotic drugs above BNF upper limit.

Antipsychotic depot injections
Long-acting depot injections are used for maintenance therapy especially when compliance with oral treatment is unreliable. However, depot injections of conventional antipsychotics may give rise to a higher incidence of extrapyramidal reactions than oral preparations; extrapyramidal reactions occur less frequently with second-generation antipsychotic depot preparations, such as risperidone p. 402 and olanzapine embonate p. 404.

Choice
There is no clear-cut division in the use of the conventional antipsychotics, but zuclopenthixol p. 391 may be suitable for the treatment of agitated or aggressive patients whereas flupenthixol decanoate p. 392 can cause over-excitement in such patients. Zuclopenthixol decanoate p. 394 may be more effective in preventing relapses than other conventional antipsychotic depot preparations. The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.

Dosage
Individual responses to neuroleptic drugs are variable and to achieve optimum effect, dosage and dosage interval must be titrated according to the patient’s response.

Equivalent doses of depot antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic drug/interval</th>
<th>Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupenthixol decanoate / 2 weeks</td>
<td>40</td>
</tr>
<tr>
<td>Fluphenazine decanoate / 2 weeks</td>
<td>25</td>
</tr>
<tr>
<td>Haloperidol (as decanoate) / 4 weeks</td>
<td>100</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate / 2 weeks</td>
<td>200</td>
</tr>
</tbody>
</table>

Important: These equivalences must not be extrapolated beyond the maximum dose for the drug.

These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication.
ANTIPSYCHOTICS

Antipsychotic drugs

- **CAUTIONS** Blood dyscrasias - cardiovascular disease - conditions predisposing to seizures - depression - diabetes (may raise blood glucose) - epilepsy - history of jaundice - myasthenia gravis - Parkinson’s disease (may be exacerbated) (in adults) - photosensitisation (may occur with higher dosages) - prostatic hypertrophy (in adults) - severe respiratory disease - susceptibility to angle-closure glaucoma

- **SIDE-EFFECTS**
  - Common or very common Agitation - amenorrhoea - arrhythmias - constipation - dizziness - drowsiness - dry mouth - erectile dysfunction - galactorrhoea - gynaecomastia - hyperprolactinaemia - hypertension (dose-related) - insomnia - leucopenia - movement disorders - neutropenia - parkinsonism - QT interval prolongation - rash - seizure - tremor - urinary retention - vomiting - weight increased
  - Uncommon Agranulocytosis - embolism and thrombosis - neuroleptic malignant syndrome (discontinue—potentially fatal)
  - Rare or very rare Sudden death - withdrawal syndrome neonatal

- **SIDE-EFFECTS, FURTHER INFORMATION**
  For depot antipsychotics—side-effects may persist until the drug has been cleared from its depot site.

- **Overdose** Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. For details on the management of poisoning see Antipsychotics under Emergency treatment of poisoning p. 1359.

- **PREGNANCY** Extrapyramidal effects and withdrawal syndrome have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy. Following maternal use of antipsychotic drugs in the third trimester, neonates should be monitored for symptoms including agitation, hypotonia, hypotonia, tremor, drowsiness, feeding problems, and respiratory distress.

- **BREAST FEEDING** There is limited information available on the short- and long-term effects of antipsychotic drugs on the breast-fed infant. Animal studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary. Phenothiazine derivatives are sometimes used in breast-feeding women for short-term treatment of nausea and vomiting.

- **MONITORING REQUIREMENTS**
  - It is advisable to monitor prolactin concentration at the start of therapy, at 6 months, and then yearly. Patients taking antipsychotic drugs not normally associated with symptomatic hyperprolactinaemia should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia (such as breast enlargement and galactorrhoea).
  - Patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year.
  - In children Regular clinical monitoring of endocrine function should be considered when children are taking an antipsychotic drug known to increase prolactin levels; this includes measuring weight and height, assessing sexual maturation, and monitoring menstrual function.

- **TREATMENT CESSATION** There is a high risk of relapse if medication is stopped after 1–2 years. Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse. Patients should be monitored for 2 years after withdrawal of antipsychotic medication for signs and symptoms of relapse.

- **PATIENT AND CARER ADVICE** As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

**Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

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**ANTIPSYCHOTICS › FIRST-GENERATION**

| Chlorpromazine hydrochloride | 09-Jul-2018 |

- **INDICATIONS AND DOSE**
  - Schizophrenia and other psychoses | Mania | Short-term adjunctive management of severe anxiety | Psychomotor agitation, excitement, and violent or dangerously impulsive behaviour
  - **BY MOUTH**
    - Adult: Initially 25 mg 3 times a day, adjusted according to response, alternatively initially 75 mg once daily, adjusted according to response, dose to be taken at night; maintenance 75–300 mg daily, increased if necessary up to 1 g daily, this dose may be required in psychoses; use a third to half adult dose in the elderly or debilitated patients
  - **BY RECTUM**
    - Adult: 100 mg every 6–8 hours, dose expressed as chlorpromazine base

  - **Intractable hiccup**
    - **BY MOUTH**
      - Adult: 25–50 mg 3–4 times a day
    - **Relief of acute symptoms of psychoses (under expert supervision)**
      - **BY DEEP INTRAMUSCULAR INJECTION**
        - Adult: 25–50 mg every 6–8 hours
    - **Nausea and vomiting in palliative care (where other drugs have failed or are not available)**
      - **BY MOUTH**
        - Child 1–5 years: 500 micrograms/kg every 4–6 hours; maximum 40 mg per day
        - Child 6–11 years: 500 micrograms/kg every 4–6 hours; maximum 75 mg per day
        - Child 12–17 years: 10–25 mg every 4–6 hours
        - Adult: 10–25 mg every 4–6 hours
      - **BY DEEP INTRAMUSCULAR INJECTION**
        - Child 1–5 years: 500 micrograms/kg every 6–8 hours; maximum 40 mg per day
        - Child 6–11 years: 500 micrograms/kg every 6–8 hours; maximum 75 mg per day
        - Child 12–17 years: Initially 25 mg, then 25–50 mg every 3–4 hours until vomiting stops
        - Adult: Initially 25 mg, then 25–50 mg every 3–4 hours until vomiting stops
      - **BY RECTUM**
        - Adult: 100 mg every 6–8 hours
  - **DOSE EQUIVALENCE AND CONVERSION**
    - For equivalent therapeutic effect 100 mg chlorpromazine base given rectally as a suppository ≡ 20–25 mg chlorpromazine hydrochloride by intramuscular injection ≡ 40–50 mg of chlorpromazine base or hydrochloride given by mouth.
Psychoses and schizophrenia 385

Flupentixol
(Flupentixol)

23-Jul-2018

Nervous System

Flupentixol

INDICATIONS AND DOSE

Schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity

BY MOUTH

Adult: Initially 3–9 mg twice daily, adjusted according to response, for debilitated patients, use elderly dose; maximum 18 mg per day

Elderly: Initially 0.75–4.5 mg twice daily, adjusted according to response

Depressive illness

BY MOUTH

Adult: Initially 1 mg once daily, dose to be taken in the morning, increased if necessary to 2 mg after 1 week, doses above 2 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 3 mg per day

Elderly: Initially 500 micrograms daily, dose to be taken in the morning, then increased if necessary to 1 mg after 1 week, doses above 1 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 1.5 mg per day

CONTRA-INDICATIONS

Circulatory collapse - CNS depression - comatose states - excitable patients - impaired consciousness - overactive patients - pheochromocytoma

CAUTIONS

Cardiac disorders - cardiovascular disease - cerebral arteriosclerosis - elderly - hyperthyroidism - hypothyroidism - parkinsonism - QT-interval prolongation - senile confusional states

INTERATIONS

Appendix 1: flupentixol

SIDE-EFFECTS

Common or very common

- Anxiety - glucose tolerance impaired - mood altered - muscle tone increased

Frequency not known

- Accommodation disorder - angioedema - atroventricular block - cardiac arrest - eye deposit - eye disorders - gastrointestinal disorders - hepatic disorders - hyperglycaemia - hypertglycicrideriaemia - hyponatraemia - photosensitivity reaction - respiratory disorders - sexual dysfunction - SIADH - skin reactions - systemic lupus erythematosus (SLE) - temperature regulation disorder - trismus

SIDE-EFFECTS, FURTHER INFORMATION

Acute dystonic reactions may occur; children are particularly susceptible.

HEPATIC IMPAIRMENT

Manufacturer advises caution in severe hepatic failure (increased risk of accumulation).

RENAI IMPAIRMENT

Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS

With intramuscular use Patients should remain supine, with blood pressure monitoring for 30 minutes after intramuscular injection.

PARIS CRITICATING INFORMATION

Palliative care For further information on the use of chlorpromazine hydrochloride in palliative care, see www.medicinescomplete.com/#content/palliative/antipsychotics.

HANDLING AND STORAGE

Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

MEDIHCIAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, suppository

Tablet

CAUTIONARY AND ADVISORY LABELS

BY MOUTH

Chlorpromazine hydrochloride (Non-proprietary)

Chlorpromazine hydrochloride 25 mg Chlorpromazine 25mg tablets | 28 tablet (Pres) £4.78 DT = £41.72
Chlorpromazine hydrochloride 50 mg Chlorpromazine 50mg tablets | 28 tablet (Pres) £48.00 DT = £41.81
Chlorpromazine hydrochloride 100 mg Chlorpromazine 100mg tablets | 28 tablet (Pres) £46.25 DT = £41.56

Solution for injection

Largactil (Sanofi)

Chlorpromazine hydrochloride 25 mg per 1 ml Largactil 50mg/2ml solution for injection ampoules | 10 ampoule (Pres) £7.51

Oral solution

CAUTIONARY AND ADVISORY LABELS

Largactil (Sanofi)

Chlorpromazine hydrochloride 5 mg per 1 ml Chlorpromazine 25mg/5ml syrup | 150 ml (Pres) £2.35 DT = £3.35
Chlorpromazine hydrochloride 25mg/5ml oral solution sugar free - sugar free | 150 ml (Pres) £2.35 DT = £2.35
Chlorpromazine hydrochloride 25mg/5ml oral solution | 150 ml (Pres) £2.35 DT = £2.35
Chlorpromazine hydrochloride 20 mg per 1 ml Chlorpromazine 100mg/5ml oral solution | 150 ml (Pres) £5.50 DT = £5.50

www.getintopharma.com
Haloperidol

**INDICATIONS AND DOSE**

**Prophylaxis of postoperative nausea and vomiting [in patients at moderate to high risk and when alternatives ineffective or not tolerated]**
- By Intramuscular Injection
  - Adult: 1–2 mg, to be given at induction or 30 minutes before the end of anaesthesia
  - Elderly: 500 micrograms, to be given at induction or 30 minutes before the end of anaesthesia

**Combination treatment of postoperative nausea and vomiting [when alternatives ineffective or not tolerated]**
- By Intramuscular Injection
  - Adult: 1–2 mg
  - Elderly: 500 micrograms

**Nausea and vomiting in palliative care**
- By Mouth
  - Adult: Initially 1.5 mg 1–2 times a day, increased if necessary to 5–10 mg daily in divided doses
  - By Subcutaneous Infusion
    - Adult: 2.5–10 mg/24 hours

**Schizophrenia and schizoaffective disorder**
- By Mouth
  - Adult: 2–10 mg daily in 1–2 divided doses; usual dose 2–4 mg daily, in first-episode schizophrenia, up to 10 mg daily, in multiple-episode schizophrenia, dose adjusted according to response at intervals of 1–7 days. Individual benefit-risk should be assessed when considering doses above 10 mg daily; maximum 20 mg per day
  - Elderly: Initially, use half the lowest adult dose, then adjust gradually according to response up to maximum 5 mg daily, doses above 5 mg daily should only be considered in patients who have tolerated higher doses and after reassessment of the individual benefit-risk

**Acute delirium [when non-pharmacological treatments ineffective]**
- By Mouth
  - Adult: 1–10 mg daily in 1–3 divided doses, treatment should be started at the lowest possible dose and adjusted in increments at 2–4 hourly intervals if required; maximum 10 mg per day
  - Elderly: Initially, use half the lowest adult dose, then adjust gradually according to response up to maximum 5 mg daily, doses above 5 mg daily should only be considered in patients who have tolerated higher doses and after reassessment of the individual benefit-risk
- By Intramuscular Injection
  - Adult: 1–10 mg, treatment should be started at the lowest possible dose and adjusted in increments at 2–4 hourly intervals if required; maximum 10 mg per day
  - Elderly: Initially 500 micrograms, dose adjusted gradually according to response up to maximum 5 mg daily, doses above 5 mg daily should only be considered in patients who have tolerated higher doses and after reassessment of the individual benefit-risk

**Moderate to severe manic episodes associated with bipolar I disorder**
- By Mouth
  - Adult: 2–10 mg daily in 1–2 divided doses, dose adjusted according to response at intervals of 1–3 days.
Mild to moderate chorea in Huntington’s disease [when alternatives ineffective or not tolerated and oral therapy inappropriate]
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 2–5 mg, dose may be repeated hourly if required; maximum 10 mg per day.
  - Elderly: Initially 1 mg, dose may be repeated hourly if required up to maximum 5 mg daily, doses above 5 mg daily should only be considered in patients who have tolerated higher doses and after reassessment of the individual benefit-risk

### Restlessness and confusion in palliative care
- **BY MOUTH**
  - Adult: 2 mg, then 2 mg every 2 hours if required
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 2.5 mg, then 2.5 mg every 2 hours if required
  - **BY SUBCUTANEOUS INFUSION**
  - Adult: 5–15 mg/24 hours

### UNLICENSED USE
Not licensed for use in palliative care.

### IMPORTANT SAFETY INFORMATION
When prescribing, dispensing or administering, check that this injection is the correct preparation—this preparation is usually used in hospital for the rapid control of an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

### CONTRA-INDICATIONS
- CNS depression - comatose states - congenital long QT syndrome - dementia with Lewy bodies - history of torsade de pointes - history of ventricular arrhythmia - Parkinson’s disease - progressive supranuclear palsy - QTC-interval prolongation - recent acute myocardial infarction - uncompensated heart failure - uncorrected hypokalaemia

### CAUTIONS
- Bradycardia - electrolyte disturbances (correct before treatment initiation) - family history of QTC-interval prolongation - history of heavy alcohol exposure - hyperthyroidism - hypotension (including orthostatic hypotension) - lactation - dependent tumours - prolactin - risk factors for stroke

### INTERACTIONS
- Appendix 1: haloperidol

### SIDE-EFFECTS

#### GENERAL SIDE-EFFECTS
- Common or very common Depression - eye disorders - headache - hypersalivation - nausea - neuromuscular dysfunctions - psychiatric disorder - vision disorders - weight decreased

#### Uncommon
- Breast abnormalities - confusion - dysphoria - gait abnormal - hepatic disorders - hyperhidrosis - menstrual cycle irregularity - muscle complaints - musculoskeletal stiffness - oedema - photosensitivity - reaction - restlessness - sexual dysfunction - skin reactions - temperature regulation disorders

#### Rare or very rare
- Hypoglycaemia - respiratory disorders - SIADH - tinnitus

#### Frequency not known
- Hypersensitivity vasculitis - pancytopenia - rhabdomyolysis - thrombocytopenia

### SPECIFIC SIDE-EFFECTS
- With oral use Angioedema
- With parenteral use Hypertension - severe cutaneous adverse reactions (SCARs)

### SIDE-EFFECTS, FURTHER INFORMATION
Haloperidol is a less sedating antipsychotic.

### PREGNANCY
Manufacturer advises it is preferable to avoid—moderate amount of data indicate no malformative or fetal/neonatal toxicity, however there are isolated case reports of birth defects following fetal exposure, mostly in combination with other drugs; reproductive toxicity shown in animal studies.

### HEPATIC IMPAIRMENT
Manufacturer advises caution.

#### Dose adjustments
Manufacturer advises halve initial dose and then adjust if necessary with smaller increments and at longer intervals.

### RENAL IMPAIRMENT
Manufacturer advises use with caution.

#### Dose adjustments
Manufacturer advises consider lower initial dose in severe impairment and then adjust if necessary with smaller increments and at longer intervals.

### MONITORING REQUIREMENTS
- Manufacturer advises monitor electrolytes before treatment initiation and periodically during treatment.
- Manufacturer advises perform ECG before treatment initiation and assess need for further ECGs during treatment on an individual basis; continuous ECG monitoring is recommended for repeated intramuscular doses, and for up to 6 hours after administration of intramuscular doses for prophylaxis or treatment of postoperative nausea and vomiting.

### PRESCRIBING AND DISPENSING INFORMATION

#### Palliative Care
For further information on the use of haloperidol in palliative care, see www.medicinescomplete.com/#/content/palliative/haloperidol.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Tablet

#### CAUTIONARY AND ADVISORY LABELS
- Haloperidol (Non-proprietary)
  - Haloperidol 500 microgram Haloperidol 500microgram tablets | 28 tablet (Pst) £22.05-$30.00 DT = £29.59
  - Haloperidol 1.5 mg Haloperidol 1.5mg tablets | 28 tablet (Pst) £15.10 DT = £15.10
  - Haloperidol 5 mg Haloperidol 5mg tablets | 28 tablet (Pst) £16.58 DT = £16.50
  - Haloperidol 10 mg Haloperidol 10mg tablets | 28 tablet (Pst) £19.85 DT = £19.36

### Solution for injection
- Haloperidol (Non-proprietary)
  - Haloperidol 5 mg per 1 ml Haloperidol 5mg/1ml solution for injection ampoules | 10 ampoule (Pst) £35.00 DT = £35.00

### Oral solution

#### CAUTIONARY AND ADVISORY LABELS
- Haloperidol (Non-proprietary)
  - Haloperidol 1 mg per 1 ml Haloperidol 5mg/5ml oral solution sugar free sugar free | 100 ml (Pst) £35.99 DT = £8.47 sugar-free | 500 ml (Pst) £20.25
  - Haloperidol 2 mg per 1 ml Haloperidol 10mg/5ml oral solution sugar free sugar-free | 100 ml (Pst) £46.75 DT = £10.29 sugar-free | 500 ml (Pst) £55.50
  - Haldol (Janssen-Cilag Ltd)
    - Haloperidol 2 mg per 1 ml Haldol 2mg/ml oral solution sugar-free | 100 ml (Pst) £4.45 DT = £7.10
  - Halkid (Thame Laboratories Ltd)
    - Haloperidol 200 microgram per 1 ml Halkid 200micrograms/ml oral solution sugar-free | 100 ml (Pst) £89.90

### Capsule

#### CAUTIONARY AND ADVISORY LABELS
- Haloperidol (Non-proprietary)
  - Haloperidol 500 microgram Serenace 500microgram capsules | 30 capsule (Pst) £1.18 DT = £1.18

www.getintopharma.com
Loxapine

**DRUG ACTION** Loxapine is a dopamine D₂, and serotonin 5-HT₂A receptor antagonist. It also binds to noradrenergic, histaminergic, and cholinergic receptors.

**INDICATIONS AND DOSE** Rapid control of mild-to-moderate agitation in patients with schizophrenia or bipolar disorder (specialist supervision in hospital)

- **BY INHALATION**
  - Adult: 9.1 mg as a single dose, followed by 9.1 mg after 2 hours if required, alternatively 4.5 mg as a single dose, followed by 4.5 mg after 2 hours if required, lower dose may be given if more appropriate or if the higher dose not previously tolerated

**CONTRA-INDICATIONS** Acute respiratory symptoms - asthma - cardiovascular disease - cerebrovascular disease - chronic obstructive pulmonary disease - dehydradergic disease - hypotension - elderly patients (especially those with dementia-related psychosis) - hypovolaemia - risk of hypotension

**CAUTIONS** Bronchodilator treatment should be available during this time

**INTERACTIONS** → Appendix 1: loxapine

**SIDE-EFFECTS**
- **Common or very common** Fatigue - taste altered - throat irritation
- **Uncommon** Bronchospasm - ocugleryation - restlessness
- **Frequency not known** Dry eye - hyperpnea - syncope - vision blurred

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises to avoid for 48 hours after dose (express and discard milk produced during this time) - present in milk in animal studies.

**MONITORING REQUIREMENTS** Manufacturer advises to observe patient during the first hour after each dose for signs and symptoms of bronchospasm.

**DIRECTIONS FOR ADMINISTRATION** Manufacturer advises to remove pull-tab and wait for green light to turn on (product must be used within 15 minutes of pulling tab); instruct patient to inhale through mouthpiece and then hold breath briefly. When green light turns off, this indicates the dose has been delivered.

**PRESCRIBING AND DISPENSING INFORMATION** Educational risk minimisation materials are available for health care professionals.

Adasuve® 4.5 mg inhalation powder may be difficult to obtain.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**
- **Adasuve (Galen Ltd)**
  - **Loxapine 9.1 mg** Adasuve 9.1mg/dose inhalation powder
    - 1 dose £6.30 (Hospital only)

Pericyazine (Pericazine)

**INDICATIONS AND DOSE**

**Schizophrenia | Psychoses**

- **BY MOUTH**
  - Adult: Initially 75 mg daily in divided doses, then increased in steps of 25 mg every week, adjusted according to response; maximum 300 mg per day
  - Elderly: Initially 15–30 mg daily in divided doses, then increased in steps of 25 mg every week, adjusted according to response; maximum 300 mg per day

**Short-term adjunctive management of severe anxiety, psychomotor agitation, and violent or dangerously impulsive behaviour**

- **BY MOUTH**
  - Adult: Initially 15–30 mg daily in 2 divided doses, adjusted according to response, larger dose to be taken at bedtime
  - Elderly: Initially 5–10 mg daily in 2 divided doses, adjusted according to response, larger dose to be taken at bedtime

**CONTRA-INDICATIONS** CNS depression - comatos states - phaeochromocytoma

**CAUTIONS** Hypothyroidism

**INTERACTIONS** → Appendix 1: phenothiazines

**SIDE-EFFECTS** Atioventricular block - cardiac arrest - consciousness impaired - contact dermatitis - glucose tolerance impaired - hepatic disorders - hyperglycaemia - hyperthermia - nasal congestion - priapism - respiratory depression

**HEPATIC IMPAIRMENT** Can precipitate coma; phenothiazines are hepatotoxic.

**RENAL IMPAIRMENT** Avoid in renal impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tbody>
<tr>
<td>Pericyazine (Non-proprietary)</td>
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| Pericyazine 2 mg per 1 ml       | Pericyazine 10mg/5ml oral solution
| 100 ml                         | £82.80 DT = £82.80 |

**Tablet**

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<tr>
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<tr>
<td>Pericyazine 2.5 mg</td>
<td>Pericyazine 2.5mg tablets</td>
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<tr>
<td>Pericyazine 10 mg</td>
<td>Pericyazine 10mg tablets</td>
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Pimozide

**INDICATIONS AND DOSE**

**Schizophrenia**

- **BY MOUTH**
  - Adult: Initially 2 mg daily, adjusted according to response, then increased in steps of 2–4 mg at intervals of not less than 1 week; usual dose 2–20 mg daily
  - Elderly: Initially 1 mg daily, adjusted according to response, increased in steps of 2–4 mg at intervals of not less than 1 week; usual dose 2–20 mg daily
**Prochlorperazine**

**INDICATIONS AND DOSE**

- **Schizophrenia and other psychoses** | **Mania**
  - **BY MOUTH**
    - Adult: 12.5 mg twice daily for 7 days, dose to be adjusted at intervals of 4–7 days according to response; usual dose 75–100 mg daily
    - **BY DEEP INTRAMUSCULAR INJECTION**
      - Adult: 12.5–25 mg 2–3 times a day

- **Short-term adjunctive management of severe anxiety**
  - **BY MOUTH**
    - Adult: 15–20 mg daily in divided doses; maximum 40 mg per day

- **Nausea and vomiting, acute attack**
  - **BY MOUTH**
    - Adult: Initially 20 mg, then 10 mg after 2 hours

- **SIDE-EFFECTS**

  - **Rare or very rare**
    - Muscle rigidity
    - Photosensitivity reaction
    - Skin

  - **Common or very common**
    - Appetite decreased
    - Depression
    - Fatigue
    - Headache
    - Hyperhidrosis
    - Hypersalivation
    - Muscle complaints
    - Restlessness
    - Sebaceous gland overactivity
    - Urinary disorders
    - Vision blurred

- **Frequency not known**

  - Cardiac arrest
  - Generalised tonic-clonic seizure
  - Glucose tolerance impaired
  - Muscle rigidity
  - Neuroleptic malignant syndrome
  - Orthostatic hypotension
  - Photosensitivity reaction
  - Skin
  - Sudden unexplained death

**CONTRA-INDICATIONS**

- CNS depression
- Comatose states
- History of arrhythmias
- History or family history of congenital QT prolongation
- Phaeochromocytoma

**INTERACTIONS**

- Appendix 1: phenothiazines

**SIDE-EFFECTS**

- **Common or very common**
  - Appetite decreased
  - Depression
  - Fatigue
  - Headache
  - Hyperhidrosis
  - Hypersalivation
  - Muscle complaints
  - Restlessness
  - Sebaceous gland overactivity
  - Urinary disorders
  - Vision blurred

- **Uncommon**
  - Dysarthria
  - Face oedema
  - Oclocyric crisis
  - Skin reactions

- **Frequency not known**

  - Cardiac arrest
  - Generalised tonic-clonic seizure
  - Glucose tolerance impaired
  - Muscle rigidity
  - Neuroleptic malignant syndrome
  - Orthostatic hypotension
  - Photosensitivity reaction
  - Skin
  - Sudden unexplained death

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution.

**RENAAL IMPAIRMENT**

- Dose adjustments: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS**

- ECG monitoring: Following reports of sudden unexplained death, an ECG is recommended before treatment. It is also recommended that patients taking pimozide should have an annual ECG (if the QT interval is prolonged, treatment should be reviewed and either withdrawn or dose reduced under close supervision) and that pimozide should not be given with other antipsychotic drugs (including depot preparations), tricyclic antidepressants or other drugs which prolong the QT interval, such as certain antimalarials, antiarthymic drugs and certain antihistamines and should not be given with drugs which cause electrolyte disturbances (especially diuretics).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS**
    - 2
    - **Orap** (Eumedica Pharmaceuticals)

- **Pimozide 4 mg**
  - Orap 4 mg tablets | 100 tablet | £40.31 DT = £60.31

- **Pimozide 20 mg**
  - Orap 20 mg tablets | 100 tablet | £60.31 DT = £80.41

**REFERENCES**

- **BNF 78**

**PSYCHOTIC DISORDERS**

- **Nausea and vomiting, prevention**
  - **BY MOUTH**
    - Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

- **Nausea and vomiting, prevention**
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: 5–10 mg 2–3 times a day

- **Prevention and treatment of nausea and vomiting**
  - **BY MOUTH**
    - Child 1–4 years (body-weight 10 kg and above): 250 micrograms/kg 2–3 times a day
    - Child 12–17 years: 5–10 mg up to 3 times a day if required

- **PROPHYLACTIC MANAGEMENT**
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Child 2–4 years: 1.25–2.5 mg up to 3 times a day if required
    - Child 5–11 years: 5–6.25 mg up to 3 times a day if required
    - Child 12–17 years: 12.5 mg up to 3 times a day if required

- **Labyrinthine disorders**
  - **BY MOUTH**
    - Adult: 5 mg 3 times a day, increased if necessary to 30 mg daily in divided doses, dose to be increased gradually, then reduced to 5–10 mg daily, dose is reduced after several weeks

- **Nausea and vomiting in previously diagnosed migraine**
  - **BY MOUTH USING BUCCAL TABLET**
    - Child 12–17 years: 3–6 mg twice daily, tablets to be placed high between upper lip and gum and left to dissolve
    - Adult: 3–6 mg twice daily, tablets to be placed high between upper lip and gum and left to dissolve

- **DOSE EQUIVALENCE AND CONVERSION**
  - Doses are expressed as prochlorperazine maleate or prochlorperazine mesilate.
  - 1 mg prochlorperazine maleate = 1 mg prochlorperazine mesilate

- **UNLICENSED USE**

- **CONTRA-INDICATIONS**
  - Avoid oral route in child under 10 kg
  - Children (in psychotic disorders) CNS depression
  - Comatose states
  - Phaeochromocytoma

- **CAUTIONS**

  - **GENERAL CAUTIONS**
    - Elderly: hypotension (more likely after intramuscular injection)

  - **SPECIFIC CAUTIONS**
    - With systemic use Hypothyroidism (in adults)

- **INTERACTIONS**
  - Appendix 1: phenothiazines

- **SIDE-EFFECTS**

  - **General side-effects**
    - Photosensitivity reaction
    - Skin

  - **Rare or very rare**
    - Glucose tolerance impaired
    - Hyperglycaemia
    - Hypoglycaemia
    - SIADH

  - **Frequency not known**

    - Photosensitivity reaction
    - Skin

  - **Specific side-effects**

    - Photosensitivity reaction
    - Skin
hyperthermia, jaundice, muscle rigidity, nasal congestion, oculogyric crisis, respiratory depression

SIDE-EFFECTS, FURTHER INFORMATION

Acute dystonias are more common with potent first-generation antipsychotics. The risk is increased in men, young adults, children, antipsychotic-naive patients, rapid dose escalation, and abrupt treatment discontinuation.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid.
- **RENAL IMPAIRMENT**

  **Dose adjustments** Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **DIRECTIONS FOR ADMINISTRATION**

  - With buccal use Buccal tablets are placed high between upper lip and gum and left to dissolve.
  - **PATIENT AND CARER ADVICE**

    - With buccal use Patients or carers should be given advice on how to administer prochlorperazine buccal tablets.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - **CAUTIONARY AND ADVISORY LABELS 2**
    - Prochlorperazine (Non-proprietary) Prochlorperazine maleate 5 mg Prochlorperazine 5mg tablets | 28 tablet PG £1.98 DT = £0.73 | 84 tablet PG £2.10 DT = £0.58
    - Stemetil (Sanofi) Prochlorperazine maleate 5 mg Stemetil 5mg tablets | 28 tablet PG £1.98 DT = £0.73 | 84 tablet PG £5.94

  **Solution for injection**

    - Stemetil (Sanofi) Prochlorperazine mesilate 12.5 mg per 1 ml Stemetil 12.5mg/1ml solution for injection ampoules | 10 ampoule PG £5.23 DT = £5.23

  **Buccal tablet**

    - **CAUTIONARY AND ADVISORY LABELS 2**
      - Prochlorperazine (Non-proprietary) Prochlorperazine maleate 3 mg Prochlorperazine 3mg buccal tablets | 50 tablet PG £50.27 DT = £37.23
      - Buccastem (Alliance Pharmaceuticals Ltd) Prochlorperazine maleate 3 mg Buccastem M 3mg tablets | 8 tablet PG £4.01

  **Oral solution**

    - **CAUTIONARY AND ADVISORY LABELS 2**
      - Stemetil (Sanofi) Prochlorperazine mesilate 1 mg per 1 ml Stemetil 5mg/5ml syrup | 100 ml PG £3.34 DT = £3.34

**Sulpiride**

- **INDICATIONS AND DOSE**

  **Schizophrenia with predominantly negative symptoms**

    - **BY MOUTH**
      - Adult: 200–400 mg twice daily; maximum 800 mg per day
      - Elderly: Lower initial dose to be given, increased gradually according to response

  **Schizophrenia with mainly positive symptoms**

    - **BY MOUTH**
      - Adult: 200–400 mg twice daily; maximum 2.4 g per day
      - Elderly: Lower initial dose to be given, increased gradually according to response

- **CONTRA-INDICATIONS** CNS depression, comatose states, phaeochromocytoma

- **CAUTIONS** Aggressive patients (even low doses may aggravate symptoms) - agitated patients (even low doses may aggravate symptoms) - excited patients (even low doses may aggravate symptoms)

- **INTERACTIONS** Appendix 1: sulpiride

- **SIDE-EFFECTS**

  - **Common or very common** Breast abnormalities

  - **Uncommon**

    - Hypersalivation - muscle tone increased - orgasm abnormal

- **RARE OR VERY RARE**

  - Oculogyric crisis

  - Frequency not known Cardiac arrest - confusion - dyspnoea - hyponatraemia - SIADH - trismus - urticaria

- **RENAI IMPAIRMENT**

  **Dose adjustments** Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MONITORING REQUIREMENTS** Sulpiride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include lemon and aniseed.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Oral solution**

    - **CAUTIONARY AND ADVISORY LABELS 2**
      - Sulpiride (Non-proprietary) Sulpiride 40 mg per 1 ml Sulpiride 200mg/5ml oral solution sugar free sugar-free | 150 ml PG £31.00 DT = £31.00

  **Tablet**

    - **CAUTIONARY AND ADVISORY LABELS 2**
      - Sulpiride (Non-proprietary) Sulpiride 200 mg Sulpiride 200mg tablets | 30 tablet PG £8.70 DT = £4.40
      - Sulpiride 400 mg Sulpiride 400mg tablets | 30 tablet PG £23.50 DT = £11.80
      - Dolmatil (Sanofi) Sulpiride 200 mg Dolmatil 200mg tablets | 100 tablet PG £6.00
      - Sulpiride 400 mg Dolmatil 400mg tablets | 100 tablet PG £19.00

**Trifluoperazine**

- **INDICATIONS AND DOSE**

  **Schizophrenia and other psychoses: Short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour**

    - **BY MOUTH**
      - Adult: Initially 5 mg twice daily, daily dose may be increased by 5 mg after 1 week. If necessary, dose may be further increased in steps of 5 mg at intervals of 3 days. When satisfactory control has been achieved, reduce gradually until an effective maintenance level has been established
      - Elderly: Initially up to 2.5 mg twice daily, daily dose may be increased by 5 mg after 1 week. If necessary, dose may be further increased in steps of 5 mg at intervals of 3 days. When satisfactory control has been achieved, reduce gradually until an effective maintenance level has been established

  **Short-term adjunctive management of severe anxiety**

    - **BY MOUTH**
      - Adult: 2–4 mg daily in divided doses, increased if necessary to 6 mg daily
      - Elderly: Up to 2 mg daily in divided doses, increased if necessary to 6 mg daily

  **Severe nausea and vomiting**

    - **BY MOUTH**
      - Adult: 2–4 mg daily in divided doses; maximum 6 mg per day

- **CONTRA-INDICATIONS** CNS depression, comatose states, phaeochromocytoma

- **INTERACTIONS** Appendix 1: phenothiazines

- **SIDE-EFFECTS** Alertness decreased - anxiety - appetite decreased - blood disorder - cardiac arrest - confusion - fatigue - hyperpyrexia - jaundice cholestatic - lens opacity - muscle weakness - oedema - pancytopenia - photosensitivity reaction - postural hypotension (dose-
related) · skin reactions · thrombocytopenia · urinary hesitation · vision blurred · withdrawal syndrome

SIDE-EFFECTS, FURTHER INFORMATION Extra pyramidal symptoms are more frequent at doses exceeding 6mg daily. Acute dystonias are more common with potent first generation antipsychotics. The risk is increased in men, young adults, children, antipsychotic-naive patients, rapid dose escalation, and abrupt treatment discontinuation.

● HEPATIC IMPAIRMENT Manufacturer advises avoid.

● RENAL IMPAIRMENT
  Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

● MONITORING REQUIREMENTS Trifluoperazine does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral solution
  CAUTIONARY AND ADVISORY LABELS 2
  Trifluoperazine (Non-proprietary)
  Trifluoperazine (as Trifluoperazine hydrochloride) 200 microgram per 1 ml Trifluoperazine 1mg/5ml oral solution sugar free sugar-free | 200 ml £112.25 DT + £112.25
  Trifluoperazine (as Trifluoperazine hydrochloride) 1 mg per 1 ml Trifluoperazine 5mg/5ml oral solution sugar free sugar-free | 150 ml £12.50–£27.00 DT + £27.00

Tablet
  CAUTIONARY AND ADVISORY LABELS 2
  Trifluoperazine (Non-proprietary)
  Trifluoperazine (as Trifluoperazine hydrochloride) 1 mg Trifluoperazine 1mg tablets | 112 tablet £59.12–£99.80
  DT + £59.12
  Trifluoperazine (as Trifluoperazine hydrochloride) 5 mg Trifluoperazine 5mg tablets | 112 tablet £134.89–£165.00 DT + £134.89

Zuclopenthixol

● INDICATIONS AND DOSE
  Psychoses and schizophrenia
  | Short-term management of acute psychosis | Short-term management of mania | Short-term management of exacerbation of chronic psychosis

  BY MOUTH
  Adult: Initially 20–30 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg), for debilitated patients, use elderly dose
  Elderly: Initially 5–15 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg)

  CONTRA-INDICATIONS Apathetic states · CNS depression · comatose states · phaeochromocytoma · withdrawn states
  CAUTIONS Hyperthyroidism · hypothyroidism
  INTERACTIONS → Appendix 1: zuclopenthixol
  SIDE-EFFECTS Anxiety · appetite abnormal · asthenia · concentration impaired · confusion · depression · diarrhoea · dysphoria · eye disorders · fever · flatulence · gait abnormal · gastrointestinal discomfort · glucose tolerance impaired · headaches · hepatic disorders · hot flush · hyperacusia · hyperglycaemia · hyperhidrosis · hyperlipidaemia · hypersalivation · hypothermia · malaise · memory loss · muscle complaints · nasal congestion · nausea · neuromuscular dysfunction · pain · palpitations · paraesthesia · photosensitivity reaction · reflexes increased · seborrhoea · sexual dysfunction · skin reactions · sleep disorders · speech disorder · syncope · thirst · thrombocytopenia · tinnitus · urinary disorders · vertigo · vision disorders · vulvovaginal dryness · weight decreased · withdrawal syndrome
  HEPATIC IMPAIRMENT Can precipitate coma.

Dose adjustments Halve dose.
Monitoring Consider serum-level monitoring in patients with hepatic impairment.

● RENAL IMPAIRMENT
  Dose adjustments Halve dose in renal failure; smaller starting doses used in severe renal impairment because of increased cerebral sensitivity.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
  CAUTIONARY AND ADVISORY LABELS 2
  Clopixol (Lundbeck Ltd)
  Zuclopenthixol (as Zuclopenthixol dihydrochloride) 2 mg Clopixol 2mg tablets | 100 tablet £3.14 DT + £3.14
  Zuclopenthixol (as Zuclopenthixol dihydrochloride) 10 mg Clopixol 10mg tablets | 100 tablet £8.06 DT + £8.06
  Zuclopenthixol (as Zuclopenthixol dihydrochloride) 25 mg Clopixol 25mg tablets | 100 tablet £16.13 DT + £16.13

Zuclopenthixol acetate

● INDICATIONS AND DOSE
  Short-term management of acute psychosis · Short-term management of mania · Short-term management of exacerbation of chronic psychosis

  BY DEEP INTRAMUSCULAR INJECTION
  Adult: 50–150 mg, then 50–150 mg after 2–3 days if required, (1 additional dose may be needed 1–2 days after the first injection); maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections; maximum duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; to be administered into the gluteal muscle or lateral thigh
  Elderly: 50–100 mg, then 50–100 mg after 2–3 days if required, (1 additional dose may be needed 1–2 days after the first injection); maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections; maximum duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; to be administered into the gluteal muscle or lateral thigh

IMPORTANT SAFETY INFORMATION
When prescribing, dispensing, or administering, check that this is the correct preparation—this preparation is usually used in hospital for an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

SAFE PRACTICE
Zuclopenthixol acetate has been confused with zuclopenthixol decanoate; care must be taken to ensure the correct drug is prescribed and dispensed.

● CONTRA-INDICATIONS CNS depression · comatose states · phaeochromocytoma
  CAUTIONS Hyperthyroidism · hypothyroidism
  INTERACTIONS → Appendix 1: zuclopenthixol
  SIDE-EFFECTS Anxiety · appetite abnormal · asthenia · concentration impaired · confusion · depression · diarrhoea · dysphoria · eye disorders · fever · flatulence · gait abnormal · gastrointestinal discomfort · glucose tolerance impaired · headaches · hepatic disorders · hot flush · hyperacusia · hyperglycaemia · hyperhidrosis · hyperlipidaemia · hypersalivation · hypothermia · malaise · memory loss · muscle complaints · nasal congestion · nausea · neuromuscular dysfunction · pain · palpitations · paraesthesia · photosensitivity reaction · reflexes increased · seborrhoea · sexual dysfunction · skin reactions · sleep disorders · speech disorder · syncope · thirst · thrombocytopenia · tinnitus · urinary disorders · vertigo · vision disorders · vulvovaginal dryness · weight decreased · withdrawal syndrome

HEPATIC IMPAIRMENT Can precipitate coma.

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hyperglycaemia · hyperhidrosis · hyperlipidaemia · hypersalivation · hyperthermia (dose-related) · malaise · memory loss · muscle complaints · nasal congestion · nausea · neuromuscular dysfunction · pain · palpitations · paraesthesia · photosensitivity reaction · reflexes increased · seborrhoea · sexual dysfunction · skin reactions · sleep disorders · speech disorder · syncope · thirst · thrombocytopenia · tinnitus · urinary disorders · vertigo · vision disorders · vulvovaginal dryness · weight decreased · withdrawal syndrome

- **HEPATIC IMPAIRMENT** Can precipitate coma.

- **RENAL IMPAIRMENT** Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - Clopiexol Acuphase (Lundbeck Ltd)
  - Flupentixol decanoate 20 mg per 1 ml
  - Flupentixol decanoate 50 mg per 1 ml
  - Flupentixol decanoate 100 mg per 1 ml
  - Flupentixol decanoate 200 mg per 1 ml

  **Flupentixol decanoate**

  (Flupentixol Decanoate)

  **INDICATIONS AND DOSE**

  Maintenance in schizophrenia and other psychoses

  - By deep intramuscular injection
    - Adult: Test dose 20 mg, dose to be injected into the upper outer buttock or lateral thigh, then 20–40 mg after at least 7 days, then 20–40 mg every 2–4 weeks, adjusted according to response, usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; maximum 400 mg per week
    - Elderly: Dose is initially quarter to half adult dose

  **CONTRA-INDICATIONS** Children · CNS depression · comatose states · excitable patients · overactive patients · phaeochromocytoma

  **CAUTIONS** An alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear · hyperthyroidism · hypothyroidism · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

  **SIDE-EFFECTS**

  - Common or very common Appetite abnormal · asthenia · concentration impaired · depression · diarrhoea · dyspnoea · gastrointestinal discomfort · headache · hyperhidrosis · hypersalivation · muscle complaints · nervousness · palpitations · sexual dysfunction · skin reactions · urinary disorder · vision disorders
    - Uncommon Confusion · flatulence · hot flush · nausea · oculogyric reaction · photosensitivity reaction · speech disorder
    - Rare or very rare Glucose tolerance impaired · hyperglycaemia · jaundice · thrombocytopenia
    - Frequency not known Suicidal tendencies

  **SIDE-EFFECTS, FURTHER INFORMATION** Side-effects may persist until the drug has been cleared from its depot site.

  **HEPATIC IMPAIRMENT** Manufacturer advises caution—monitor serum drug concentration.

  **Dose adjustments** Manufacturer advises initiate at low dose orally to check for tolerability before switching to depot formulation.

- **RENAI IMPAIRMENT** Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MONITORING REQUIREMENTS** Treatment requires careful monitoring for optimum effect.

- **DIRECTIONS FOR ADMINISTRATION** In general not more than 2–3 ml of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained—release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  - Depixol (Lundbeck Ltd)
  - Psytixol (Mylan)

  **Fluphenazine decanoate**

  (Fluphenazine Decanoate)

  **INDICATIONS AND DOSE**

  Maintenance in schizophrenia and other psychoses

  - By deep intramuscular injection
    - Adult: Test dose 12.5 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response
    - Elderly: Test dose 6.25 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response

  **CONTRA-INDICATIONS** Children · CNS depression · comatose states · marked cerebral atherosclerosis · phaeochromocytoma

  **CAUTIONS** Hypothyroidism · QT-interval prolongation · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

  **INTERACTIONS** → Appendix 1: phenothiazines

  **SIDE-EFFECTS** Acute kidney injury · blood disorder · cognitive impairment · epileptiform seizure · headache · hepatic disorders · hyponatraemia · lens opacity · leucocytosis · nasal congestion · oculogyric crisis · oedema · oligomenorrhoea · sexual dysfunction · SADH · skin pigmentation change · systemic lupus erythematosus (SLE) · temperature regulation disorder · thrombocytopenia · urinary disorders · vision blurred

  **SIDE-EFFECTS, FURTHER INFORMATION** Side-effects may persist until the drug has been cleared from its depot site.

- **RENAL IMPAIRMENT** Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **HEPATIC IMPAIRMENT** Can precipitate coma.

- **RENAI IMPAIRMENT** Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  - Depixol (Lundbeck Ltd)
  - Flupentixol decanoate 20 mg per 1 ml
  - Fluphenazine decanoate 20 mg per 1 ml

  **Flupentixol decanoate**

  (Flupentixol Decanoate)

  **INDICATIONS AND DOSE**

  Maintenance in schizophrenia and other psychoses

  - By deep intramuscular injection
    - Adult: Test dose 20 mg, dose to be injected into the upper outer buttock or lateral thigh, then 20–40 mg after at least 7 days, then 20–40 mg every 2–4 weeks, adjusted according to response, usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; maximum 400 mg per week
    - Elderly: Dose is initially quarter to half adult dose

  **CONTRA-INDICATIONS** Children · CNS depression · comatose states · excitable patients · overactive patients · phaeochromocytoma

  **CAUTIONS** An alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear · hyperthyroidism · hypothyroidism · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

  **SIDE-EFFECTS**

  - Common or very common Appetite abnormal · asthenia · concentration impaired · depression · diarrhoea · dyspnoea · gastrointestinal discomfort · headache · hyperhidrosis · hypersalivation · muscle complaints · nervousness · palpitations · sexual dysfunction · skin reactions · urinary disorder · vision disorders
    - Uncommon Confusion · flatulence · hot flush · nausea · oculogyric reaction · photosensitivity reaction · speech disorder
    - Rare or very rare Glucose tolerance impaired · hyperglycaemia · jaundice · thrombocytopenia
    - Frequency not known Suicidal tendencies

  **SIDE-EFFECTS, FURTHER INFORMATION** Side-effects may persist until the drug has been cleared from its depot site.

  **HEPATIC IMPAIRMENT** Manufacturer advises caution—monitor serum drug concentration.

  **Dose adjustments** Manufacturer advises initiate at low dose orally to check for tolerability before switching to depot formulation.
DOSE EQUIVALENCE AND CONVERSION

- A range of equivalent doses is quoted in the literature; the consensus is that 2 mg per day of oral haloperidol is approximately equivalent to 15 mg per week of haloperidol decanoate depot injection.

IMPORTANT SAFETY INFORMATION

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the rapid control of an acute episode.

CONTRA-INDICATIONS
- Children: CNS depression; comatose states; congenital long QT syndrome; dementia with Lewy bodies; history of torsade de pointes; history of ventricular arrhythmia; Parkinson’s disease; progressive supranuclear palsy; QT-interval prolongation; recent acute myocardial infarction; uncompensated heart failure; uncorrected hypokalaemia
- Bradycardia; electrolyte disturbances (correct before treatment initiation); family history of QTc-interval prolongation; history of heavy alcohol exposure; hyperthyroidism; hypothermia (including orthostatic hypotension); prolactin-dependent tumours; prolactinaemia; risk factors for stroke; when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

INTERACTIONS
- Appendix A: haloperidol
- Appendix B: further information

SIDE-EFFECTS
- Common or very common: Depression; hypersalivation; muscle complaints; sexual dysfunction
- Uncommon: Eye disorders; headache; neuromuscular dysfunction; vision disorders
- Frequency not known: Angioedema; breast abnormalities; cardiac arrest; confusion; dyspnoea; gait abnormal; hepatic disorders; hypoglycaemia; menorrhagia; menstrual cycle irregularities; musculoskeletal stiffness; nausea; oedema; pancytopenia; photosensitivity reaction; psychotic disorder; respiratory disorders; restlessness; rhabdomyolysis; SIADH; skin reactions; temperature regulation disorders; thrombocytopenia; trismus; weight decreased

SIDE-EFFECTS, FURTHER INFORMATION

Haloperidol is a less sedating antipsychotic.
- Pregnancy
  - Manufacturer advises caution.
  - Dose adjustments
    - Manufacturer advises halve initial dose and then adjust if necessary with smaller increments and at longer intervals.
- Hepatic impairment
  - Manufacturer advises caution.
  - Dose adjustments
    - Manufacturer advises consider lower initial dose in severe impairment and then adjust if necessary with smaller increments and at longer intervals.
- Renal impairment
  - Manufacturer advises use with caution.
  - Dose adjustments
    - Manufacturer advises consider lower initial dose in severe impairment and then adjust if necessary with smaller increments and at longer intervals.
- Monitoring requirements
  - Manufacturer advises perform ECG before treatment initiation and assess need for further ECGs during treatment on an individual basis.
  - Manufacturer advises monitor electrolytes before treatment initiation and periodically during treatment.
- Directions for administration
  - In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.
preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **EXCIPIENTS:** May contain Benzy1 alcohol, sesame oil
- **Haloperidol decanoate (Janssen-Cilag Ltd)**
- **Haloperidol (as Haloperidol decanoate) 50 mg per 1 ml Haloperidol Decanoate 50mg/1ml solution for injection ampoules | 5 ampoule £19.06 DT + £13.06**
- **Haloperidol (as Haloperidol decanoate) 100 mg per 1 ml Haloperidol Decanoate 100mg/1ml solution for injection ampoules | 5 ampoule £25.26 DT + £25.26**

**Zuclopenthixol decanoate**

- **INDICATIONS AND DOSE**
  - Maintenance in schizophrenia and paranoid psychoses
    - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: Test dose 100 mg, dose to be administered into the upper outer buttock or lateral thigh, followed by 200–500 mg after at least 7 days, then 200–500 mg every 1–4 weeks, adjusted according to response; higher doses of more than 500mg can be used; do not exceed 600 mg weekly
    - Elderly: A quarter to half usual starting dose to be used

- **CONTRA-INDICATIONS** Children · CNS depression · comatose states · phaeochromocytoma
- **CAUTIONS** Hyperthyroidism · hypothyroidism · QT interval prolongation · when transferring from oral to depot therapy, the dose by mouth should be reduced gradually
- **INTERACTIONS** → Appendix 1: zuclopenthixol

**SIDE-EFFECTS** Anxiety · appetite abnormal · asthenia · concentration impaired · confusion · depression · diarrhoea · dysphoria · eye disorders · fever · flatulence · gait abnormal · gastrointestinal discomfort · glucose tolerance impaired · headaches · hepatic disorders · hot flush · hyacrusia · hyperglycaemia · hyperhidrosis · hyperlipidaemia · hypersalivation · hypothermia · malaise · memory loss · muscle complaints · nasal congestion · nausea · neuromuscular dysfunction · pain · palpitations · paraesthesia · photosensitivity reaction · reflexes increased · sebhorhoea · sexual dysfunction · skin reactions · sleep disorders · speech disorder · syncope · thirst · thrombocytopenia · tinnitus · urinary disorders · vertigo · vision disorders · vulvovaginal dryness · weight decreased · withdrawal syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** Side-effects may persist until the drug has been cleared from its depot site.

- **HEPATIC IMPAIRMENT** Can precipitate coma.
- **RENAL IMPAIRMENT** Dose adjustments Start with small doses in severe renal impairment because of increased cerebral sensitivity.
- **MONITORING REQUIREMENTS** Treatment requires careful monitoring for optimum effect.
- **DIRECTIONS FOR ADMINISTRATION** In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Clopixol (Lundbeck Ltd)**
  - **Zuclopenthixol decanoate 200 mg per 1 ml Clopixol 200mg/1ml solution for injection ampoules | 10 ampoule £33.15 DT = £31.51**
  - **Zuclopenthixol decanoate 500 mg per 1 ml Clopixol Conc 500mg/1ml solution for injection ampoules | 5 ampoule £37.18 DT = £37.18**

**ANTIPSYCHOTICS > SECOND-GENERATION**

**Amisulpride**

- **DRUG ACTION** Amisulpride is a selective dopamine receptor antagonist with high affinity for mesolimbic D₄ and D₃ receptors.

**INDICATIONS AND DOSE**

- **Acute psychotic episode in schizophrenia**
  - **BY MOUTH**
  - Adult: 400–800 mg daily in 2 divided doses, adjusted according to response; maximum 1.2 g per day

- **Schizophrenia with predominantly negative symptoms**
  - **BY MOUTH**
  - Adult: 50–300 mg daily

**CONTRA-INDICATIONS** CNS depression · comatose states · phaeochromocytoma · prolactin-dependent tumours

**INTERACTIONS** → Appendix 1: amisulpride

**SIDE-EFFECTS**

- Common or very common
  - Anxiety · breast pain · hypersalivation · muscle rigidity · nausea · oculogyric crisis · orgasm abnormal · trismus
- Uncommon
  - Hyperglycaemia
- Frequency not known
  - Angioedema · bone disorders · cardiac arrest · confusion · dyslipidaemia · hyponatraemia · nasal congestion · neoplasms · SIADH · urticaria · vision blurred

- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid—no information available.

**RENAL IMPAIRMENT** No information available if eGFR less than 10 mL/minute/1.73 m².

**Dose adjustments** Halve dose if eGFR 30–60 mL/minute/1.73 m². Use one-third dose if eGFR 10–30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Amisulpride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include caramel.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS** 2

- **Amisulpride (Non-proprietary)**
  - **Amisulpride 100 mg per 1 ml** Amisulpride 100mg/ml oral solution sugar free sugar-free | 60 ml £87.48 DT + £40.64

www.getintopharma.com
**Aripiprazole**

**DRUG ACTION** Aripiprazole is a dopamine D₂ partial agonist with weak 5-HT₁A partial agonism and 5-HT₂A receptor antagonism.

**INDICATIONS AND DOSE**

- **Maintenance of schizophrenia in patients stabilised with oral aripiprazole (CYP2D6 poor metabolisers)**
  - **By intramuscular injection**
    - Adult: 300 mg every month, to be injected into the gluteal or deltoid muscle, minimum of 26 days between injections, treatment with 10–20 mg oral aripiprazole daily should be continued for 14 consecutive days after the first injection, for dose adjustment due to side-effects and for advice on missed doses, consult product literature

- **Maintenance of schizophrenia in patients stabilised with oral aripiprazole**
  - **By intramuscular injection**
    - Adult: 400 mg every month, to be injected into the gluteal or deltoid muscle, minimum of 26 days between injections, treatment with 10–20 mg oral aripiprazole daily should be continued for 14 consecutive days after the first injection, for dose adjustment due to side-effects and for advice on missed doses, consult product literature

- **Schizophrenia**
  - **By mouth**
    - Adult: 10–15 mg once daily; usual dose 15 mg once daily (max. per dose 30 mg once daily)

- **Treatment and recurrence prevention of mania**
  - **By mouth**
    - Adult: 15 mg once daily, increased if necessary up to 30 mg once daily

- **Control of agitation and disturbed behaviour in schizophrenia**
  - **By intramuscular injection**
    - Adult: Initially 5.25–15 mg for 1 dose, alternatively usual dose 9.75 mg for 1 dose, followed by 5.25–15 mg after 2 hours if required, maximum 3 injections daily; maximum daily combined oral and parenteral dose 30 mg

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- With oral use Manufacturer advises reduce dose by half with concurrent use of potent inhibitors of CYP3A4 or CYP2D6.

- With intramuscular use For dose adjustments due to concurrent use of interacting drugs—consult product literature.

**IMPORTANT SAFETY INFORMATION**

When prescribing, dispensing, or administering, check that the correct preparation is used—the preparation usually used in hospital for the rapid control of an acute episode (solution for injection containing aripiprazole 7.5 mg/mL) should not be confused with depot preparations (aripiprazole 400-mg vial with solvent), which are usually used in the community or clinics for maintenance treatment.

- **CONTRA-INDICATIONS** CNS depression - comatose state - phaeochromocytoma

- **CAUTIONS**
  - **GENERAL CAUTIONS** Cerebrovascular disease - elderly (reduce initial dose)

- **SPECIFIC CAUTIONS**
  - With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

- **INTERACTIONS** → Appendix 1: aripiprazole

- **SIDE-EFFECTS**
  - **Common or very common** Anxiety - appetite abnormal - diabetes mellitus - fatigue - gastrointestinal discomfort - headache - hypersalivation - nausea - vision disorders
  - **Uncommon** Depression - hiccups - hyperglycaemia - sexual dysfunction

- **PREGNANCY** Use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (oral treatment preferred to intramuscular administration; limited information available).

- **MONITORING REQUIREMENTS**
  - Aripiprazole does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.
  - With intramuscular use Treatment requires careful monitoring for optimum effect.

- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use Orodispersible tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed.
  - With intramuscular use Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential.

- **PATIENT AND CARER ADVICE**
  - With oral use Patients or carers should be given advice on how to administer aripiprazole orodispersible tablets.
Concepcion and contraception Manufacturer advises highly effective contraception in women of childbearing potential during treatment and for at least 10 weeks after the last dose; addition of barrier method recommended in women using systemically-acting hormonal contraceptives.

Pregnancy Manufacturer advises avoid—toxicity in animal studies.

Breastfeeding Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment Manufacturer advises avoid in severe impairment (no information available).

Renal impairment Manufacturer advises avoid in severe impairment (no information available).

Medicinal forms There can be variation in the licensing of different medicines containing the same drug.

Clozapine

• Drug action Clozapine is a dopamine D2, dopamine D4, 5-HT2A, alpha-adrenoceptor, and muscarinic-receptor antagonist.

• Indications and dose Schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs

- By mouth
  - Adult 18–59 years: 12.5 mg 1–2 times a day for day 1, then 25–50 mg for day 2, then increased, if tolerated, in steps of 25–50 mg daily, up to 300 mg daily in divided doses, larger dose at bedtime; in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dose 200–450 mg daily, max. 900 mg per day, if restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing
  - Adult 60 years and over: 12.5 mg once daily for day 1, then increased to 25–37.5 mg for day 2, then increased, if tolerated, in steps of up to 25 mg daily, up to 300 mg daily in divided doses, larger dose at bedtime; in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dose 200–450 mg daily, max. 900 mg per day, if restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

Psychosis in Parkinson’s disease

- By mouth
  - Adult: 12.5 mg once daily, dose to be taken at bedtime, then increased in steps of 12.5 mg up to twice weekly, adjusted according to response; usual dose 25–37.5 mg
Psychoses and schizophrenia

once daily, dose to be taken at bedtime; increased in steps of 12.5 mg once weekly, this applies only in exceptional cases, increased if necessary up to 100 mg daily in 1–2 divided doses; Usual maximum 50 mg/24 hours

IMPORTANT SAFETY INFORMATION

Clozapine has been associated with varying degrees of impairment of intestinal peristalsis—see Cautions and Contra-indications for further information. Patients and their carers should be advised to seek immediate medical advice before taking the next dose of clozapine if constipation develops.

- **CONTRA-INDICATIONS**
  - Alcoholic and toxic psychoses
  - bone-marrow disorders - coma - drug intoxication - history of agranulocytosis - history of circulatory collapse - history of neuropaenia - paralytic ileus - severe cardiac disorders (e.g. myocarditis) - severe CNS depression - uncontrolled epilepsy

- **CAUTIONS**
  - Age over 60 years - prostatic hypertrophy - susceptibility to angle-closure glaucoma - taper off other antipsychotics before starting

**CAUTIONS, FURTHER INFORMATION**

- **Agranulocytosis** Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm$^3$ or if absolute neutrophil count below 1500/mm$^3$ discontinue permanently and refer to haematologist. Patients who have a low white blood cell count because of benign ethnic neutropaenia may be started on clozapine with the agreement of a haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of infection, especially influenza-like illness.
  - **Myocarditis and cardiomyopathy** Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported.
  - Perform physical examination and take full medical history before starting
  - Specialist examination required if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk
  - Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy
  - If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist
  - Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy
  - **Intestinal obstruction** Impairment of intestinal peristalsis, including constipation, intestinal obstruction, faecal impaction, and paralytic ileus, (including fatal cases) reported. Clozapine should be used with caution in patients receiving drugs that may cause constipation (e.g. antimuscarinic drugs) or in those with a history of colonic disease or lower abdominal surgery. It is essential that constipation is recognised and actively treated.

- **INTERACTIONS** → Appendix 1: clozapine
- **SIDE-EFFECTS**
  - **Common or very common** Appetite decreased - eosinophilia - fatigue - fever - headache - hypertension - leucocytosis - muscle complaints - nausea - oral disorders - postural hypotension (dose-related) - speech impairment - sweating abnormal - syncope - temperature regulation disorders - urinary disorders - vision blurred
  - **Rare or very rare** Anaemia - cardiac arrest - cardiac inflammation - cardiomyopathy - circulatory collapse - confusion - delirium - diabetes mellitus - dyslipidaemia - dysphagia - gastrointestinal disorders - glucose tolerance impaired - hepatic disorders - hyperglycaemia - increased risk of infection - intestinal obstruction (including fatal cases) - ketoadicosis - nephritis tubulointerstitial - obsessive-compulsive disorder - pancreatitis - pericardial effusion - respiratory disorders - restlessness - sexual dysfunction - skin reactions - thrombocytopenia - thrombocytosis
  - **Frequency not known** Angina pectoris - angiodema - chest pain - cholinergic syndrome - diarrhoea - gastrointestinal discomfort - hypersensitivity vasculitis - muscle weakness - myocardial infarction - nasal congestion - pseudopheochromocytoma - renal failure - systemic lupus erythematosus (SLE)

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypersalivation associated with clozapine therapy can be treated with hycosine hydrobromide [unlicensed indication], provided that the patient is not at particular risk from the additive antimuscarinic side-effects of hycosine and clozapine.

- **PREGNANCY** Use with caution.
- **BREAST FEEDING** Avoid.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—monitor liver function (discontinue if liver enzymes are greater than 3 times the upper limit of normal or jaundice occurs); avoid in symptomatic or progressive impairment and in hepatic failure.
- **RENAL IMPAIRMENT** Avoid in severe impairment.
- **MONITORING REQUIREMENTS**
  - Monitor leucocyte and differential blood counts. Clozapine requires differential white blood cell monitoring weekly for 18 weeks, then fortnightly for up to one year, and then monthly as part of the clozapine patient monitoring service.
  - Close medical supervision during initiation (risk of collapse because of hypotension and convulsions).
  - Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotics. Patients taking clozapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.
  - Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking clozapine should have fasting blood glucose tested at baseline, after one months’ treatment, then every 4–6 months.
  - Patient, prescriber, and supplying pharmacist must be registered with the appropriate Patient Monitoring Service—it takes several days to do this.

**TREATMENT CESSATION**

On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe patient carefully.

**DIRECTIONS FOR ADMINISTRATION**

Shake oral suspension well for 90 seconds when dispensing or if visibly settled and stand for 24 hours before use; otherwise shake well for 10 seconds before use. May be diluted with water.

**PRESCRIBING AND DISPENSING INFORMATION**

Clozapine has been used for psychosis in Parkinson’s disease in children aged 16 years and over.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer clozapine oral suspension.
Dose adjustments Manufacturer advises initially 18.5 mg once daily in moderate to severe impairment, increased if necessary up to 74 mg once daily in moderate impairment, or up to max. 37 mg once daily in severe impairment.

Renal impairment Manufacturer advises use only if potential benefit outweighs risk if eGFR less than 15 mL/minute/1.73 m². Dose adjustments Initially 18.5 mg once daily, up to max. 74 mg once daily if eGFR less than 50 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION Patients on doses higher than 111 mg once daily whose treatment is interrupted for longer than 3 days should restart on 111 mg once daily and titrate to usual dose; for all other doses, restart on usual dose.

MEDICAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet CAUTIONARY AND ADVISORY LABELS 2, 10
- Lurasidone (as Lurasidone hydrochloride) 18.5 mg Latura 18.5mg tablets | 28 tablet (PO) £90.72 DT | £90.72
- Lurasidone (as Lurasidone hydrochloride) 37 mg Latura 37mg tablets | 28 tablet (PO) £90.72 DT | £90.72
- Lurasidone (as Lurasidone hydrochloride) 74 mg Latura 74mg tablets | 28 tablet (PO) £90.72 DT | £90.72

Olanzapine

DRUG ACTION Olanzapine is a dopamine D₆, D₇, 5-HT₁b, histamine-1-, and muscarinic-receptor antagonist.

INDICATIONS AND DOSE Schizophrenia | Combination therapy for mania
- BY MOUTH
  - Adult: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 10 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

Preventing recurrence in bipolar disorder
- BY MOUTH
  - Adult: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 10 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

Monotherapy for mania
- BY MOUTH
  - Adult: 15 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 15 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day

Control of agitation and disturbed behaviour in schizophrenia or mania
- BY INTRAMUSCULAR INJECTION
  - Adult: Initially 5–10 mg for 1 dose; usual dose 10 mg for 1 dose, followed by 5–10 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase
Elderly: Initially 2.5–5 mg, followed by 2.5–5 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase.

**CONTRA-INDICATIONS**
- With intramuscular use: Acute myocardial infarction - bradycardia - recent heart surgery - severe hypotension - sickle cell anemia - cor pulmonale - unstable angina

**CAUTIONS**
- Bone-marrow depression - hypersesosinophilic disorders - low leucocyte count - low neutrophil count - myeloproliferative disease - paralytic ileus

**FREQUENCY NOT KNOWN**
- With oral use
- With intramuscular use

**SPECIFIC SIDE-EFFECTS**
- CNS and respiratory depression
- With intramuscular use: Blood pressure, pulse and respiratory rate should be monitored for at least one hour between administration of olanzapine intramuscular injection and parenteral benzodiazepines.

**GENERAL SIDE-EFFECTS**
- Common or very common: Appetite increased - arthralgia - oedema
- Uncommon: Alopecia - epistaxis - memory loss
- Rare or very rare: Hepatic disorders - pancreatitis - rhabdomyolysis

**CAUTIONARY AND ADVISORY LABELS**
- Prescribing and dispensing information
- With intramuscular use: When prescribing, dispensing, or administering, check that this injection is the correct preparation — this preparation is usually used in hospital for the rapid control of an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

**PATIENT AND CARER ADVICE**
- Patients or carers should be given advice on how to administer orodispersible tablets.

**MEDITCINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

**Olanzapine (Non-proprietary)**
- Olanzapine 2.5 mg: Olanzapine 2.5 mg tablets | 28 tablet £\( \text{12.15} \times 28 \text{ (£0.437)} \)
- Olanzapine 5 mg: Olanzapine 5 mg tablets | 28 tablet £\( \text{24.30} \times 28 \text{ (£0.861)} \)
- Olanzapine 7.5 mg: Olanzapine 7.5 mg tablets | 28 tablet £\( \text{36.45} \times 28 \text{ (£1.301)} \)
- Olanzapine 10 mg: Olanzapine 10 mg tablets | 28 tablet £\( \text{48.60} \times 28 \text{ (£1.714)} \)
- Olanzapine 15 mg: Olanzapine 15 mg tablets | 28 tablet £\( \text{60.75} \times 28 \text{ (£2.128)} \)
- Olanzapine 20 mg: Olanzapine 20 mg tablets | 28 tablet £\( \text{72.90} \times 28 \text{ (£2.582)} \)

**Zalasta (Consilient Health Ltd)**
- Olanzapine 2.5 mg: Zalasta 2.5 mg tablets | 28 tablet £\( \text{18.57} \times 28 \text{ (£0.662)} \)
- Olanzapine 5 mg: Zalasta 5 mg tablets | 28 tablet £\( \text{37.14} \times 28 \text{ (£1.324)} \)
- Olanzapine 7.5 mg: Zalasta 7.5 mg tablets | 28 tablet £\( \text{55.71} \times 28 \text{ (£1.986)} \)
- Olanzapine 10 mg: Zalasta 10 mg tablets | 28 tablet £\( \text{74.29} \times 28 \text{ (£2.652)} \)
- Olanzapine 15 mg: Zalasta 15 mg tablets | 28 tablet £\( \text{91.03} \times 28 \text{ (£3.220)} \)
- Olanzapine 20 mg: Zalasta 20 mg tablets | 28 tablet £\( \text{113.06} \times 28 \text{ (£3.966)} \)

**Zyprexa (Eli Lilly and Company Ltd)**
- Olanzapine 2.5 mg: Zyprexa 2.5 mg tablets | 28 tablet £\( \text{12.85} \times 28 \text{ (£0.453)} \)
- Olanzapine 5 mg: Zyprexa 5 mg tablets | 28 tablet £\( \text{24.70} \times 28 \text{ (£0.882)} \)
- Olanzapine 7.5 mg: Zyprexa 7.5 mg tablets | 28 tablet £\( \text{34.55} \times 28 \text{ (£1.234)} \)
- Olanzapine 10 mg: Zyprexa 10 mg tablets | 28 tablet £\( \text{45.40} \times 28 \text{ (£1.614)} \)
- Olanzapine 15 mg: Zyprexa 15 mg tablets | 28 tablet £\( \text{59.53} \times 28 \text{ (£2.119)} \)
- Olanzapine 20 mg: Zyprexa 20 mg tablets | 28 tablet £\( \text{72.90} \times 28 \text{ (£2.582)} \)

**Oral Lophylisate**
- Zyprexa (Eli Lilly and Company Ltd)
- Olanzapine 5 mg: Zyprexa 5 mg Velotabs sugar-free | 28 tablet £\( \text{48.07} \times 28 \text{ (£1.714)} \)

**Orodispersible tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

**EXCIPIENTS:** May contain Aspartame

**Olanzapine (Non-proprietary)**
- Olanzapine 2.5 mg: Olanzapine 2.5 mg orodispersible tablets sugar free sugar-free | 28 tablet £\( \text{48.07} \times 28 \text{ (£1.714)} \)
- Olanzapine 5 mg: Olanzapine 5 mg orodispersible tablets sugar free sugar-free | 28 tablet £\( \text{90.14} \times 28 \text{ (£3.174)} \)
- Olanzapine 7.5 mg: Olanzapine 7.5 mg orodispersible tablets sugar free sugar-free | 28 tablet £\( \text{114.21} \times 28 \text{ (£4.007)} \)
- Olanzapine 10 mg: Olanzapine 10 mg orodispersible tablets sugar free sugar-free | 28 tablet £\( \text{138.28} \times 28 \text{ (£4.939)} \)

**Olanzapine 10 mg: Olanzapine 10 mg orodispersible tablets | 28 tablet £\( \text{50.00} \times 28 \text{ (£1.786)} \)
- Olanzapine 10 mg: Olanzapine 10 mg orodispersible tablets sugar free sugar-free | 28 tablet £\( \text{49.74} \times 28 \text{ (£1.762)} \)

www.getintopharma.com
400 Mental health disorders

Paliperidone

**DRUG ACTION** Paliperidone is a metabolite of risperidone.

### INDICATIONS AND DOSE

#### SCHIZOPHRENIA | Psychotic or manic symptoms of schizoaffective disorder

- **BY MOUTH**
  - Adult: 6 mg once daily, dose to be taken in the morning, then adjusted in steps of 3 mg if required, dose to be adjusted over at least 5 days; usual dose 3–12 mg daily

**ZALASTA** PRE-FILLED SYRINGES

Maintenance of schizophrenia in patients who are clinically stable on once-monthly intramuscular paliperidone

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: Initially 175–525 mg every 3 months, adjusted according to response, to be administered into the deltoid or gluteal muscle, dose is based on previous once-monthly intramuscular paliperidone and should be initiated in place of the next scheduled dose—consult product literature

**XEPLION** PRE-FILLED SYRINGES

Maintenance in schizophrenia in patients previously responsive to paliperidone or risperidone

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 150 mg for 1 dose on day 1, then 100 mg for 1 dose on day 8, to be injected into the deltoid muscle, dose subsequently adjusted at monthly intervals according to response; maintenance 75 mg once a month, alternatively maintenance 25–150 mg once a month, following the second dose, monthly maintenance doses can be administered into either the deltoid or gluteal muscle

### CAUTIONS

#### GENERAL CAUTIONS
Cataract surgery (risk of intraoperative floppy iris syndrome) • dementia with Lewy bodies • elderly patients with dementia • elderly patients with risk factors for stroke • predisposition to gastrointestinal obstruction • prolactin-dependent tumours

#### SPECIFIC CAUTIONS
- With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

### INTERACTIONS
- Appendix 1: paliperidone

### SIDE-EFFECTS

#### GENERAL SIDE-EFFECTS
- Common or very common: Anxiety • appetite abnormal • asthenia • cardiac conduction disorders • cough • depression • diarrhoea • fever • gastrointestinal discomfort • headache • hyperglycaemia • hypertension • increased risk of infection • joint disorders • laryngeal pain • mood altered • nasal congestion • nausea • oral disorders • pain • skin reactions • vision disorders
- Uncommon: Alopecia • anaemia • breast abnormalities • chest discomfort • chills • conjunctivitis • cystitis • dry eye • dysarthria • dysphagia • dyspnoea • ear pain • epistaxis • fall • gait abnormal • gastrointestinal disorders • generalised tonic-clonic seizure • hypoglycaemia • induration • malaise • menstrual cycle irregularities • muscle spasms • muscle weakness • oedema • palpitations • respiratory disorders • sensation abnormal • sexual dysfunction • sleep disorders • syncope • taste altered • thirst • thombocytopenia • tinnitus • urinary disorders • vertigo
- Rare or very rare: Angioedema • cerebrovascular insufficiency • coma • consciousness impaired • dandruff • diabetic ketoacidosis • dysphonia • eye disorders • flushing • glaucoma • hypothermia • ischaemia • jaundice • pancreatitis • polydipsia • posture abnormal • rhabdomyolysis • SIADH • sleep apnoea • vaginal discharge • water intoxication • withdrawal syndrome

#### SPECIFIC SIDE-EFFECTS
- Common or very common:
  - With oral use: Weight decreased
  - Uncommon:
    - With oral use: Concentration impaired • confusion • diabetes mellitus
    - Frequency not known:
      - With intramuscular use: Injection site necrosis
      - PREGNANCY
        - Use only if potential benefit outweighs risk—toxicity in animal studies; if discontinuation during pregnancy is necessary, withdraw gradually
      - **TREVICTA** PRE-FILLED SYRINGES
        - Manufacturer advises to consider long-acting nature of formulation—paliperidone detected in plasma up to 18 months after single dose
      - **BREAST FEEDING**
        - Manufacturer advises avoid—present in milk
      - **TREVICTA** PRE-FILLED SYRINGES
        - Manufacturer advises to consider long-acting nature of formulation—paliperidone detected in plasma up to 18 months after single dose
      - **HEPATIC IMPAIRMENT**
        - Manufacturer advises caution in severe impairment (no information available)
      - **RENAL IMPAIRMENT**
        - With oral use: Manufacturer advises avoid if creatinine clearance less than 10 mL/minute
        - With intramuscular use: Manufacturer advises avoid if creatinine clearance less than 50 mL/minute
        - Dose adjustments:
          - With oral use: Manufacturer advises reduce initial dose to 3 mg once daily if creatinine clearance 50–80 mL/minute (max. 6 mg once daily). Manufacturer advises reduce initial dose to 1.5 mg once daily if creatinine clearance 10–50 mL/minute (max. 3 mg once daily)
      - **TREVICTA** PRE-FILLED SYRINGES
        - **DOSE ADJUSTMENTS**
          - Manufacturer advises initial dose 100 mg on day 1 and then 75 mg on day 8 if creatinine clearance 50–80 mL/minute; recommended maintenance dose 50 mg (range 25–100 mg) monthly if creatinine clearance 50–80 mL/minute

### MONITORING REQUIREMENTS
- With intramuscular use: Treatment requires careful monitoring for optimum effect

### DIRECTIONS FOR ADMINISTRATION
- With intramuscular use: Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential
With oral use. Always take with breakfast or always take on an empty stomach.

**PRESCRIBING AND DISPENSING INFORMATION**

**NEPHROLOGICAL FORMS**

With oral use. Always take with breakfast or always take on an empty stomach.

**PATIENT AND CARER ADVICE**

With oral use. Patients or carers should be given advice on how to administer paliperidone tablets.

**Missed doses**

With intramuscular use. For missed doses see product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

TREVICITA® PRE-FILLED SYRINGES

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium (SMC) has advised (September 2016) that paliperidone palmitate (Trevicta®) is accepted for use within NHS Scotland for the maintenance treatment of schizophrenia in patients who are clinically stable on one-monthly paliperidone palmitate injectable product.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Prolonged-release suspension for injection**

**Trevicta** (Janssen-Cilag Ltd)

Paliperidone (as Paliperidone palmitate) 200 mg per 1 ml Trevicta 175mg/0.875ml prolonged-release suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $51.76 DT + $551.76

Trevicta 263mg/1.315ml prolonged-release suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $734.70 DT + $734.70

Trevicta 350mg/1.75ml prolonged-release suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $942.21 DT + $942.21

Trevicta 525mg/2.625ml prolonged-release suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $1,177.77 DT + $1,177.77

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 2, 25

**Invega** (Janssen-Cilag Ltd)

Paliperidone 3 mg

Invega 3mg modified-release tablets | 28 tablet

Brazil: $97.28 DT + $97.28

Paliperidone 6 mg

Invega 6mg modified-release tablets | 28 tablet

Brazil: $97.28 DT + $97.28

**Invega** (Janssen-Cilag Ltd)

Paliperidone 9 mg

Invega 9mg modified-release tablets | 28 tablet

Brazil: $145.92 DT + $145.92

**Suspension for injection**

**Xeplion** (Janssen-Cilag Ltd)

Paliperidone (as Paliperidone palmitate) 100 mg per 1 ml Xeplion 150mg/1.5ml suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $392.59 DT + $392.59

Xeplion 75mg/0.75ml suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $244.90 DT + $244.90

Xeplion 100mg/1ml suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $314.07 DT + $314.07

Xeplion 50mg/0.5ml suspension for injection pre-filled syringes | 1 pre-filled disposable injection

Brazil: $183.92 DT + $183.92

**Quetiapine**

**DRUG ACTION**

Quetiapine is a dopamine D1, dopamine D2, 5-HT2, alpha-adrenergic, and histamine-1 receptor antagonist.

**INDICATIONS AND DOSE**

**Schizophrenia**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: 25 mg twice daily for day 1, then 50 mg twice daily for day 2, then 100 mg twice daily for day 3, then 150 mg twice daily for day 4, then, adjusted according to response, usual dose 300–450 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 750 mg per day.

**DOSE EQUIVALENCE AND CONVERSION**

Patients can be switched from immediate-release to modified-release tablets at the equivalent daily dose; to maintain clinical response, dose titration may be required.

**CAUTIONS**

Cerebrovascular disease - elderly - patients at risk of aspiration pneumonia - treatment of depression in patients under 25 years (increased risk of suicide)

**INTERACTIONS**

Appendix 1: quetiapine

**Treatment of mania in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: 50 mg twice daily for day 1, then 100 mg twice daily for day 2, then 150 mg twice daily for day 3, then 200 mg twice daily for day 4, then adjusted in steps of up to 200 mg daily, adjusted according to response, usual dose 400–800 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 800 mg per day.

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

Adult: 300 mg once daily for day 1, then 600 mg once daily for day 2, then, adjusted according to response, usual dose 600 mg once daily, maximum dose under specialist supervision; maximum 800 mg per day.

Elderly: Initially 50 mg once daily, adjusted according to response, adjusted in steps of 50 mg daily.

**Treatment of depression in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: 50 mg once daily for day 1, then 100 mg once daily for day 2, then 150 mg twice daily for day 3, then 200 mg twice daily for day 4, then adjusted in steps of up to 200 mg daily, adjusted according to response, usual dose 400–800 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 800 mg per day.

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

Adult: 300 mg once daily for day 1, then 600 mg once daily for day 2, then, adjusted according to response, usual dose 400–800 mg once daily.

Elderly: Initially 50 mg once daily, adjusted according to response, adjusted in steps of 50 mg daily.

**Prevention of mania and depression in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg daily in 2 divided doses.

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg once daily.

**Adjuventive treatment of major depression**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

Adult: 50 mg once daily for 2 days, dose to be taken at bedtime, then 150 mg once daily for 2 days, then, adjusted according to response, usual dose 300–800 mg once daily.

Elderly: Initially 50 mg once daily for 3 days, then increased if necessary to 100 mg once daily for 4 days, then adjusted in steps of 50 mg, adjusted according to response, usual dose 50–300 mg once daily, dose of 300 mg should not be reached before day 22 of treatment.

**DOSE EQUIVALENCE AND CONVERSION**

Patients can be switched from immediate-release to modified-release tablets at the equivalent daily dose; to maintain clinical response, dose titration may be required.

**CAUTIONS**

Cerebrovascular disease - elderly - patients at risk of aspiration pneumonia - treatment of depression in patients under 25 years (increased risk of suicide)

**INTERACTIONS**

Appendix 1: quetiapine
SIDE-EFFECTS

- Common or very common: Appetite increased, asthenia, dysarthria, dyspepsia, dysphonia, fever, headache, hyperglycaemia, irritability, palpititations, peripheral oedema, rhinitis, sleep disorders, suicidal behaviour (particularly on initiation), suicidal ideation (particularly on initiation), syncope, vision blurred, withdrawal syndrome

- Uncommon: Anaemia, diabetes mellitus, dysphagia, hypoglycaemia, hypotension, hyperthyroidism, sexual dysfunction, skin reactions, thrombocytopenia

- Rare or very rare: Angio-oedema, breast swelling, gastrointestinal disorders, hepatic disorders, hypothermia, menorrhagia, menstrual disorder, metabolic syndrome, pancreatitis, rhabdomyolysis, severe cutaneous adverse reactions (SCARs), SIADH

PREGNANCY

Use only if potential benefit outweighs risk.

BREAST FEEDING

Manufacturer advises avoid.

HEPATIC IMPAIRMENT

Manufacturer advises caution (risk of increased plasma concentrations).

Dose adjustments

Manufacturer advises for immediate-release tablets, initially 25 mg daily, increased daily in steps of 25–50 mg.

Manufacturer advises for modified-release tablets, initially 50 mg daily, increased daily in steps of 50 mg.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 2, 23, 25

- Atrolak XL (Accord Healthcare Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg tablets | 60 tablet (PO) £67.66 DT = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg tablets | 60 tablet (PO) £107.45 DT = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg tablets | 60 tablet (PO) £113.09 DT = £113.10

- Biquelle XL (Aspire Pharma Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg tablets | 60 tablet (PO) £29.45 DT = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg tablets | 60 tablet (PO) £40.45 DT = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg tablets | 60 tablet (PO) £45.45 DT = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg tablets | 60 tablet (PO) £74.45 DT = £170.00

- Mintreleq XL (Aristo Pharma Ltd)
  - Quetiapine (as Quetiapine fumarate) 50 mg tablets | 60 tablet (PO) £12.00 DT = £67.66
  - Quetiapine (as Quetiapine fumarate) 150 mg tablets | 60 tablet (PO) £26.00 DT = £113.10
  - Quetiapine (as Quetiapine fumarate) 200 mg tablets | 60 tablet (PO) £26.00 DT = £113.10
  - Quetiapine (as Quetiapine fumarate) 300 mg tablets | 60 tablet (PO) £45.00 DT = £170.00

- Seroquel XL (AstraZeneca UK Ltd)
  - Quetiapine (as Quetiapine fumarate) 20 mg tablets | 60 tablet (PO) £70.00 DT = £170.00
  - Quetiapine (as Quetiapine fumarate) 25 mg tablets | 60 tablet (PO) £80.00 DT = £204.00

Tablet

CAUTIONARY AND ADVISORY LABELS 2

- Quetiapine (Non-proprietary)
  - Quetiapine (as Quetiapine fumarate) 5 mg tablets | 60 tablet (PO) £19.00 DT = £67.66
  - Quetiapine (as Quetiapine fumarate) 25 mg tablets | 60 tablet (PO) £48.60 DT = £170.00
  - Quetiapine (as Quetiapine fumarate) 50 mg tablets | 60 tablet (PO) £135.72 DT = £43.46

- Seroquel XL (Astrazeneca UK Ltd)
  - Quetiapine (as Quetiapine fumarate) 20 mg tablets | 60 tablet (PO) £19.00 DT = £67.66

Oral suspension

CAUTIONARY AND ADVISORY LABELS 2

- Quetiapine (Non-proprietary)
  - Quetiapine (as Quetiapine fumarate) 20 mg per 1 ml tablets | Oral suspension sugar-free sugar-free | 150 ml (PO) £95.00 DT = £95.00

Risperidone

- DRUG ACTION
  - Risperidone is a dopamine D2, 5-HT2A, alpha-, adrenoreceptor, and histamine-1 receptor antagonist.

- INDICATIONS AND DOSE
  - Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone up to 4 mg daily
  - By deep intramuscular injection
  - Adult: Initially 25 mg every 2 weeks, to be administered into the deltoid or gluteal muscle, adjusted in steps of 12.5 mg (max. per dose 50 mg every 2 weeks) at intervals of at least 4 weeks, during initiation
Psychoses and schizophrenia

Risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection.

Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone over 4 mg daily

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adults: Initially 37.5 mg every 2 weeks, adjusted in steps of 12.5 mg (max. per dose 50 mg every 2 weeks) at intervals of at least 4 weeks, during initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection.

Acute and chronic psychosis

- **BY MOUTH**
  - Adults: 2 mg daily in 1–2 divided doses for day 1, then 4 mg daily in 1–2 divided doses for day 2, slower titration is appropriate in some patients, usual dose 4–6 mg daily, doses above 10 mg daily only if benefit considered to outweigh risk; maximum 16 mg per day.
  - Elderly: Initially 500 micrograms twice daily, then increased in steps of 500 micrograms twice daily, increased to 1–2 mg twice daily.

Mania

- **BY MOUTH**
  - Adults: Initially 2 mg once daily, then increased in steps of 1 mg daily if required; usual dose 1–6 mg daily.
  - Elderly: Initially 500 micrograms twice daily, then increased in steps of 500 micrograms twice daily, increased to 1–2 mg twice daily.

Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others

- **BY MOUTH**
  - Adults: Initially 250 micrograms twice daily, then increased in steps of 250 micrograms twice a day on alternate days, adjusted according to response; usual dose 500 micrograms twice daily (max. per dose 1 mg twice daily).

**IMPORTANT SAFETY INFORMATION**

SAFE PRACTICE

Risperidone has been confused with ropinirole; care must be taken to ensure the correct drug is prescribed and dispensed.

- **CAUTIONS**
  - **GENERAL CAUTIONS** Avoid in Acute porphyrias p. 1058 - cataract surgery (risk of intra-operative floppy iris syndrome) - dehydration - dementia with Lewy bodies - prolactin-dependent tumours.
  - **SPECIFIC CAUTIONS**
    - With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually.
  - **INTERACTIONS**
    - **Appendix 1:** risperidone
  - **SIDE-EFFECTS**
    - **Common or very common** Anemia - anxiety - appetite abnormal - asthenia - chest discomfort - conjunctivitis - cough - depression - diarrhoea - dyspepsia - epistaxis - fall - fever - gastrointestinal discomfort - headache - hyperglycaemia - hypertension - increased risk of infection - joint disorders - laryngeal pain - muscle spasms - nasal congestion - nausea - oedema - oral disorders - pain - sexual dysfunction - skin reactions - sleep disorders - urinary disorders - vision disorders - weight decreased
    - **Uncommon** Alopecia - breast abnormalities - cardiac conduction disorders - cerebrovascular insufficiency - chills - coma - concentration impaired - confusion
    - **Rare or very rare** Angioedema - anaphylaxis - phlebitis - allergic drug reaction - agranulocytosis - aplastic anaemia - cyanosis - drowsiness - eczema - fever - gynecomastia - hives - transitory - hypoglycaemia - hyperthermia - jaundice - pancreatitis - peripheral coldness - rhabdomyolysis - SIADH - sleep apnoea - water intoxication - withdrawal syndrome.
    - **Frequency not known** Cardiac arrest.
    - **PREGNANCY** Use only if potential benefit outweighs risk.
    - **BREAST FEEDING** Use only if potential benefit outweighs risk—small amount present in milk.
    - **HEPATIC IMPAIRMENT** Manufacturer advises caution.
    - **Dose adjustments** With intramuscular use Manufacturer advises if an oral dose of at least 2 mg daily tolerated, 25 mg as a depot injection can be given every 2 weeks (no information available).
    - **With oral use** Manufacturer advises dose reduction to half the usual dose, and slower dose titration.
    - **RENAL IMPAIRMENT**
    - **Dose adjustments** Initial and subsequent oral doses should be reduced to half.
    - **MONITORING REQUIREMENTS**
    - **With intramuscular use** Treatment requires careful monitoring for optimum effect.
    - **DIRECTIONS FOR ADMINISTRATION**
    - **With oral use** Orodispersible tablets should be placed on the tongue, allowed to dissolve and swallowed. Oral liquid may be diluted with any non-alcoholic drink, except tea.
    - **With intramuscular use** Correct injection technique (including the use of 2-track technique) and rotation of injection sites are essential.
    - **PATIENT AND CARER ADVICE**
    - **With oral use** Patients or carers should be given advice on how to administer risperidone orodispersible tablets and oral liquid (counselling on use of dose syringe advised).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Risperidone (Non-proprietary)**
  - **Risperidone 500 microgram**
    - Risperidone 500 microgram tablets 20 tablet P&G £0.95 DT = £2.76
    - Risperidone 1 mg
      - Risperidone 1 mg tablets 20 tablet P&G £0.16 DT = £4.02 60 tablet P&G £1.56-£13.75
      - Risperidone 2 mg
        - Risperidone 2 mg tablets 60 tablet P&G £0.10 DT = £21.55
        - Risperidone 3 mg
          - Risperidone 3 mg tablets 60 tablet P&G £88.38 DT = £26.86
          - Risperidone 4 mg
            - Risperidone 4 mg tablets 60 tablet P&G £116.67 DT = £32.74
            - Risperidone 6 mg
              - Risperidone 6 mg tablets 28 tablet P&G £50.91 DT = £43.58
              - Risperidone 7 mg
                - Risperidone 7 mg tablets 28 tablet P&G £50.91 DT = £43.58
      - Risperidone 2 mg
        - Risperidone 2 mg tablets 60 tablet P&G £34.62 DT = £21.55
      - Risperidone 3 mg
        - Risperidone 3 mg tablets 60 tablet P&G £50.91 DT = £26.86
      - Risperidone 4 mg
        - Risperidone 4 mg tablets 60 tablet P&G £67.20 DT = £32.74
      - Risperidone 6 mg
        - Risperidone 6 mg tablets 28 tablet P&G £67.88 DT = £43.58
  - **Risperdal (Janssen-Cilag Ltd)**
    - Risperidone 500 microgram
      - Risperdal 500 microgram tablets 20 tablet P&G £5.08 DT = £2.76
      - Risperdal 1 mg
        - Risperdal 1 mg tablets 20 tablet P&G £8.36 DT = £4.02 60 tablet P&G £17.56
      - Risperdal 2 mg
        - Risperdal 2 mg tablets 60 tablet P&G £34.62 DT = £21.55
      - Risperdal 3 mg
        - Risperdal 3 mg tablets 60 tablet P&G £50.91 DT = £26.86
      - Risperdal 4 mg
        - Risperdal 4 mg tablets 60 tablet P&G £67.20 DT = £32.74
  - **Risperidone 6 mg**
    - Risperidone 6 mg tablets 28 tablet P&G £67.88 DT = £43.58

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Olanzapine embonate

**INDICATIONS AND DOSE**

**Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 10 mg oral olanzapine daily)**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult 18-75 years: Initially 210 mg every 2 weeks, alternately initially 405 mg every 4 weeks, then maintenance 150 mg every 2 weeks, alternatively maintenance 300 mg every 4 weeks, maintenance dose to be started after 2 months of initial treatment, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required

**Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 20 mg oral olanzapine daily)**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: Initially 300 mg every 2 weeks, then maintenance 300 mg every 2 weeks (max. per dose 300 mg every 2 weeks), adjusted according to response, dose to be administered into the gluteal muscle,

**Consult product literature if supplementation with oral olanzapine required**

**IMPORTANT SAFETY INFORMATION**

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for **maintenance** treatment and should not be used for the rapid control of an acute episode.

- **CONTRA-INDICATIONS** Children
- **CAUTIONS** Bone-marrow depression - hyper eosinophilic disorders - low leucocyte count - low neutrophil count - myeloproliferative disease - paralytic ileus - when transferring from oral to depot therapy, the dose by mouth should be reduced gradually
- **INTERACTIONS** → Appendix 1: olanzapine
- **SIDE-EFFECTS**
  - Common or very common Anticholinergic syndrome - appetite increased - arthralgia - asthenia - eosinophilia - fever - glycosuria - oedema - sexual dysfunction
  - Rare or very rare Drug reaction with eosinophilia and systemic symptoms (DRESS) - hepatic disorders - hypothermia - pancreatitis - rhabdomyolysis - thrombocytopenia
  - Frequency not known Erythema - gait abnormal - increased risk of fall - pneumonia - visual hallucinations
  - **SIDE-EFFECTS, FURTHER INFORMATION** Side-effects may persist until the drug has been cleared from its depot site.

**Overdose** Post-injection reactions have been reported leading to signs and symptoms of overdose.

- **PREGNANCY** Use only if potential benefit outweighs risk; neonatal lethargy, tremor, and hypertonia reported when used in third trimester.

- **BREAST FEEDING** Avoid—present in milk.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution.

- **Dose adjustments** Manufacturer advises consider initial dose of 150 mg every 4 weeks.

- **RENAL IMPAIRMENT**

- **Dose adjustments** Initially 150 mg every 4 weeks.

- **MONITORING REQUIREMENTS**

- **OBSERVE patient for at least 3 hours after injection.**

- **TREATMENT requires careful monitoring for optimum effect.**

- **Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotic drugs. Patients taking olanzapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.**

- **Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking olanzapine should have fasting blood glucose tested at baseline, after one months' treatment, then every 4–6 months.**

- **DIRECTIONS FOR ADMINISTRATION** Correct injection technique (including use of z-track technique) and rotation of injection sites are essential.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for suspension for injection**

  - **Zypadhera** (Eli Lilly and Company Ltd)
    - Olanzapine (as Olanzapine embonate monohydrate)
      - 210 mg Zypadhera 210mg powder and solvent for suspension for injection vials | 1 vial £142.76 DT = £142.76
      - Olanzapine (as Olanzapine embonate monohydrate)
      - 300 mg Zypadhera 300mg powder and solvent for suspension for injection vials | 1 vial £222.64 DT = £222.64

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4 Movement disorders

Motor neurone disease

Description of condition
Motor neurone disease is a neurodegenerative condition affecting the brain and spinal cord. Degeneration of motor neurones leads to progressive muscle weakness; resulting symptoms include muscle cramps, wasting and stiffness, loss of dexterity, reduced respiratory function and cognitive dysfunction. The most common form is amyotrophic lateral sclerosis.

Patients suspected of having developed motor neurone disease should be referred to a neurologist without delay.

Aims of treatment
As there is no cure, treatment focuses on maintaining functional ability and managing symptoms.

Non-drug treatment
Non-drug treatment includes nutrition, psychosocial support, physiotherapy, exercise programmes and use of special equipment or mobility aids.

Management of symptoms

Muscular symptoms
Quinine p. 619 [unlicensed indication] is recommended as first line treatment for muscle cramps. If quinine is ineffective, not tolerated or contra-indicated, baclofen p. 1128 [unlicensed indication] should be considered as second line treatment. Subsequent treatment options include tizanidine p. 1129 [unlicensed indication], dantrolene sodium p. 1346 [unlicensed indication] or gabapentin p. 315 [unlicensed indication].

Symptoms of muscle stiffness, spasticity or increased tone can be managed with baclofen, tizanidine, dantrolene sodium or gabapentin [unlicensed indication]. Treatment of severe spasticity may require specialist referral.

Saliva problems
A trial of an antimuscarinic drug [unlicensed indication] can be considered for excessive drooling of saliva. Glycopyrronium bromide p. 1335 is recommended in patients who have cognitive impairment as it has fewer central nervous system side-effects. If initial treatment is ineffective, not tolerated or contra-indicated, referral for specialist administration of botulinum toxin type A p. 407 [unlicensed indication] may be required.

Humidification, nebulisers and carbocisteine p. 291 can be used to treat patients with thick, tenacious saliva.

Respiratory symptoms
Reversible causes of worsening respiratory impairment (such as respiratory tract infections or secretion problems) should be treated before considering other options.

Patients experiencing breathlessness can be treated with opioids [unlicensed indication], or benzodiazepines [unlicensed indication] if the patient’s symptoms are exacerbated by anxiety. Non-invasive ventilation should be considered in patients with respiratory impairment.

Amyotrophic lateral sclerosis
Riluzole p. 1123 is licensed for use in patients with amyotrophic lateral sclerosis to extend life or to extend the time to mechanical ventilation—see National funding/access decisions under riluzole.

Useful Resources

www.nice.org.uk/guidance/ng42

4.1 Dystonias and other involuntary movements

Essential tremor, chorea, tics, and related disorders

Drugs used in essential tremor, chorea, tics, and related disorders
Tetrabenazine p. 406 is mainly used to control movement disorders in Huntington’s chorea and related disorders. Tetrabenazine can also be prescribed for the treatment of tardive dyskinesia if switching or withdrawing the causative antipsychotic drug is not effective. It acts by depleting nerve endings of dopamine. It is effective in only a proportion of patients and its use may be limited by the development of depression.

Haloperidol p. 386 [unlicensed indication], olanzapine p. 398 [unlicensed indication], risperidone p. 402 [unlicensed indication], and quetiapine p. 401 [unlicensed indication], can also be used to suppress chorea in Huntington’s disease.

Haloperidol can also improve motor tics and symptoms of Tourette syndrome and related choras. Other treatments for Tourette syndrome include pimozide p. 388 [unlicensed indication] (important: ECG monitoring required), clonidine hydrochloride p. 145 [unlicensed indication], and sulpiride p. 390 [unlicensed indication]. Trihexyphenidyl hydrochloride p. 412 in high dosage can also improve some movement disorders; it is sometimes necessary to build the dose up over many weeks. Chlorpromazine hydrochloride p. 384 and haloperidol are used to relieve intractable hiccup. Propranolol hydrochloride p. 150 or another beta-adrenoceptor blocking drug may be useful in treating essential tremor or tremors associated with anxiety or thyrotoxicosis.

Primidone p. 336 in some cases provides relief from benign essential tremor; the dose is increased slowly to reduce side-effects.

Piracetam p. 406 is used as an adjunctive treatment for myoclonus of cortical origin. After an acute episode, attempts should be made every 6 months to decrease or discontinue treatment.

Riluzole p. 1123 is used to extend life in patients with motor neurone disease who have amyotrophic lateral sclerosis.

Torsion dystonia and other involuntary movements

Treatment with botulinum toxin type A p. 407 can be considered after an acquired non-progressive brain injury if rapid-onset spasticity causes postural or functional difficulties.

Other drugs used for Dystonias and other involuntary movements
Clozapine, p. 396 • Diazepam, p. 343 • Orphenadrine hydrochloride, p. 411 • Pericyazine, p. 388 • Pramipexole, p. 422 • Prochlorperazine, p. 389 • Procyclidine hydrochloride, p. 411 • Rolipram, p. 424 • Rotigotine, p. 426 • Trifluoperazine, p. 390

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**Antipsychotics > First-Generation**

**Promazine hydrochloride**

- **Indications and Dose**
  - Short-term adjunctive management of psychomotor agitation
    - **By Mouth**
      - Adult: 100–200 mg 4 times a day
      - Elderly: 25–50 mg 4 times a day

- **Contra-Indications**
  - CNS depression - comatose states - phaeochromocytoma

- **Caution**
  - Cerebral arteriosclerosis

- **Interactions**
  - Appendix 1: Phenothiazines

- **Side-Effects**

- **Hepatic Impairment**
  - Manufacturer advises caution.

- **Renal Impairment**
  - Dose adjustments: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **Less Suitable for Prescribing**
  - Promazine hydrochloride is less suitable for prescribing.

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

  **Oral Solution**

  - Cautionary and Advisory Labels 2
    - Promazine hydrochloride (Non-proprietary)
    - Promazine hydrochloride 5 mg per 1 ml Promazine 25mg/5ml syrup | 150 ml £15.00 DT + £15.00
    - Promazine 25mg/5ml oral solution | 150 ml £15.00 DT + £15.00
    - Promazine hydrochloride 10 mg per 1 ml Promazine 50mg/5ml syrup | 150 ml £30.00 DT + £30.00
    - Promazine 50mg/5ml oral solution | 150 ml £30.00 DT + £30.00

  - Cautionary and Advisory Labels 2
    - Promazine hydrochloride (Non-proprietary)
    - Promazine hydrochloride 25 mg Promazine 25mg tablets | 100 tablet £49.99 DT + £45.34
    - Promazine hydrochloride 50 mg Promazine 50mg tablets | 100 tablet £78.49 DT + £76.18

**CNS Stimulants**

**Piracetam**

- **Indications and Dose**
  - Adjunctive treatment of cortical myoclonus
    - **By Mouth**
      - Adult: Initially 7.2 g daily in 2–3 divided doses, then increased in steps of 4.8 g every 3–4 days, adjusted according to response, subsequently, attempts should be made to reduce dose of concurrent therapy; maximum 24 g per day

  - **Contra-Indications**
    - Cerebral haemorrhage
    - Huntington’s chorea

**Monoamine Depleting Drugs**

**Tetrabenazine**

- **Indications and Dose**
  - Movement disorders due to Huntington’s chorea, hemiballismus, senile chorea, and related neurological conditions
    - **By Mouth**
      - Adult: Initially 25 mg 3 times a day, then increased, in steps of 25 mg every 3–4 days; maximum 200 mg per day
      - Elderly: Lower initial dose may be necessary
      - Moderate to severe tardive dyskinesia
        - **By Mouth**
          - Adult: Initially 12.5 mg daily, dose to be gradually increased according to response

- **Contra-Indications**
  - Depression - parkinsonism - phaeochromocytoma - prolactin-dependent tumours

- **Caution**
  - Susceptibility to QT-interval prolongation

- **Interactions**
  - Appendix 1: Tetrabenazine
Dystonias and other involuntary movements

- **SIDE-EFFECTS**

  - **Common or very common** Anxiety, confusion, constipation, depression, diarrhoea, drowsiness, hypotension, insomnia, nausea, parkinsonism, vomiting
  - **Uncommon** Consciousness impaired, hyperthermia
  - **Rare or very rare** Neuroleptic malignant syndrome, skeletal muscle damage
  - **Frequency not known** Bradycardia, dizziness, dry mouth, epigastric pain, suicidal ideation

- **PREGNANCY** Avoid unless essential—toxicity in animal studies.

- **BREAST FEEDING** Avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (increased risk of exposure), particularly in severe impairment (no information available).

- **RENAL IMPAIRMENT** Use with caution.

- **TREATMENT CESSION** Avoid abrupt withdrawal.

- **PATIENT AND CARER ADVICE** Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension Tablet

  **CAUTIONARY AND ADVISORY LABELS** 2

  - **Tetrabenazine (Non-proprietary)**
    - Tetrabenazine 25 mg: Tablet 112 tablet £107.69 DT = £107.69
    - Tetrabenazine 25 mg: Tablet 112 tablet PSL £100.00 DT = £107.69
  - **Xenazine (Alliance Pharmaceuticals Ltd)**
    - Tetrabenazine 25 mg: Tablet 112 tablet PSL £100.00 DT = £107.69

- **MUSCLE RELAXANTS** PERIPHERALLY ACTING NEUROTOXINS (BOUTULINUM TOXINS)

### Botulinum toxin type A

- **INDICATIONS AND DOSE**

  Treatment of focal spasticity (including hand and wrist disability associated with stroke) (specialist use only) • Blepharospasm (specialist use only) • Hemifacial spasm (specialist use only) • Spasmodic torticollis (specialist use only) • Severe hyperhidrosis of the axillae (specialist use only) • Prophylaxis of headaches in adults with chronic migraine (specialist use only) • Temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years (specialist use only) • Ankle disability due to lower limb spasticity associated with stroke (specialist use only) • Management of bladder dysfunctions (specialist use only) • Temporary improvement of moderate to severe crow's feet (specialist use only)

  - **BY SUBCUTANEOUS INJECTION, OR BY INTRADERMAL INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - **Adults** (consult product literature)

  **DOSE EQUIVALENCE AND CONVERSION**

  **Important:** information is specific to each individual preparation.

- **CONTRA-INDICATIONS** Acute urinary retention (specific to use in bladder disorders only) • cathectisation difficulties (specific to use in bladder disorders only) • generalised disorders of muscle activity • infection at injection site • myasthenia gravis • presence of bladder calculi (specific to use in bladder disorders only) • urinary tract infection (specific to use in bladder disorders only)

- **CAUTIONS**

  **GENERAL CAUTIONS** Atrophy in target muscle • chronic respiratory disorder • elderly • excessive weakness in target muscle • history of aspiration • history of dysphagia • inflammation in target muscle • neurological disorders • neuromuscular disorders • off-label use (fateful adverse events reported)

  **SPECIFIC CAUTIONS**

  - When used for blepharospasm or hemifacial spasm Risk of angle-closure glaucoma

  **CAUTIONS, FURTHER INFORMATION** Neuromuscular or neurological disorders can lead to increased sensitivity and exaggerated muscle weakness including dysphagia and respiratory compromise.

- **Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (June 2012)** NICE TA260

  Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine, (defined as headaches on at least 15 days per
Nervous system

INTERACTIONS

CAUTIONS

CONTRA-INDICATIONS

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection

- Azzalure® (Galderma (UK) Ltd)
  Botulinum toxin type A 125 unit Azzalure® 125unit powder for solution for injection vials | 1 vial (Prs) £64.00 | 2 vial (Prs) £128.00
- Bocouture® (Merz Pharma UK Ltd)
  Botulinum toxin type A 50 unit Bocouture® 50unit powder for solution for injection vials | 1 vial (Prs) £72.00
- Bocouture® (Allergan Ltd)
  Botulinum toxin type A 100 unit Bocouture® 100unit powder for solution for injection vials | 1 vial (Prs) £229.00
- Botox® (Allergan Ltd)
  Botulinum toxin type A 50 unit Botox® 50unit powder for solution for injection vials | 1 vial (Prs) £77.50
  Botulinum toxin type A 100 unit Botox® 100unit powder for solution for injection vials | 1 vial (Prs) £138.20
- Botulinum toxin type A 200 unit Botox® 200unit powder for solution for injection vials | 1 vial (Prs) £276.40
- Dysport® (Ipsen Ltd)
  Botulinum toxin type A 300 unit Dysport® 300unit powder for solution for injection vials | 1 vial (Prs) £92.40
  Botulinum toxin type A 500 unit Dysport® 500unit powder for solution for injection vials | 2 vial (Prs) £308.00
- Xeomin® (Merz Pharma UK Ltd)
  Botulinum toxin type A 50 unit Xeomin® 50unit powder for solution for injection vials | 1 vial (Prs) £72.00
  Botulinum toxin type A 100 unit Xeomin® 100unit powder for solution for injection vials | 1 vial (Prs) £129.90
  Botulinum toxin type A 200 unit Xeomin® 200unit powder for solution for injection vials | 1 vial (Prs) £259.80 (Hospital only)

BREAST FEEDING

Low risk of systemic absorption but avoid unless essential.

DIRECTIONS FOR ADMINISTRATION

Injection may be diluted with sodium chloride 0.9%.

PRESCRIBING AND DISPENSING INFORMATION

Important: not interchangeable with other botulinum toxin preparations.

PATIENT AND CARER ADVICE

Patients should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties; they should be advised to seek immediate medical attention if swallowing, speech or breathing difficulties occur.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- NeuroBloc® (Sloan Pharma Sarl)
  Botulinum toxin type B 5000 unit per 1 ml NeuroBloc® 5,000units/1ml solution for injection vials | 1 vial (POM) £148.27 (Hospital only)
  NeuroBloc® 10,000units/2ml solution for injection vials | 1 vial (POM) £197.69 (Hospital only)
  NeuroBloc® 2,500units/0.5ml solution for injection vials | 1 vial (POM) £111.20 (Hospital only)

NEUROPROTECTIVE DRUGS

Inotersen

24-Apr-2019

DRUG ACTION

Inotersen is an antisense oligonucleotide inhibitor which inhibits transthyretin production.

INDICATIONS AND DOSE

Stage 1 or stage 2 polyneuropathy in patients with hereditary transthyretin amyloidosis (hATTR) (initiated by a specialist)

BY SUBCUTANEOUS INJECTION

Adult: 284 mg once weekly, for dose adjustments due to side-effects and information on Vitamin A supplementation—consult product literature

CONTRA-INDICATIONS

Patients undergoing liver transplantation (no information available) - platelet count less than 100x10^9/litre before starting treatment - urine protein to creatinine ratio (UPCR) greater than or equal to 115 mg/mmol before starting treatment

CAUTIONS

Concomitant administration with nephrotoxic drugs - elderly - history of major bleeding

INTERACTIONS

Appendix 1: inotersen

SIDE-EFFECTS

Common or very common
- Dry mouth - dysphagia - dysphonia - headache - influenza-like illness - muscle weakness - neck pain - taste altered - vision disorders
- Frequency not known
  - Angioedema - arthralgia - axillary oedema - dyspnoea - pneumoconiosis - ptosis - skin reactions - vomiting

PREGNANCY

Low risk of systemic absorption but avoid unless essential.

CONCEPTION AND CONTRACEPTION

Manufacturer advises women of childbearing potential should use effective contraception during treatment; if conception is planned, inotersen and vitamin A supplementation should be avoided unless essential.

Appendix
stopped and vitamin A levels monitored—consult product literature.

- **PREGNANCY** Manufacturer advises avoid unless essential (limited information available)—potentially teratogenic risk due to unbalanced vitamin A levels, consult product literature.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment (no information available).

- **RENAL IMPAIRMENT** Manufacturer advises avoid if eGFR less than 45 mL/minute/1.73 m².

- **PRE-TREATMENT SCREENING** Manufacturer advises plasma vitamin A levels below the lower limit of normal should be corrected and any ocular symptoms or signs of vitamin A deficiency should have resolved before starting treatment.

- **MONITORING REQUIREMENTS**
  - Manufacturers advise monitor platelet count before starting treatment, every 2 weeks during treatment, and for 8 weeks after stopping treatment—consult product literature.
  - Manufacturer advises monitor UPCR and eGFR before starting treatment, every 3 months or more frequently as clinically indicated during treatment, and for 8 weeks after stopping treatment—consult product literature.
  - Manufacturer advises monitor hepatic enzymes before starting treatment, then 4 months after starting treatment, and annually thereafter or more frequently as clinically indicated.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises to take the syringe out of the refrigerator at least 30 minutes before administration. Patients may self-administer Tegsedi® after appropriate training in subcutaneous injection technique.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8°C) and protect from light—consult product literature for further information regarding storage outside refrigerator.

- **PATIENT AND CARER ADVICE**
  - Manufacturer advises patients should immediately report any signs of unusual or prolonged bleeding, neck stiffness, or atypical severe headache.
  - Self-administration: Manufacturer advises patients and carers should be given training in subcutaneous injection technique.

- **Missed doses**
  - If a dose is missed, the next dose should be administered as soon as possible, unless the next scheduled dose is within 2 days, in which case the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - Tegsedi (Akeso Therapeutics UK Ltd) ▼
    - Inotersen (as Inotersen sodium) 189.33 mg per 1 ml Tegsedi 284mg/1.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £33.035.00

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### Parkinson’s disease

**4.2 Parkinson’s disease**

**Description of condition**

Parkinson’s disease is a progressive neurodegenerative condition resulting from the death of dopaminergic cells of the substantia nigra in the brain. Patients with Parkinson’s disease classically present with motor symptoms including hypokinesia, bradykinesia, rigidity, rest tremor, and postural instability.

Non-motor symptoms include dementia, depression, sleep disturbances, bladder and bowel dysfunction, speech and language changes, swallowing problems, and weight loss. Patients with suspected Parkinson’s disease should be referred to a specialist and reviewed every 6 to 12 months.

When Parkinson’s disease diagnosis is confirmed, patients should be advised to inform the DVLA and their car insurer.

**Aims of treatment**

Parkinson’s disease is an incurable progressive condition, and the aim of treatment is to control the symptoms and to improve the patient’s quality of life.

**Non-drug treatment**

Parkinson’s disease patients should be offered physiotherapy if balance or motor function problems are present, speech and language therapy if they develop communication, swallowing or saliva problems, and occupational therapy if they experience difficulties with their daily activities. Dietitian referral should be considered.

**Drug treatment**

**Drug management of motor symptoms in Parkinson’s disease**

**First-line treatment**

In early stages of Parkinson’s disease, patients whose motor symptoms decrease their quality of life should be offered levodopa combined with carbidopa (co-careldopa p. 415) or benserazide (co-beneldopa p. 414).

Parkinson’s disease patients whose motor symptoms do not affect their quality of life, could be prescribed a choice of levodopa, non-ergot-derived dopamine-receptor agonists (pramipexole p. 422, ropinirole p. 424 or rotigotine p. 426) or monoamine-oxidase-B inhibitors (rasagiline p. 427 or selegiline hydrochloride p. 428).

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### Tafamidis

**INDICATIONS AND DOSE**

Treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in patients with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment (initiated under specialist supervision)

- **By mouth**
  - Adult: 20 mg once daily
Before starting antiparkinsonian treatment, the patient’s individual circumstances, including symptoms, comorbidities and preferences, should be discussed together with the potential benefits and harms from the different drugs available.

Patients and their carers should be informed about the risk of adverse reactions from antiparkinsonian drugs, including psychotic symptoms, excessive sleepiness and sudden onset of sleep with dopamine-receptor agonists, and impulse control disorders with all dopaminergic therapy (especially dopamine-receptor agonists). For further information see Impulse control disorders.

Levodopa treatment is associated with motor complications, including response fluctuations and dyskinesias. Response fluctuations are characterised by large variations in motor performance, with normal function during the ‘on’ period, and weakness and restricted mobility during the ‘off’ period. ‘End-of-dose’ deterioration with progressively shorter duration of benefit can also occur. Modified-release preparations may help with ‘end-of-dose’ deterioration or nocturnal immobility.

The overall improvement in motor performance is more noticeable with levodopa than with dopamine-receptor agonists, and motor complications are less likely to occur with dopamine-receptor agonists when used alone long-term. Conversely, excessive sleepiness, hallucinations, and impulse control disorders are more likely to occur with dopamine-receptor agonists than with levodopa.

To avoid the potential for acute akinesia or neuroleptic malignant syndrome, antiparkinsonian drug concentrations should not be allowed to fall suddenly due to poor absorption or abrupt withdrawal.

**Adjuvant therapy**

If a patient with Parkinson’s disease develops dyskinesia or motor fluctuations, specialist advice should be sought before modifying antiparkinsonian drug therapy.

Patients who develop dyskinesia or motor fluctuations despite optimal levodopa therapy should be offered a choice of non-ergot dopamine-receptor agonists (pramipexole, ropinirole, rotigotine), monoamine oxidase B inhibitors (rasagiline or selegiline hydrochloride) or COMT inhibitors (entacapone p. 412 or tolcapone p. 413) as an adjunct to levodopa.

An ergot-derived dopamine-receptor agonist (bromocriptine p. 419, cabergoline p. 421 or pergolide p. 422) should only be considered as an adjunct to levodopa if symptoms are not adequately controlled with a non-ergot-derived dopamine-receptor agonist.

If dyskinesia is not adequately managed by modifying existing therapy, amantadine hydrochloride p. 418 should be considered.

**Drug management of non-motor symptoms in Parkinson’s disease**

**Daytime sleepiness and sudden onset of sleep**

Patients who experience daytime sleepiness or sudden onset of sleep, should have their Parkinson’s drug treatment adjusted under specialist medical guidance. If reversible pharmacological and physical causes have been excluded, modafinil p. 492 should be considered to treat excessive daytime sleepiness, and treatment should be reviewed at least every 12 months.

Patients with Parkinson’s disease who have daytime sleepiness or sudden onset of sleep should be advised not to drive, to inform the DVLA about their symptoms, and to think about any occupational hazards.

**Nocturnal akinesia**

When treating nocturnal akinesia in patients with Parkinson’s disease, levodopa or oral dopamine-receptor agonists should be considered as first-line options and rotigotine p. 426 as second-line (if both levodopa or oral dopamine-receptor agonists are ineffective).

**Postural hypotension**

Patients with Parkinson’s disease who develop postural hypotension should have their drug treatment reviewed to address any pharmacological cause. If drug therapy is required, midodrine hydrochloride p. 188 should be considered as the first option and fluocortolone acetate p. 676 [unlicensed indication] as an alternative.

**Depression**

See Antidepressant drugs p. 359.

**Psychotic symptoms**

Hallucinations and delusions need not be treated if they are well tolerated. Otherwise, the dosage of any antiparkinsonism drugs that might have triggered hallucinations or delusions should be reduced, taking into account the severity of symptoms and possible withdrawal effects. Specialist advice should be sought before modifying drug treatment.

In Parkinson’s disease patients with no cognitive impairment, quetiapine p. 401 [unlicensed indication] can be considered to treat hallucinations and delusions. If standard treatment is not effective, clozapine p. 396 should be offered to treat hallucinations and delusions in patients with Parkinson’s disease.

It is important to acknowledge that other antipsychotic medicines (such as phenothiazines and butyrophenones) can worsen the motor features of Parkinson’s disease.

**Rapid eye movement sleep behaviour disorder**

Clonazepam p. 337 [unlicensed indication] or melatonin p. 489 [unlicensed indication] should be considered to treat rapid eye movement sleep behaviour disorder in Parkinson’s patients once possible pharmacological causes have been addressed.

**Drooling of saliva**

Drug treatment for drooling of saliva in patients with Parkinson’s disease should only be considered if non-drug treatment such as speech and language therapy is not available or is ineffective.


Other antimuscarinic drugs, should only be considered if the risk of cognitive adverse effects is thought to be minimal; topical preparations, such as atropine [unlicensed indication], should be used if possible to reduce the risk of adverse events.

**Parkinson’s disease dementia**

An acetylcholinesterase inhibitor should be offered to patients with mild-to-moderate Parkinson’s disease dementia and considered for patients with severe Parkinson’s disease dementia [unlicensed indications apart from rivastigmine capsules and oral solution p. 303 for the treatment of mild-to-moderate dementia in patients with Parkinson’s disease]. If acetylcholinesterase inhibitors are not tolerated or contra-indicated, memantine hydrochloride p. 304 [unlicensed indication] should be considered.

For further information see Dementia p. 300

**Advanced Parkinson’s disease**

Patients with advanced Parkinson’s disease can be offered apomorphine hydrochloride p. 418 as intermittent injections or continuous subcutaneous infusions. To control nausea and vomiting associated with apomorphine, administration of domperidone p. 431 is usually started two days before apomorphine therapy, and then discontinued as soon as possible. To reduce the risk of serious arrhythmia due to QT prolongation associated to the concomitant use of domperidone p. 431 and apomorphine hydrochloride p. 418, the MHRA recommends an assessment of cardiac risk factors and ECG monitoring and to ensure that the benefits outweighs the risks when initiating treatment.

Levodopa-carbidopa intestinal gel is used for the treatment of advanced levodopa-responsive Parkinson’s disease dementia.

**Dementia**

See Dementia p. 300
disease with severe motor fluctuations and hyperkinesia or dyskinesia. The gel is administered with a portable pump directly into the duodenum or upper jejunum. Deep brain stimulation should only be considered for patients with advanced Parkinson’s disease whose symptoms are not adequately controlled by best drug therapy. A

**Impulse control disorders**

Impulse control disorders (compulsive gambling, hypersexuality, binge eating, or obsessive shopping) can develop in a person with Parkinson’s disease who is on any dopaminergic therapy at any stage in the disease course particularly if the patient has a history of previous impulsive behaviours, alcohol consumption, or smoking. Patients should be informed about the different types of impulse control disorders and that dopamine-receptor agonist withdrawal may be reduced or stopped if problematic impulse control disorders develop.

When managing impulse control disorders, dopamine-receptor agonist doses should be reduced gradually and patients should be monitored for symptoms of dopamine agonist withdrawal. Specialist cognitive behavioural therapy should be offered if modifying dopaminergic therapy is not effective. A

**Useful Resources**


**Antimuscarinics**

**Orphenadrine hydrochloride**

- **Drug action** Orphenadrine exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

- **Indications and dose**

  **Parkinsonism** Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)

  > By mouth
  > Adult: Initially 150 mg daily in divided doses, then increased in steps of 50 mg every 2–3 days, adjusted according to response; usual dose 150–300 mg daily in divided doses; maximum 400 mg per day
  > Elderly: Preferably dose at lower end of range

- **Contra-indications** Acute porphyrias p. 1058 - gastro-intestinal obstruction - myasthenia gravis

- **CAUTIONS** Cardiovascular disease - elderly - hypertension - in patients susceptible to angle-closure glaucoma - liable to abuse - prostatic hypertrophy - psychotic disorders - pyrexia

- **Interactions** → Appendix 1: orphenadrine

- **Side-effects**

  - Common or very common Accommodation disorder - anxiety - dizziness - dry mouth - gastrointestinal disorder - nausea
  - Uncommon Confusion - constipation - coordination abnormal - euphoric mood - hallucination - insomnia - sedation - seizure - tachycardia - urinary retention
  - Rare or very rare Memory loss

- **Pregnancy** Caution.

- **Breast Feeding** Caution.

- **Hepatic Impairment** Manufacturer advises caution.

- **Renal Impairment** Use with caution.

- **Treatment Cessation** Avoid abrupt withdrawal in patients taking long-term treatment.

- **Patient and carer advice**

  - Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).

- **Medicinal forms**

  - **Oral solution**

    - Orphenadrine hydrochloride (Non-proprietary)

    - Orphenadrine hydrochloride 10 mg per 1 ml Orphenadrine 50mg/5ml oral solution sugar free sugar-free | 150 ml (Use) £40.00 DT = £40.00

- **Procyclidine hydrochloride**

  - **Drug action** Procyclidine exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

  - **Indications and dose**

    - Parkinsonism: Extrapyramidal symptoms (but not tardive dyskinesia)

    > By mouth

    - Adult: 2.5 mg 3 times a day, then increased in steps of 2.5–5 mg daily if required; increased if necessary up to 30 mg daily in 2–4 divided doses, to be increased at 2–3 day intervals. Maximum daily dose only to be used in exceptional circumstances; maximum 60 mg per day

    - Elderly: Lower end of range preferable

  - **Acute dystonia**

    - By intramuscular injection, or by intravenous injection

    - Adult: 5–10 mg, occasionally, more than 10 mg, dose usually effective in 5–10 minutes but may need 30 minutes for relief

    - Elderly: Lower end of range preferable

  - **Contra-indications** Gastro-intestinal obstruction - myasthenia gravis

  - **CAUTIONS** Cardiovascular disease - elderly - hypertension - liable to abuse - prostatic hypertrophy - psychotic disorders - pyrexia - those susceptible to angle-closure glaucoma

  - **Interactions** → Appendix 1: procyclidine

  - **Side-effects**

    - Common or very common Constipation - dry mouth - urinary retention - vision blurred

    - Uncommon Anxiety - cognitive impairment - confusion - dizziness - gingivitis - hallucination - memory loss - nausea - rash - vomiting

    - Rare or very rare Psychotic disorder

  - **Pregnancy** Use only if potential benefit outweighs risk.

  - **Breast Feeding** No information available.

  - **Hepatic Impairment** Manufacturer advises caution.

  - **Renal Impairment** Use with caution.

  - **Treatment Cessation** Avoid abrupt withdrawal in patients taking long-term treatment.

  - **Patient and carer advice**

    - Driving and skilled tasks May affect performance of skilled tasks (e.g. driving).

  - **Medicinal forms**

    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

      - **Orphenadrine hydrochloride** (Non-proprietary)

      - Procyclidine hydrochloride 5 mg per 1 ml Procyclidine 10mg/2ml solution for injection ampoules | 5 ampoule (Use) £60.00–£78.75 DT = £72.50

www.getintopharma.com
### Trihexyphenidyl hydrochloride (Benzhexol hydrochloride)

**DRUG ACTION** Trihexyphenidyl exerts its effects by reducing the effects of the relative central cholinergic excess that occurs as a result of dopaminergic deficiency.

**INDICATIONS AND DOSE**

- **Parkinson's disease (if used in combination with co-careldopa or co-beneldopa)**
  - **BY MOUTH**
    - Adult: Maintenance 2–6 mg daily in divided doses, use not recommended because of toxicity in the elderly and the risk of aggravating dementia.

- **Parkinsonism | Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)**
  - **BY MOUTH**
    - Adult: 1 mg daily, then increased in steps of 2 mg every 3–5 days, adjusted according to response; maintenance 5–15 mg daily in 3–4 divided doses, not recommended for use in Parkinson’s disease because of toxicity in the elderly and the risk of aggravating dementia; maximum 20 mg per day.
    - Elderly: Lower end of range preferable, not recommended for use in Parkinson’s disease because of toxicity in the elderly and the risk of aggravating dementia.

**CONTRA-INDICATIONS**

- Gastro-intestinal obstruction - myasthenia gravis
- Cardiovascular disease - elderly - hypertension - liable to abuse - prostatic hypertrophy - psychotic disorders - pyrexia - those susceptible to angle-closure glaucoma.

**INTERACTIONS** → Appendix 1: trihexyphenidyl

**SIDE-EFFECTS**


**PREGNANCY**

- Use only if potential benefit outweighs risk.

**BREAST FEEDING**

- Avoid.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution.

**RENAL IMPAIRMENT**

- Use with caution.

**TREATMENT CESSATION**


**DIRECTIONS FOR ADMINISTRATION**

- Tablets should be taken with or after food.

**PATIENT AND CARER ADVICE**

- Driving and skilled tasks: May affect performance of skilled tasks (e.g. driving).

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### DOPAMINERGIC DRUGS > CATECHOL-O-METHYLTRANSFERASE INHIBITORS

#### Entacapone

**DRUG ACTION** Entacapone prevents the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain.

**INDICATIONS AND DOSE**

- Adjunct to co-beneldopa or co-careldopa in Parkinson’s disease with ‘end-of-dose’ motor fluctuations (under expert supervision)
  - **BY MOUTH**
    - Adult: 200 mg, dose to be given with each dose of levodopa with dopa-decarboxylase inhibitor; maximum 2 g per day.

**CONTRA-INDICATIONS**

- History of neuroleptic malignant syndrome - history of non-traumatic rhabdomyolysis - phaeochromocytoma.

**CAUTIONS**

- Concurrent levodopa dose may need to be reduced by about 10–30% - ischaemic heart disease.

**INTERACTIONS** → Appendix 1: entacapone

**SIDE-EFFECTS**


- Uncommon: Myocardial infarction.

- Rare or very rare: Agitation - appetite decreased - skin reactions - weight decreased.

**FREQUENCY NOT KNOWN**

- Colitis - hair colour changes - hepatic disorders - impulse-control disorder - nail discoloration - neuroleptic malignant syndrome - rhabdomyolysis.

**PREGNANCY**

- Avoid—no information available.

**BREAST FEEDING**

- Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

- Manufacturer advises avoid.

**TREATMENT CESSATION**

- Avoid abrupt withdrawal.

**PATIENT AND CARER ADVICE**

- Patient counselling is advised (may cause urine reddish-brown, concomitant iron containing products).

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### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Oral solution**

- **Trihexyphenidyl hydrochloride (Non-proprietary)**
  - **Procyclidine hydrochloride 500 microgram per 1 ml**
    - Procyclidine 2.5mg/5ml oral solution sugar free sugar-free | 150 ml £11.00 - £14.63 DT = £14.01
  - **Procyclidine hydrochloride 1 mg per 1 ml**
    - Procyclidine 5mg/5ml oral solution sugar free sugar-free | 150 ml £17.00 - £21.68 DT = £21.66

**Tablet**

- **Trihexyphenidyl hydrochloride (Non-proprietary)**
  - **Procyclidine hydrochloride 5 mg**
    - Procyclidine 5mg tablets | 28 tablet £12.05 DT = £2.94 | 100 tablet £8.94-£14.89 | 500 tablet £44.63-£74.46
  - **Kemadrin (Aspen Pharma Trading Ltd)**
    - Procyclidine hydrochloride 5 mg | 100 tablet £4.72 | 500 tablet £23.62

**Oral solution**

- **Entacapone (Non-proprietary)**
  - **Entacapone 200 mg**
    - Entacapone 200mg tablets | 30 tablet £16.38 DT = £3.49 | 100 tablet £21.47-£54.58
Opicapone

**DRUG ACTION** Opicapone prevents the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain.

**INDICATIONS AND DOSE**

**Adjunct to co-beneldopa or co-careldopa in Parkinson’s disease with ‘end-of-dose’ motor fluctuations (under expert supervision)**

- **BY MOUTH**
  - Adult: 50 mg once daily, dose to be taken at bedtime, at least one hour before or after levodopa combinations

**CONTRA-INDICATIONS**

- Catecholamine-secreting neoplasms - history of neuroleptic malignant syndrome - history of non-traumatic rhabdomyolysis - paraganglioma - phaeochromocytoma

**CAUTIONS**

- Concurrent levodopa dose may need to be reduced - elderly over 85 years (limited information available)

**INTERACTIONS** → Appendix 1: opicapone

**SIDE-EFFECTS**

- **Common or very common**
  - Constipation - dizziness - drowsiness - dry mouth - hallucinations - headache - hypotension - movement disorders - muscle complaints - sleep disorders - vomiting

- **Uncommon**
  - Anxiety - appetite decreased - depression - dry eye - dysphoria - ear congestion - gastrointestinal discomfort - hypertension - hypertriglyceridaemia - musculoskeletal stiffness - nocturia - pain in extremity - palpitations - syncope - taste altered - urine discolouration - weight decreased

**SIDE-EFFECTS, FURTHER INFORMATION**

Manufacturer advises consider liver function tests in patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time.

**PREGNANCY**

Manufacturer advises avoid—limited information available.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in severe impairment.

**Dose adjustments**

Manufacturer advises use with caution in moderate impairment—dose adjustment may be necessary.

**MEDICINAL FORMS**

- **Capsule**
  - **Ongentys (BIAL Pharma UK Ltd)**
    - Opicapone 50 mg: Ongentys 50mg capsules | 30 capsule £93.90

**INDICATIONS AND DOSE**

Adjunct to co-beneldopa or co-careldopa in Parkinson’s disease with ‘end-of-dose’ motor fluctuations if another inhibitor of peripheral catechol-O-methyltransferase is inappropriate (under expert supervision)

- **BY MOUTH**
  - Adult: 100 mg 3 times a day (max. per dose 200 mg 3 times a day) continuing beyond 3 weeks only if substantial improvement, leave 6 hours between each dose; first daily dose should be taken at the same time as levodopa with dopa-decarboxylase inhibitor, dose maximum only in exceptional circumstances

**CONTRA-INDICATIONS**

- Phaeochromocytoma - previous history of hyperthermia - previous history of neuroleptic malignant syndrome - previous history of rhabdomyolysis - severe dyskinesia

**CAUTIONS**

- Most patients receiving more than 600 mg levodopa daily require reduction of levodopa dose by about 30%

**CAUTIONS, FURTHER INFORMATION**

- Hepatotoxicity Potentially life-threatening hepatotoxicity including fulminant hepatitis reported rarely, usually in women and during the first 6 months, but late-onset liver injury also reported; discontinue if abnormal liver function tests or symptoms of liver disorder; do not re-introduce tolcapone once discontinued.

**INTERACTIONS** → Appendix 1: tolcapone

**SIDE-EFFECTS**

- **Common or very common**

- **Uncommon**
  - Hepatocellular injury

- **Rare or very rare**
  - Eating disorders - neuroleptic malignant syndrome (reported on dose reduction or withdrawal) - neurological disorders - pathological gambling - psychiatric disorders - sexual dysfunction

**PREGNANCY**

Toxicity in animal studies—use only if potential benefit outweighs risk.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid.

**RENAL IMPAIRMENT**

Caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and then every 8 weeks thereafter (restart monitoring schedule if dose increased).

**TREATMENT CESSATION**

Avoid abrupt withdrawal.

**PATIENT AND CARER ADVICE**

Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop.

www.getintopharma.com
Nervous system

414 Movement disorders

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 14, 25</th>
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<tr>
<td>Tasmar (Meda Pharmaceuticals Ltd)</td>
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<td>Tolcapone 100 mg Tasmar 100mg tablets</td>
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**DOPAMINERGIC DRUGS**

**DOPAMINE PRECURSORS**

| Co-beneldopa Q2-Mar-2017 |

**INDICATIONS AND DOSE**

**Parkinson’s disease**

- **Adult:** Initially 50 mg 3–4 times a day, then increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; maintenance 400–800 mg daily in divided doses
- **Elderly:** Initially 50 mg 1–2 times a day, then increased in steps of 50 mg daily, dose to be increased every 3–4 days according to response

**Parkinson’s disease (in advanced disease)**

- **Adult:** Initially 100 mg 3 times a day, then increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; maintenance 400–800 mg daily in divided doses

**Parkinson’s disease (patients not taking levodopa/dopa-decarboxylase inhibitor therapy)**

- **Adult:** Initially 1 capsule 3 times a day; maximum 6 capsules per day

**Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)**

- **Adult:** Initially 1 capsule substituted for every 100 mg of levodopa and given at same dosage frequency, increased every 2–3 days according to response; average increase of 50% needed over previous levodopa dose and titration may take up to 4 weeks, supplementary dose of immediate-release Madopar® may be needed with first morning dose; if response still poor to total daily dose of Madopar® CR plus Madopar® corresponding to 1.2 g levodopa—consider alternative therapy.

**DOSE EQUIVALENCE AND CONVERSION**

- Dose is expressed as levodopa.

**IMPORTANT SAFETY INFORMATION**

**IMPULSE CONTROL DISORDERS**

Treatment with levodopa is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

**CAUTIONS** Cushing’s syndrome · diabetes mellitus · endocrine disorders · history of convulsions · history of myocardial infarction with residual arrhythmia · history of peptic ulcer · hyperthyroidism · osteomalacia · phaeochromocytoma · psychiatric illness (avoid if severe and discontinue if deterioration) · severe cardiovascular disease · severe pulmonary disease · susceptibility to angle-closure glaucoma

**INTERACTIONS** → Appendix 1: levodopa

**SIDE-EFFECTS**

- **Common or very common** Anxiety · appetite decreased · arrhythmia · depression · diarrhoea · hallucination · movement disorders · nausea · parkinsonism · postural hypotension · sleep disorders · taste altered · vomiting
- **Rare or very rare** Leucopenia
- **Frequency not known** Aggression · compulsions · confusion · delusions · dopamine dysregulation syndrome · drowsiness · eating disorders · euphoric mood · flushing · gastrointestinal haemorrhage · haemolytic anaemia · hyperhidrosis · oral disorders · pathological gambling · psychosis · sexual dysfunction · skin reactions · thrombocytopenia · tongue discoloration · tooth discoloration · urine discolouration

**PREGNANCY** Caution in pregnancy—toxicity has occurred in animal studies.

**BREAST FEEDING** May suppress lactation; present in milk—avoid.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in decompensated hepatic function.

**RENAL IMPAIRMENT** Use with caution.

**EFFECT ON LABORATORY TESTS** False positive tests for urinary ketones have been reported.

**TREATMENT CESSATION** Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis).

**DIRECTIONS FOR ADMINISTRATION** The dispersible tablets can be dispersed in water or orange squash (not orange juice) or swallowed whole.

**PRESCRIBING AND DISPENSING INFORMATION**

Co-beneldopa is a mixture of benserazide hydrochloride and levodopa in mass proportions corresponding to 1 part of benserazide and 4 parts of levodopa. When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued 12 hours before (although interval can be shorter).

When switching from modified-release levodopa to dispersible co-beneldopa, reduce dose by approximately 30%.

When administered as an adjunct to other antiparkinsonian drugs, once therapeutic effect apparent, the other drugs may be reduced or withdrawn.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer co-beneldopa dispersible tablets.

Dopamine dysregulation syndrome Manufacturer advises patients and their carers should be informed of the risk of developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.

Driving and skilled tasks Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with co-beneldopa.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

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DOSE EQUIVALENCE AND CONVERSION
- The proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.
- 2 tablets Sinemet® 12.5 mg/50 mg is equivalent to 1 tablet Sinemet® Plus 25 mg/100 mg.

CARMET® CR
Parkinson’s disease (patients not receiving levodopa/dopa-decarboxylase inhibitor preparations, expressed as levodopa)
- BY MOUTH USING MODIFIED-RELEASE TABLETS
  - Adult: Initially 100–200 mg twice daily, dose to be given at least 6 hours apart; dose adjusted according to response at intervals of at least 2 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)
- BY MOUTH USING MODIFIED-RELEASE TABLETS
  - Adult: Discontinue previous preparation at least 12 hours before first dose of Caramet® CR; substitute Caramet® CR to provide a similar amount of levodopa daily and extend dosing interval by 30–50%; dose then adjusted according to response at intervals of at least 2 days.

DUODOPA®
Severe Parkinson’s disease inadequately controlled by other preparations
- Adult: Administered as intestinal gel, for use with enteral tube (consult product literature)

HALF SINEMET® CR
Parkinson’s disease (for fine adjustment of Sinemet® CR dose)
- BY MOUTH
- Adult: (consult product literature)

SINEMET® CR
Parkinson’s disease (patients not receiving levodopa/dopa-decarboxylase inhibitor therapy)
- BY MOUTH
  - Adult: Initially 1 tablet twice daily, both dose and interval then adjusted according to response at intervals of not less than 3 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)
- BY MOUTH
  - Adult: 1 tablet twice daily, dose can be substituted for a daily dose of levodopa 300–400 mg in immediate-release Sinemet® tablets (substitute Sinemet® CR to provide approximately 10% more levodopa per day and extend dosing interval by 30–50%); dose and interval then adjusted according to response at intervals of not less than 3 days.

IMPORANT SAFETY INFORMATION
IMPULSE CONTROL DISORDERS
Treatment with levodopa is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

CAUTIONS
- Cushing’s syndrome
- diabetes mellitus
- endocrine disorders
- history of convulsions
- history of myocardial infarction with residual arrhythmia
- history of peptic ulcer
- hyperthyroidism
- osteomalacia
- phaeochromocytoma
- psychiatric illness (avoid if severe and discontinue if deterioration)
- severe cardiovascular
disease - severe pulmonary disease - susceptibility to angle-closure glaucoma

- **INTERACTIONS** ▶ Appendix 1: carbidopa - levodopa

- **SIDE-EFFECTS** ▶ Rare or very rare

  - Drowsiness - seizure - sleep disorders
  - Frequency not known

- **PREGNANCY** Use with caution — toxicity has occurred in animal studies.

- **BREAST FEEDING** May suppress lactation; present in milk — avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises use with caution in hepatic disease.

- **DOSE ADJUSTMENTS** Manufacturer advises titrate dose with caution in severe impairment.

- **RENAL IMPAIRMENT** Use with caution.

- **EFFECT ON LABORATORY TESTS** False positive tests for malaise.

- **TREATMENT CESSATION** Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis).

- **PRESCRIBING AND DISPENSING INFORMATION** Co-careldopa is a mixture of carbidopa and levodopa; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.

  - When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued at least 12 hours before.

  - Co-careldopa 25/100 provides an adequate dose of carbidopa when low doses of levodopa are needed.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and their carers should be informed of the risk of developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.

- **Driving and skilled tasks** Sudden onset of sleep

  - Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa.

  - Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  - Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **DUODOPA®**

    - **Scottish Medicines Consortium (SMC) decisions**

      - SMC No. 316/06

        - The Scottish Medicines Consortium has advised (June 2016) that co-careldopa (Duodopa®) intestinal gel is accepted for restricted use within NHS Scotland, for the treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results, only in patients not eligible for deep brain stimulation. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

    - **All Wales Medicines Strategy Group (AWMSG) decisions**

      - AWMSG No. 3397

        - The All Wales Medicines Strategy Group has advised (March 2018) that Duodopa® intestinal gel is recommended as an option for restricted use within NHS Wales, for the treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results, only in patients not eligible for deep brain stimulation. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Modified-release tablet** CAUTIONARY AND ADVISORY LABELS 10, 14, 25

  - **Caretom CR** (Teva UK Ltd)

    - Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Caretom 25mg/100mg CR tablets | 60 tablet | £11.47 DT = £11.60

  - **Half Sinemet CR** (Merck Sharp & Dohme Ltd)

    - Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Carbidopa 25mg/100mg CR tablets | 60 tablet | £11.60 DT = £11.60

  - **Lecado (Sanofiz Ltd)**

    - Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Lecado 100mg/25mg modified-release tablets | 60 tablet | £9.86 DT = £11.60

  - **Sinemet CR** (Merck Sharp & Dohme Ltd)

    - Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg Sinemet CR 50mg/200mg modified-release tablets | 60 tablet | £9.86 DT = £11.60

  - **Duodopa®**

    - **Scottish Medicines Consortium (SMC) decisions**

      - SMC No. 316/06

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  - **Lecado (Sanofiz Ltd)**

    - Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg Lecado 100mg/25mg modified-release tablets | 60 tablet | £9.86 DT = £11.60

  - **Sinemet CR** (Merck Sharp & Dohme Ltd)

    - Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg Sinemet CR 50mg/200mg modified-release tablets | 60 tablet | £9.86 DT = £11.60

  - **Duodopa®**

    - **Scottish Medicines Consortium (SMC) decisions**

      - SMC No. 316/06

        - The Scottish Medicines Consortium has advised (June 2016) that co-careldopa (Duodopa®) intestinal gel is accepted for restricted use within NHS Scotland, for the treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results, only in patients not eligible for deep brain stimulation. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

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Levodopa with carbidopa and entacapone

The properties listed below are those particular to the combination only. For the properties of the components please consider, co-carbidopa p. 415, entacapone p. 412.

**INDICATIONS AND DOSE**

**STALEVO® 100/25/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 125/31.25/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 150/37.5/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 175/43.75/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 7 tablets per day

**STALEVO® 200/50/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 8 tablets per day

**STALEVO® 250/62.5/200**

Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

- **BY MOUTH**
- Adult: 1 tablet for each dose; maximum 7 tablets per day

<table>
<thead>
<tr>
<th>STALEVO® 75/18.75/200</th>
<th>Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
<td>Adult: 1 tablet for each dose; maximum 10 tablets per day</td>
</tr>
</tbody>
</table>

**INTERACTIONS**

Appendix 1: carbidopa - entacapone - levodopa

**PRESCRIBING AND DISPENSING INFORMATION**

Patients receiving standard-release co-carbidopa or co-beneldopa alone, initiate Stalevo® at a dose that provides similar (or slightly lower) amount of levodopa.

Patients with dyskinesia or receiving more than 800 mg levodopa daily, introduce entacapone before transferring to Stalevo® (levodopa dose may need to be reduced by 10–30% initially).

Patients receiving entacapone and standard-release co-carbidopa or co-beneldopa, initiate Stalevo® at a dose that provides similar (or slightly higher) amount of levodopa.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks  Sudden onset of sleep  Excessive daytime sleepiness and sudden onset of sleep can occur with carbidopa with entacapone and levodopa.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Stalevo (Orion Pharma (UK) Ltd)
  - Carbidopa 25 mg, Levodopa 100 mg, Entacapone 200 mg
  - Stalevo 100mg/25mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 18.75 mg, Levodopa 75 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 25mg/18.75mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 37.5 mg, Levodopa 150 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 50mg/37.5mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 12.5 mg, Levodopa 50 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 12.5mg/50mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 31.25 mg, Levodopa 125 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 31.25mg/125mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 43.75 mg, Levodopa 175 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 43.75mg/175mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
  - Carbidopa 50 mg, Entacapone
    - Stalevo 200 mg
    - Stalevo 50mg/200mg tablets  | 30 tablet (POM) £20.79 D + £20.79 | 100 tablet (POM) £69.31 D + £69.31
DOPAMINERGIC DRUGS > DOPAMINE RECEPTOR AGONISTS

Amantadine hydrochloride 08-Feb-2019

- **DRUG ACTION** Amantadine is a weak dopamine agonist with modest antiparkinsonian effects.

- **INDICATIONS AND DOSE**
  - Parkinson’s disease
    - **BY MOUTH**
      - Adult: 100 mg daily for 1 week, then increased to 100 mg twice daily, usually administered in conjunction with other treatment. Some patients may require higher doses; maximum 400 mg per day
      - Elderly: 100 mg daily, adjusted according to response
  - Post-herpetic neuralgia
    - **BY MOUTH**
      - Adult: 100 mg twice daily for 14 days (continued for another 14 days if necessary)

- **TREATMENT OF INFLUENZA A (but not recommended)**
  - **BY MOUTH**
    - Adult: 100 mg daily 4–5 days

- **SIDE-EFFECTS**
  - Common or very common
    - Anxiety, appetite decreased, concentration impairment, confusion, constipation, depression, dizziness, dry mouth, hallucination, headache, hyperhidrosis, lethargy, mood altered, movement disorders, myalgia, nausea, palpitations, peripheral oedema, postural hypotension, skin reactions, sleep disorders, speech slurred, vision disorders, vomiting

- **CONTRA-INDICATIONS** Epilepsy, history of gastric ulceration

- **CAUTIONS** Confused or hallucinatory states, congestive heart disease (may exacerbate oedema), elderly, tolerance to the effects of amantadine may develop in Parkinson’s disease

- **INTERACTIONS** Appendix 1: dopamine receptor agonists

- **MEDICINAL FORMS**
  - Capsule Amantadine hydrochloride 100 mg Amantadine 100mg capsule | 14 capsule (£0.12–£0.24) | £41.00 DT = £40.93

Apomorphine hydrochloride 13-Jun-2018

- **INDICATIONS AND DOSE**
  - Refractory motor fluctuations in Parkinson’s disease (‘off’ episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (for capable and motivated patients) (under expert supervision)
    - **BY CONTINUOUS SUBCUTANEOUS INFUSION**
      - Adult: Initially 1 mg, dose to be administered at the first sign of ‘off’ episode, then 2 mg after 30 minutes, dose to be given if inadequate or no response following initial dose, thereafter increase dose at minimum 40-minute intervals until satisfactory response obtained, this determines threshold dose; usual dose 3–30 mg daily in divided doses (max. per dose 10 mg), subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses; maximum 100 mg per day

  - Refractory motor fluctuations in Parkinson’s disease (‘off’ episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (in patients requiring division into more than 10 injections daily) (under expert supervision)
    - **BY CONTINUOUS SUBCUTANEOUS INFUSION**
      - Adult: Initially 1 mg/hour, adjusted according to response, then increased in steps of up to 500 micrograms/hour, dose to be increased at intervals not more often than every 4 hours; usual dose 1–4 mg/hour, alternatively usual dose 15–60 micrograms/kg/hour, change infusion site every 12 hours and give during waking hours only (tolerance may occur unless there is a 4-hour treatment-free period at night—24-hour infusions not recommended unless severe night time symptoms); intermittent bolus doses may be needed; maximum 100 mg per day

- **IMPORTANT SAFETY INFORMATION**
  - **IMPULSE CONTROL DISORDERS**
    - Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.
CONTRA-INDICATIONS Avoid if ‘on’ response to levodopa marred by severe dyskinesia or dystonia • dementia • psychosis • respiratory depression

CAUTIONS Cardiovascular disease • history of postural hypotension (special care on initiation) • neuropsychiatric conditions • pulmonary disease • susceptibility to QT-interval prolongation

INTERACTIONS • Appendix 1: dopamine receptor agonists

SIDE-EFFECTS

Common or very common Confusion • dizziness • drowsiness • hallucinations • nausea • psychiatric disorders • subcutaneous nodule • vomiting • yawning

Uncommon Dyskinesia (may require discontinuation) • dyspnoea • haemolytic anaemia • injection site necrosis • postural hypotension • skin reactions • sudden onset of sleep • thrombocytopenia

Rare or very rare Bronchospasm • eosinophilia • hypersensitivity

Frequency not known Agitation • agitation • dopamine dysregulation syndrome • eating disorders • pathological gambling • peripheral oedema • sexual dysfunction • syncope

ALLERGY AND CROSS-SENSITIVITY Contra-indicated if history of hypersensitivity to opioids.

PREGNANCY Avoid unless clearly necessary.

BREAST FEEDING No information available; may suppress lactation.

HEPATIC IMPAIRMENT Manufacturer advises avoid in hepatic insufficiency.

RENAL IMPAIRMENT Use with caution.

MONITORING REQUIREMENTS

Monitor hepatic, haemopoietic, renal, and cardiovascular function.

With concomitant levodopa test initially and every 6 months for haemolytic anaemia and thrombocytopenia (development calls for specialist haematological care with dose reduction and possible discontinuation).

TREATMENT CESSION Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PATIENT AND CARER ADVICE Manufacturer advises patients and their carers should be informed of the risk of developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.

Driving and skilled tasks Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Drugs and driving Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

2015 legislation regarding driving whilst taking certain drugs, may also apply to apomorphine, see Drugs and driving under Guidance on prescribing p. 1.

Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10 EXCIPIENTS: May contain Sulphites

APO-go (Britannia Pharmaceuticals Ltd)

Apomorphine hydrochloride 10 mg per 1 ml APO-go 50mg/5ml solution for injection ampoules | 5 ampoule (£73.11 £73.11 £73.11

APO-go Pen (Britannia Pharmaceuticals Ltd)

Apomorphine hydrochloride 10 mg per 1 ml APO-go PEN 30mg/3ml solution for injection | 5 pre-filled disposable injection (£38 £123.91 DT £123.91

Dacepton (Ever Pharma UK Ltd)

Apomorphine hydrochloride hemihydrate 10 mg per 1 ml Dacepton 30mg/3ml solution for injection cartridges | 5 cartridge (£113.00

Solution for infusion

CAUTIONARY AND ADVISORY LABELS 10 EXCIPIENTS: May contain Sulphites

APO-go PFS (Britannia Pharmaceuticals Ltd)

Apomorphine hydrochloride 5 mg per 1 ml APO-go PFS 50mg/10ml solution for infusion pre-filled syringes | 5 pre-filled disposable injection (£38 £73.11 £73.11

Dacepton (Ever Pharma UK Ltd)

Apomorphine hydrochloride hemihydrate 5 mg per 1 ml Dacepton 100mg/20ml solution for infusion vials | 5 vial (£145.00

Bromocriptine

DRUG ACTION Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary.

INDICATIONS AND DOSE

Prevention of lactation

BY MOUTH

Adult: Initially 2.5 mg daily for 1 day, then 2.5 mg twice daily for 14 days

 Suppression of lactation

BY MOUTH

Adult: Initially 2.5 mg daily for 2–3 days, then 2.5 mg twice daily for 14 days

Hypogonadism | Galactorrhoea | Infertility

BY MOUTH

Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, increase dose gradually; usual dose 7.5 mg daily in divided doses, increased if necessary up to 30 mg daily, usual dose in infertility without hyperprolactinaemia is 2.5 mg twice daily

Acromegaly

BY MOUTH

Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually

Prolactinoma

BY MOUTH

Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually. Occasionally patients may require up to 30 mg daily

Parkinson’s disease

BY MOUTH

Adult: Initially 1–1.25 mg daily for 1 week, dose to be taken at night, then 2–2.5 mg daily for 1 week, dose to be taken at night, then 2.5 mg twice daily for 1 week, then 2.5 mg 3 times a day for 1 week, then continued →

BNF 78 Parkinson’s disease 419

Nervous System

www.getintopharma.com
420 Movement disorders

Nervous system

IMPORTANT SAFETY INFORMATION

FIBROTIC REACTIONS

Bromocriptine has been associated with pulmonary, retropertioneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson's disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful.

IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

CONTRA-INDICATIONS

Avoid in pre-eclampsia - cardiac valvulopathy (exclude before treatment) - hypertension in postpartum women or in puerperium

CONTRA-INDICATIONS, FURTHER INFORMATION

Postpartum or puerperium Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women.

INTERACTIONS

→ Appendix 1: dopamine receptor agonists

SIDE-EFFECTS

Common or very common Constipation - drowsiness - headache - nasal congestion - nausea

Uncommon Allergic dermatitis - alopecia - confusion - dizziness - dry mouth - fatigue - hallucination - hypotension - leg cramps - movement disorders - vomiting

Rare or very rare Abdominal pain - arthralgias - cardiac valvulopathy - diarrhoea - dyspnoea - gastrointestinal disorders - gastrointestinal haemorrhage - neuroleptic malignant-like syndrome - pallor - paraesthesia - pericardial effusion - pericarditis - peripheral oedema - psychotic disorder - respiratory disorders - sleep disorders - tinnitus - vision disorders

Frequency not known Eating disorders - hypertension - myocardial infarction - pathological gambling - psychiatric disorders - seizure - sexual dysfunction - stroke

SIDE-EFFECTS, FURTHER INFORMATION

Treatment should be withdrawn if gastro-intestinal bleeding occurs.

ALLERGY AND CROSS-SENSITIVITY

Bromocriptine should not be used in patients with hypersensitivity to ergot alkaloids.

CONCEPTION AND CONTRACEPTION

Caution—provide contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration).

BREAST FEEDING

Suppress lactation; avoid breast feeding for about 5 days if lactation prevention fails.

HEPATIC IMPAIRMENT

Dose adjustments Manufacturer advises dose adjustment may be necessary—risk of increased plasma concentration.

MONITORING REQUIREMENTS

Specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinaemia.

Monitor for fibrotic disease.

Monitor blood pressure for a few days after starting treatment and following dosage increase.

TREATMENT CESSATION

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PATIENT AND CARER ADVICE

Driving and skilled tasks Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions

Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 10, 21

• Bromocriptine (Non-proprietary)
  Bromocriptine (as Bromocriptine mesilate) 1 mg
  Bromocriptine 5mg tablets | 100 tablet (PSt) £67.66 DT = £67.66
  Bromocriptine (as Bromocriptine mesilate) 2.5 mg
  Bromocriptine 2.5mg tablets | 30 tablet (PSt) £74.97 DT = £74.97

Capsule

CAUTIONARY AND ADVISORY LABELS 10, 21

• Parlodel (Meda Pharmaceuticals Ltd)
  Bromocriptine (as Bromocriptine mesilate) 5 mg
  Parlodel 5mg capsules | 100 capsule (PSt) £37.57 DT = £37.57
  Bromocriptine (as Bromocriptine mesilate) 10 mg
  Parlodel 10mg capsules | 100 capsule (PSt) £69.50 DT = £69.50
Cabergoline

**DRUG ACTION** Cabergoline is a stimulant of dopamine receptors in the brain and it also inhibits release of prolactin by the pituitary.

**INDICATIONS AND DOSE**

**Prevention of lactation**
- **BY MOUTH**
- Adult: 1 mg, to be taken as a single dose on the first day postpartum.

**Suppression of established lactation**
- **BY MOUTH**
- Adult: 250 micrograms every 12 hours for 2 days.

**Hyperprolactinaemic disorders**
- **BY MOUTH**
- Adult: Initially 500 micrograms once weekly, dose may be increased to 1 mg every 7–14 days, maximum 2 mg per week.

**Alone or as adjunct to co-beneldopa or co-careldopa in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate**
- **BY MOUTH**
- Adult: Initially 1 mg daily, then increased in steps of 0.5–1 mg every 7–14 days, maximum 3 mg per day.

**IMPORANT SAFETY INFORMATION**

**FIBROTIC REACTIONS**
Cabergoline has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

**IMPULSE CONTROL DISORDERS**
Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CONTRA-INDICATIONS** Avoid in pre-eclampsia - cardiac valvulopathy (exclude before treatment) - history of pericardial fibrotic disorders - history of puerperal psychosis - history of pulmonary fibrotic disorders - history of retroperitoneal fibrotic disorders.

**CAUTIONS** Cardiovascular disease - history of peptic ulcer (particularly in acromegalic patients) - history of serious mental disorders (especially psychotic disorders) - Raynaud’s syndrome.

**CAUTIONS, FURTHER INFORMATION**
- Hyperprolactinaemic patients: In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

**INTERACTIONS**
- **Appendix 1:** dopamine receptor agonists.

**SIDE-EFFECTS**
- **Common or very common** Angina pectoris - asthenia - cardiac valvulopathy - confusion - constipation - dizziness - drowsiness - dyspepsia - dysphoria - gastritis - hallucination - headache - hypotension - movement disorders - nausea - oedema - pericardial effusion - pericarditis - sexual dysfunction - sleep disorders - vertigo - vomiting.
- **Uncommon** Delusions - erythromelalgia - hepatic function abnormal - psychotic disorder - rash - respiratory disorders.
- **Rare or very rare** Fibrosis.
- **Frequency not known** Aggression - alopecia - chest pain - digital vasospasm - leg cramps - pathological gambling - syncope - tremor - visual impairment.
- **ALLERGY AND CROSS-SENSITIVITY** Cabergoline should not be used in patients with hypersensitivity to ergot alkaloids.

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before starting and perform monthly pregnancy tests during the amenorrhoeic period. Caution—advise non-hormonal contraception if pregnancy not desired. Discontinue 1 month before intended conception (ovulatory cycles persist for 6 months).

**PREGNANCY** Discontinue if pregnancy occurs during treatment (specialist advice needed).

**BREAST FEEDING**Suppresses lactation; avoid breast-feeding if lactation prevention fails.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (risk of increased exposure).

**Dose adjustments** Manufacturer advises consider dose reduction in severe impairment.

**MONITORING REQUIREMENTS**
- Monitor for fibrotic disease.
- Monitor blood pressure for a few days after starting treatment and following dosage increase.

**TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

**PRESCRIBING AND DISPENSING INFORMATION** Dispense in original container (contains desiccant).

**PATIENT AND CARER ADVICE**
- **Driving and skilled tasks** Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine–receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine–receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.
Nervous system
Cautions
Different medicines containing the same drug.

BY MOUTH

Monotherapy in Parkinson

INDICATIONS AND DOSE

Dostinex
Cabaser

CAUTIONARY AND ADVISORY LABELS

Tablet

There can be variation in the licensing of different medicines containing the same drug.

Pergolide

INDICATIONS AND DOSE

Monotherapy in Parkinson disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

Adult: Initially 50 micrograms once daily for day 1, dose to be taken at bedtime, then 50 micrograms twice daily for days 2–4, then increased in steps of 100–250 micrograms daily, dose to be increased at intervals of 3–4 days, increased to 1.5 mg daily in 3 divided doses at day 28, then increased in steps of up to 250 micrograms every 3–4 days, this increase to be started after day 30; maintenance 2.1–2.5 mg daily; maximum 3 mg per day

Adjuvative therapy with co-beneldopa or co-careldopa in Parkinson's disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

Adult: Initially 50 micrograms daily for 2 days, then increased in steps of 100–150 micrograms every 3 days, dose to be adjusted over next 12 days following initial dose and usually given in 3 divided doses, then increased in steps of 250 micrograms every 3 days, during pergolide titration, levodopa dose may be reduced cautiously; maximum 3 mg per day

IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

CONTRA-INDICATIONS

Cardiac valvulopathy (exclude before treatment) • history of fibrotic disorders

CAUTIONS

Acute porphyrias p. 1058 • arrhythmias • dyskinesia (may exacerbate) • hallucinations • history of confusion • psychosis • underlying cardiac disease

INTERACTIONS

Appendix 1: dopamine receptor agonists

SIDE-EFFECTS

Cardiovascular disorders • compulsions • confusion • constipation • diarrhoea • diplopia • dizziness • drowsiness • dyskinesia • dry mouth • eating disorders • erythromelalgia • gastrointestinal discomfort • hallucinations • hiccup • nausea • neuroleptic malignant syndrome • pain • palpitations • pathological gambling • pericardial effusion • pericarditis • postural hypotension • pulmonary hypertension • rash • Raynaud’s phenomenon • respiratory disorders • retroperitoneal fibrosis • rhinitis • sexual dysfunction • sleep disorders • syncope • vomiting

PREGNANCY

Use only if potential benefit outweighs risk.

BREAST FEEDING

May suppress lactation.

TREATMENT CESSATION

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PARKINSON'S DISEASE

Driving and skilled tasks • Sudden onset of sleep

Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions

Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

Meditical forms

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Pergolide (Non-proprietary)

Pergolide 1 mg tablet [20 tablet (PO) £66.00 DT = £33.97]

Pergolide 2 mg tablet [20 tablet (PO) £73.14 DT = £37.57]

Cabaser (Pfizer Ltd)

Cabaser 1 mg tablet [20 tablet (PO) £83.00 DT = £41.43]

Cabaser 2 mg tablet [20 tablet (PO) £83.00 DT = £37.57]

Dostinex (Pfizer Ltd)

Dostinex 500 microgram tablet [8 tablet (PO) £30.04 DT = £34.97]

Pramipexole

INDICATIONS AND DOSE

Parkinson’s disease, used alone or as an adjunct to co-beneldopa or co-careldopa

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 88 micrograms 3 times a day, if tolerated dose to be increased by doubling dose every 5–7 days, increased to 350 micrograms 3 times a day, then increased in steps of 180 micrograms 3 times a day if required, dose to be increased at weekly intervals, during dose titration and maintenance.
Pramipexole (Non-proprietary)

Pramipexole (as Pramipexole dihydrochloride monohydrate)

30 tablet (£0.54–£0.97 DT = £14.77)

Pramipexole (as Pramipexole dihydrochloride monohydrate)

260 microgram Pramipexole 260microgram modified-release tablets £8.50–£10.87 DT = £41.74

520 microgram Pramipexole 520microgram modified-release tablets £20.00–£61.73 DT = £30.74

1.05 mg Pramipexole 1.05mg modified-release tablets £80.94–£192.24 DT = £126.82

2.1 mg Pramipexole 2.1mg modified-release tablets £50.00–£246.91 DT = £110.97

1.57 mg Pramipexole 1.57mg modified-release tablets £113.95–£320.41 DT = £222.06

BNF 73

PARKINSON’S DISEASE 423

INDICATIONS Antiparkinsonian drug therapy can be particularly problematic during the rst few days of treatment and care should be exercised when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identiﬁcation of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine receptor agonists; these can be particularly problematic during the rst few days of treatment and care should be exercised when driving or operating machinery.

MEDICATIONS There can be variation in the licensing of different medicines containing the same drug.

Modiﬁed-release tablet

CAUTIONARY AND ADVISORY LABELS 10, 25

Pramipexole (Non-proprietary)

Pramipexole (as Pramipexole dihydrochloride monohydrate)

260 microgram Pramipexole 260microgram modified-release tablets £8.50–£10.87 DT = £41.74

520 microgram Pramipexole 520microgram modified-release tablets £20.00–£61.73 DT = £30.74

1.05 mg Pramipexole 1.05mg modified-release tablets £80.94–£192.24 DT = £126.82

2.1 mg Pramipexole 2.1mg modified-release tablets £50.00–£246.91 DT = £110.97

1.57 mg Pramipexole 1.57mg modified-release tablets £113.95–£320.41 DT = £222.06

Levodopa dose may be reduced, maximum daily dose to be given in 3 divided doses; maximum 3.3 mg per day

BY MOUTH USING MODIFIED-RELEASE MEDICINES

Adult: Initially 260 micrograms once daily, dose to be increased by doubling dose every 5–7 days, increased to 1.05 mg once daily, then increased in steps of 250 micrograms every week if required, during dose titration and maintenance, levodopa dose may be reduced according to response; maximum 3.15 mg per day

Moderate to severe restless legs syndrome

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 88 micrograms once daily, dose to be taken 2–3 hours before bedtime, dose to be increased by doubling dose every 4–7 days if necessary, repeat dose titration if restarting treatment after an interval of more than a few days; maximum 540 micrograms per day

DOSE EQUIVALENCE AND CONVERSION

Doses and strengths are stated in terms of pramipexole (base).

Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for immediate-release preparations are as follows:

88 micrograms base = 125 micrograms salt;
180 micrograms base = 250 micrograms salt;
350 micrograms base = 500 micrograms salt;
700 micrograms base = 1 mg salt.

Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for modified-release preparations are as follows:

250 micrograms base = 375 micrograms salt;
520 micrograms base = 750 micrograms salt;
1.05 mg base = 1.5 mg salt;
1.57 mg base = 2.25 mg salt;
2.1 mg base = 3 mg salt;
2.62 mg base = 3.75 mg salt;
3.15 mg base = 4.5 mg salt.

IMPORTANT SAFETY INFORMATION

IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

CAUTIONS

Psychotic disorders · risk of visual disorders (ophthalmological testing recommended) · severe cardiovascular disease

INTERACTIONS Appendix 1: dopamine receptor agonists

SIDE-EFFECTS

Common or very common Appetite abnormal · behaviour abnormal · confusion · constipation · dizziness · drowsiness · fatigue · hallucination · headache · hypotension · movement disorders · nausea · peripheral oedema · psychiatric disorders · sleep disorders · vision disorders · vomiting · weight changes

Uncommon Anxiety · binging eating · delirium · delusions · dyskinesia · heart failure · hiccups · mania · memory loss · pathological gambling · pneumonia · sexual dysfunction · SIADH · skin reactions · syncpe

Frequency not known Depression · dopamine agonist withdrawal syndrome · generalised pain · sweating abnormal

PREGNANCY

Use only if potential beneﬁt outweighs risk—no information available.

BREAST FEEDING

May suppress lactation; avoid—present in milk in animal studies.

RENAL IMPAIRMENT

For modiﬁed-release tablets, avoid if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments For immediate-release tablets in Parkinson’s disease, initially 88 micrograms twice daily (max. 1.57 mg daily in 2 divided doses) if eGFR 20–50 mL/minute/1.73 m²; initially 88 micrograms once daily (max. 1.1 mg once daily) if eGFR less than 20 mL/minute/1.73 m². If renal function declines during treatment, reduce dose by the same percentage as the decline in eGFR.

For immediate-release tablets in restless legs syndrome, reduce dose if eGFR less than 20 mL/minute/1.73 m².

For modiﬁed-release tablets, initially 260 micrograms on alternate days if eGFR 30–50 mL/minute/1.73 m²; increased to 260 micrograms once daily after 1 week, further increased if necessary by 260 micrograms daily at weekly intervals to max. 1.57 mg daily.

MONITORING REQUIREMENTS Risk of postural hypotension (especially on initiation)—monitor blood pressure.

TREATMENT CESSATION Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PATIENT AND CARER ADVICE

Driving and skilled tasks Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

www.getintopharma.com
**Pramipexole (as Pramipexole dihydrochloride monohydrate)**

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<thead>
<tr>
<th>Strength</th>
<th>Dosage Form</th>
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<tr>
<td>0.15 mg</td>
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<tr>
<td>0.35 mg</td>
<td>Tablet</td>
<td>1,000 microgram</td>
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**INDICATIONS AND DOSE**

**Parkinson's disease, either used alone or as adjunct to carbidopa or co-carbidopa**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

**Adults:** Initially 750 micrograms daily in 3 divided doses, then increased in steps of 750 micrograms daily, dose to be increased at weekly intervals, increased to 3 mg daily in 3 divided doses, then increased in steps of 1.5–3 mg daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 9–16 mg daily in 3 divided doses, higher doses may be required if used with levodopa, when administered as adjunct to levodopa, concurrent dose of levodopa may be reduced by approx. 20%, daily maximum dose to be given in 3 divided doses; maximum 24 mg per day.

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

**Adults:** Initially 2 mg once daily for 1 week, then 4 mg once daily, increased in steps of 2 mg at intervals of at least 1 week, adjusted according to response, increased up to 8 mg once daily, dose to be increased further if still no response; increased in steps of 2–4 mg at intervals of at least 2 weeks if required, consider slower titration in patients over 75 years, when administered as adjunct to levodopa, concurrent dose of levodopa may gradually be reduced by approx. 30%; maximum 24 mg per day.

**PARKINSON'S DISEASE IN PATIENTS TRANSFERRING FROM ROPINIROLE IMMEDIATE-RELEASE TABLETS**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

**Adults:** Initially ropinirole modified-release once daily substituted for total daily dose equivalent of ropinirole immediate-release tablets; if control not maintained after switching, titrate dose as above.

**Mild to severe restless legs syndrome**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

**Adults:** Initially 250 micrograms once daily for 2 days, increased if tolerated to 500 micrograms once daily for 5 days, then increased if tolerated to 1 mg once daily.
TREATMENT CESSATION

RENAL IMPAIRMENT
▶ When used for Restless legs syndrome

HEPATIC IMPAIRMENT
▶ When used for eating disorders
▶ May suppress lactation
▶ Uncommon Hypotension — sexual dysfunction
▶ Rare or very rare — Hepatic reaction
▶ Frequency not known — Behaviour abnormal — compulsions — delirium — delusions — dopamine dysregulation syndrome — eating disorders — pathological gambling — psychotic disorder
▶ Pregnancy — Avoid unless potential benefit outweighs risk — toxicity in animal studies.
▶ Breast feeding — May suppress lactation — avoid.
▶ Hepatic Impairment — When used for Parkinson’s disease Manufacturer advises avoid (no information available).
▶ When used for restless legs syndrome Manufacturer advises caution in moderate impairment; avoid in severe impairment.
▶ Renal Impairment — Avoid if eGFR less than 30 mL/minute/1.73 m².
▶ Treatment Cessation — Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.
▶ Patient and Carer Advice — Manufacturer advises patients and their carers should be informed of the risk of developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.
▶ Missed doses —
  ▶ When used for Parkinson’s disease Manufacturer advises if treatment is interrupted for more than a few days, re-initiation by dose titration is recommended.
  ▶ Driving and skilled tasks
  ▶ Sudden onset of sleep — Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.
  ▶ Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.
  ▶ Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.
▶ Hypotensive reactions — Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

INTERACTIONS
▶ Caution in moderate impairment; avoid in severe risk of neuroleptic malignant syndrome.
▶ Should never be stopped abruptly as this carries a small risk.
▶ Manufacturer advises.

Nervous System

Manufacturer advises if treatment is stopped, dosage possibly should be reduced until the symptoms resolve.

SAFE PRACTICE

IMPULSE CONTROL DISORDERS
Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

CAUTIONS
Elderly — major psychotic disorders — severe cardiovascular disease (risk of hypotension — monitor blood pressure).

INTERACTIONS
▶ Appendix 1: dopamine receptor agonists

SIDE-EFFECTS
▶ Common or very common — Confusion — dizziness — drowsiness — early morning awakening — fatigue — gastrointestinal discomfort — hallucination — movement disorders — nausea — nervousness — peripheral oedema — syncope — vertigo — vomiting
▶ Uncommon — Hypotension — sexual dysfunction
▶ Rare or very rare — Hepatic reaction
▶ Frequency not known — Behaviour abnormal — compulsions — delirium — delusions — dopamine dysregulation syndrome — eating disorders — pathological gambling — psychotic disorder
▶ Pregnancy — Avoid unless potential benefit outweighs risk — toxicity in animal studies.
▶ Breast feeding — May suppress lactation — avoid.
▶ Hepatic impairment — When used for Parkinson’s disease Manufacturer advises avoid (no information available).
▶ When used for Restless legs syndrome Manufacturer advises caution in moderate impairment; avoid in severe impairment.
▶ Renal Impairment — Avoid if eGFR less than 30 mL/minute/1.73 m².
▶ Treatment Cessation — Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.
▶ Patient and Carer Advice — Manufacturer advises patients and their carers should be informed of the risk of developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.
▶ Missed doses —
  ▶ When used for Parkinson’s disease Manufacturer advises if treatment is interrupted for more than a few days, re-initiation by dose titration should be considered — consult product literature.
  ▶ When used for Moderate to severe restless legs syndrome Manufacturer advises if treatment is interrupted for more than a few days, re-initiation by dose titration is recommended.
▶ Driving and skilled tasks
▶ Sudden onset of sleep — Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.
▶ Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.
▶ Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.
▶ Hypotensive reactions — Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

INTERACTIONS
▶ Caution in moderate impairment; avoid in severe risk of neuroleptic malignant syndrome.
▶ Should never be stopped abruptly as this carries a small risk.
▶ Manufacturer advises.
**Movement disorders**

- **ReQuip XL** (GlaxoSmithKline UK Ltd)
  Ropinirole (as Ropinirole hydrochloride) 2 mg ReQuip XL 2mg tablets | 28 tablet [POD] £12.54 DT + £12.54
  Ropinirole (as Ropinirole hydrochloride) 4 mg ReQuip XL 4mg tablets | 28 tablet [POD] £25.09 DT + £25.09
  Ropinirole (as Ropinirole hydrochloride) 8 mg ReQuip XL 8mg tablets | 28 tablet [POD] £42.11 DT + £42.11

- **Ropilynz XL** (Lupin Healthcare (UK) Ltd)
  Ropinirole (as Ropinirole hydrochloride) 8 mg Ropilynz XL 8mg tablets | 28 tablet [POD] £21.00 DT + £21.11

- **Spiroco XL** (Teva UK Ltd)
  Ropinirole (as Ropinirole hydrochloride) 2 mg Spiroco XL 2mg tablets | 28 tablet [POD] £12.54 DT + £12.54
  Ropinirole (as Ropinirole hydrochloride) 4 mg Spiroco XL 4mg tablets | 28 tablet [POD] £25.09 DT + £25.09
  Ropinirole (as Ropinirole hydrochloride) 8 mg Spiroco XL 8mg tablets | 28 tablet [POD] £42.11 DT + £42.11

- **Ropiqual XL** (MILPHARM LTD)
  Ropinirole (as Ropinirole hydrochloride) 2 mg Ropiqual XL 2mg tablets | 28 tablet [POD] £21.32 DT + £25.09
  Ropinirole (as Ropinirole hydrochloride) 8 mg Ropiqual XL 8mg tablets | 28 tablet [POD] £35.79 DT + £42.11

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 10, 21**

- **Ropinirole (Non-proprietary)**
  Ropinirole (as Ropinirole hydrochloride) 250 microgram Ropinirole 250microgram tablets | 12 tablet [POD] £5.00 DT + £3.02
  Ropinirole (as Ropinirole hydrochloride) 500 microgram Ropinirole 500microgram tablets | 28 tablet [POD] £25.00 DT + £7.32
  Ropinirole (as Ropinirole hydrochloride) 1 mg Ropinirole 1mg tablets | 84 tablet [POD] £56.71 DT + £56.71
  Ropinirole (as Ropinirole hydrochloride) 2 mg Ropinirole 2mg tablets | 28 tablet [POD] £21.25–£49.99 DT + £14.56 | 84 tablet [POD] £33.35–£52.50
  Ropinirole (as Ropinirole hydrochloride) 5 mg Ropinirole 5mg tablets | 84 tablet [POD] £185.65 DT + £185.51

- **Adartrel (GlaxoSmithKline UK Ltd)**
  Ropinirole (as Ropinirole hydrochloride) 250 microgram Adartrel 250microgram tablets | 12 tablet [POD] £3.94 DT + £3.02
  Ropinirole (as Ropinirole hydrochloride) 500 microgram Adartrel 500microgram tablets | 28 tablet [POD] £13.75 DT + £7.32
  Ropinirole (as Ropinirole hydrochloride) 2 mg Ropinirole 2mg tablets | 28 tablet [POD] £31.51 DT + £14.56

- **ReQuip (GlaxoSmithKline UK Ltd)**
  Ropinirole (as Ropinirole hydrochloride) 250 microgram ReQuip 250microgram tablets | 21 tablet [POD] £5.70
  Ropinirole (as Ropinirole hydrochloride) 1 mg ReQuip 1mg tablets | 84 tablet [POD] £56.71 DT + £56.71
  Ropinirole (as Ropinirole hydrochloride) 2 mg ReQuip 2mg tablets | 84 tablet [POD] £113.44
  Ropinirole (as Ropinirole hydrochloride) 5 mg ReQuip 5mg tablets | 84 tablet [POD] £195.92 DT + £185.51

**Rotigotine**

**INDICATIONS AND DOSE**

**Monotherapy in Parkinson’s disease**

- **BY TRANSDERMAL APPLICATION USING PATCHES**
  Adult: Initially 2 mg/24 hours, then increased in steps of 2 mg/24 hours every week if required; maximum 8 mg/24 hours per day

**Adjunctive therapy with co-beneldopa or co-careldopa in Parkinson’s disease**

- **BY TRANSDERMAL APPLICATION USING PATCHES**
  Adult: Initially 4 mg/24 hours, then increased in steps of 2 mg/24 hours every week if required; maximum 16 mg/24 hours per day

**Moderate to severe restless legs syndrome**

- **BY TRANSDERMAL APPLICATION USING PATCHES**
  Adult: Initially 1 mg/24 hours, then increased in steps of 1 mg/24 hours every week if required; maximum 3 mg/24 hours per day

**IMPORATNT SAFETY INFORMATION**

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

- **CAUTIONS** Avoid exposure of patch to heat - remove patch (aluminium-containing) before magnetic resonance imaging or cardioversion

- **INTERACTIONS** ≥ Appendix 1: dopamine receptor agonists

- **SIDE-EFFECTS**

  - **Common or very common** Asthenia - behaviour abnormal - constipation - dizziness - drowsiness - dry mouth - dyskinesia - eating disorders - fall - gastrointestinal discomfort - hallucinations - headache - hiccups - hyperhidrosis - hypertension - hypotension - loss of consciousness - malaise - nausea - palpitations - pathological gambling - perception altered - peripheral oedema - psychiatric disorders - skin reactions - sleep disorders - syncope - vertigo - vomiting - weight changes

  - **Uncommon** Agitation - angioedema - arrhythmias - confusion - sexual dysfunction - vision disorders

  - **Rare or very rare** Delirium - delusions - irritability - psychotic disorder - seizure

  - **Frequency not known** Dopamine dysregulation syndrome

- **PREGNANCY** Avoid—no information available.

- **BREAST FEEDING** May suppress lactation; avoid—present in milk in animal studies

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (no information available).

- **Dose adjustments** Manufacturer advises consider dose reduction in severe impairment.

- **MONITORING REQUIREMENTS** Ophthalmic testing recommended.

- **TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises apply patch to clean, dry, intact, healthy and non-irritated skin on torso, thigh, hip, shoulder or upper arm by pressing the patch firmly against the skin for about 30 seconds. Patches should be removed after 24 hours and the replacement patch applied on a different area (avoid using the same area for 14 days)—consult product literature for further information.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and their carers should be informed of the risk of
developing dopamine dysregulation syndrome; addiction-like symptoms should be reported.

**Driving and skilled tasks**

**Sudden onset of sleep** Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

### NATIONAL FUNDING/ACCESS DECISIONS

**Scottish Medicines Consortium (SMC) decisions**

The **Scottish Medicines Consortium** has advised that **Neupro** is accepted for restricted use for the treatment of advanced Parkinson’s disease in combination with levodopa where the transdermal route would facilitate treatment (July 2007).

The **Scottish Medicines Consortium** has advised that **Neupro** is accepted as monotherapy for the treatment of early-stage idiopathic Parkinson’s disease (June 2007).

The **Scottish Medicines Consortium** has advised (April 2009) that rotigotine (Neupro) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults with a baseline score of 15 points or more on the International Restless Legs Scale.

### MEDICINAL FORMS

**Transdermal patch**

<table>
<thead>
<tr>
<th>Patch</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupro 1 mg</td>
<td>£0.70</td>
</tr>
<tr>
<td>Neupro 2 mg</td>
<td>£1.02</td>
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<tr>
<td>Neupro 3 mg</td>
<td>£1.49</td>
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<tr>
<td>Neupro 4 mg</td>
<td>£1.49</td>
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<tr>
<td>Neupro 6 mg</td>
<td>£1.49</td>
</tr>
<tr>
<td>Neupro 8 mg</td>
<td>£1.49</td>
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</tbody>
</table>

## SAFINAMIDE

**Drug action** Safinamide is a monoamine-oxidase-B inhibitor.

### INDICATIONS AND DOSE

**Parkinson’s disease, as an adjunct to levodopa alone or in combination with other antiparkinsonian drugs, for mid- to late-stage fluctuations**

- **By mouth**
  - Adult: 50 mg once daily, increased if necessary to 100 mg once daily

### CONTRA-INDICATIONS

Active retinopathy - albinism - family history of hereditary retinal disease - retinal degeneration - uveitis

### CAUTIONS

Hypertension (may raise blood pressure) - may exacerbate pre-existing dyskinesia (requiring levodopa dose reduction)

### INTERACTIONS

> Appendix 1: monoamine-oxidase B inhibitors

### SIDE-EFFECTS

- **Common or very common** Abdominal pain - angina pectoris - arthralgia - arthritis - conjunctivitis - depression - dermatitis - dry mouth - fall - fever - flatulence - hallucination - headache - increased risk of infection - leucopenia - malaise - nausea - neoplasms - pain - postural hypotension - sleep disorders - urinary urgency - vertigo - vomiting - weight decreased

- **Uncommon** Appetite decreased - confusion

- **Frequency not known** Dopamine dysregulation syndrome - drowsiness - eating disorders - pathological gambling - psychiatric disorders - sexual dysfunction

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Use with caution—may suppress lactation.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment (risk of increased exposure).

### TREATMENT CESSATION

Avoid abrupt withdrawal.
Nausea and labyrinth disorders

Selegiline hydrochloride

**DRUG ACTION** Selegiline is a monoamine-oxidase B inhibitor.

**INDICATIONS AND DOSE** Parkinson’s disease, used alone or as adjunct to co-beneldopa or co-careldopa to reduce ‘end of dose’ deterioration; Symptomatic parkinsonism

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: Initially 5 mg once daily for 2–4 weeks, then increased if tolerated to 10 mg daily, dose to be taken in the morning
- Adult: 1.25 mg once daily, dose to be taken before breakfast

**DOSE EQUIVALENCE AND CONVERSION**
- 1.25-mg oral lyophilisate is equivalent to 10-mg tablet.
- Patients receiving 10 mg conventional selegiline hydrochloride tablets can be switched to oral lyophilisates (Zelapar®) 1.25 mg.

**CONTRA-INDICATIONS** Active duodenal ulceration, active gastric ulceration, avoid or use with great caution in postural hypotension (when used in combination with levodopa)

**CAUTIONS** Angina, arrhythmias; duodenal ulceration; gastric ulceration; history of hepatic dysfunction; patients predisposed to confusion and psychosis; psychoses; uncontrolled hypertension

**INTERACTIONS** → Appendix 1: monoamine-oxidase B inhibitors

**SIDE-EFFECTS**
- **Common or very common** Arrhythmias, arthralgia, back pain, confusion, constipation, depression, diarrhoea, dizziness, dry mouth, fall, fatigue, hallucination, headache, hyperhidrosis, hypertension, hypotension, movement disorders, muscle cramps, nasal congestion, nausea, oral disorders, sleep disorders, throat pain, tremor, vertigo
- **Uncommon** Alopecia, angina pectoris, anxiety, appetite decreased, chest pain, dysphoria, leukopenia, mood altered, myopathy, palpitations, peripheral oedema, pharyngitis, psychosis, skin eruption, thrombocytopenia, urinary disorders, vision blurred
- **Frequency not known** Hypersexuality

**SIDE-EFFECTS, FURTHER INFORMATION** Side-effects of levodopa may be increased—concurrent levodopa dosage can be reduced by 10–30% in 10% every 3–4 days.

- **PREGNANCY** Avoid—no information available.
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.
- **RENAL IMPAIRMENT** Use with caution in severe impairment.
- **TREATMENT CESSATION** Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION** Oral lyophilisates should be placed on the tongue and allowed to dissolve. Advise patient not to drink, rinse, or wash mouth out for 5 minutes after taking the tablet.

- **PATIENT AND CARER ADVICE** Patients or carers should be advised on how to administer selegiline hydrochloride oral lyophilisates.
- **Driving and skilled tasks**
  - Drugs and driving: Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at [www.dvla.gov.uk](http://www.dvla.gov.uk).
  - 2015 legislation regarding driving whilst taking certain drugs, may also apply to selegiline, see [Drugs and driving](#) under Guidance on prescribing p. 1.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
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<tbody>
<tr>
<td>Xadago (Profile Pharma Ltd)</td>
</tr>
<tr>
<td>Safinamide (as Safinamide methanulfonate) 50 mg Xadago</td>
</tr>
<tr>
<td>Safinamide (as Safinamide methanulfonate) 100 mg Xadago</td>
</tr>
</tbody>
</table>

**EXCIPIENTS:** May contain Aspartame

**TREATMENT CESSATION** Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION** Oral lyophilisates should be placed on the tongue and allowed to dissolve. Advise patient not to drink, rinse, or wash mouth out for 5 minutes after taking the tablet.

- **PATIENT AND CARER ADVICE** Patients or carers should be advised on how to administer selegiline hydrochloride oral lyophilisates.
- **Driving and skilled tasks**
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  - 2015 legislation regarding driving whilst taking certain drugs, may also apply to selegiline, see [Drugs and driving](#) under Guidance on prescribing p. 1.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

<table>
<thead>
<tr>
<th>Tablet</th>
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<tbody>
<tr>
<td>Eldepryl (Orion Pharma (UK) Ltd)</td>
</tr>
<tr>
<td>Selegiline hydrochloride 5 mg Eldepryl 5mg tablets</td>
</tr>
<tr>
<td>Selegiline hydrochloride 10 mg Eldepryl 10mg tablets</td>
</tr>
</tbody>
</table>

**Oral lyophilisate**

- **EXCIPIENTS:** May contain Aspartame
- **Zelapar (Teva UK Ltd)**
  - Selegiline hydrochloride 1.25 mg Zelapar 1.25mg oral lyophilisates sugar-free | 30 tablet (£0.43 + £43.16)

5 Nausea and labyrinth disorders

**Nausea and labyrinth disorders**

**Drug treatment** Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis, particularly in children. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin p. 109 or antiepileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting.

**Antihistamines** are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of adverse effects (drowsiness and antimuscarinic effects) differ.
The **phenothiazines** are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They are of considerable value for the prophylaxis and treatment of nausea and vomiting associated with diffuse neoplastic disease, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytoxotics. Prochlorperazine p. 385, perphenazine, and trifluoperazine p. 390 are less sedating than chlorpromazine hydrochloride p. 384; severe dystonic reactions sometimes occur with phenothiazines, especially in children. Some phenothiazines are available as rectal suppositories, which can be useful in patients with persistent vomiting or with severe nausea; prochlorperazine can also be administered as a buccal tablet which is placed between the upper lip and the gum.

Other antipsychotic drugs including haloperidol p. 386 and levomepromazine p. 441 are used for the relief of nausea and vomiting in terminal illness.

Metoclopramide hydrochloride p. 432 is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide hydrochloride also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease.

Domperidone p. 431 acts at the chemoreceptor trigger zone; it is licensed only for the relief of nausea and vomiting. It has the advantage over metoclopramide hydrochloride and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. In Parkinson’s disease, it can be used to treat nausea caused by dopaminergic drugs.

Granisetron p. 435 and ondansetron p. 436 are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting. Palonosetron p. 437 is licensed for prevention of nausea and vomiting associated with moderately or highly emetogenic cytotoxic chemotherapy. Palonosetron is also available in combination with netupitant, a neurokinin 3-receptor antagonist, for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy and highly emetogenic cisplatin-based chemotherapy.

Dexamethasone p. 675 has antiemetic effects and it is used in vomiting associated with cancer chemotherapy. It can be used alone or with metoclopramide hydrochloride, prochlorperazine, lorazepam p. 339, or a 5HT3-receptor antagonist.

Aprepitant p. 433, fosaprepitant p. 434, and rolepitant p. 434 are neurokinin 1-receptor antagonists. Aprepitant is licensed for the prevention of nausea and vomiting associated with highly and moderately emetogenic chemotherapy; fosaprepitant is licensed for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy; rolepitant is licensed for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic chemotherapy. These drugs are given with dexamethasone and a 5HT3-receptor antagonist.

Nabilone p. 431 is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics.

**Vomiting during pregnancy**

Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. Prochlorperazine or metoclopramide hydrochloride are alternatives. If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought. Hyperemesis gravidarum is a more serious condition, which requires regular antiemetic therapy, intravenous fluid and electrolyte replacement and sometimes nutritional support. Supplementation with thiamine p. 1080 must be considered in order to reduce the risk of Wernicke’s encephalopathy.

**Postoperative nausea and vomiting**

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, and the type and duration of surgery. Other risk factors include female sex, non-smokers, a history of postoperative nausea and vomiting or motion sickness, and intraoperative and postoperative use of opioids. Therapy to prevent postoperative nausea and vomiting should be based on the assessed risk of postoperative nausea and vomiting in each patient. Drugs used include 5HT3-receptor antagonists, droperidol p. 440, dexamethasone, some phenothiazines (e.g. prochlorperazine), and antihistamines (e.g. cyclizine p. 430). A combination of two or more antiemetic drugs that have different mechanisms of action is often indicated in those at high risk of postoperative nausea and vomiting or where postoperative vomiting presents a particular danger (e.g. in some types of surgery). When a prophylactic antiemetic drug has failed, postoperative nausea and vomiting should be treated with one or more drugs from a different class.

**Motion sickness**

Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is hyoscine hydrobromide p. 439. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative effect is desired promethazine is useful, but generally a slightly less sedating antihistamine such as cyclizine or cinnarizine p. 438 is preferred. Domperidone, metoclopramide hydrochloride, 5HT3-receptor antagonists, and the phenothiazines (except the antihistamine phenothiazine promethazine) are ineffective in motion sickness.

**Other vestibular disorders**

Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. Vertigo and nausea associated with Ménière’s disease and middle-ear surgery can be difficult to treat.

Betahistine dihydrochloride p. 441 is an analogue of histamine and is claimed to reduce endolymphatic pressure by improving the microcirculation. Betahistine dihydrochloride is licensed for vertigo, tinnitus, and hearing loss associated with Ménière’s disease.

A diuretic alone or combined with salt restriction may provide some benefit in vertigo associated with Ménière’s disease; antihistamines (such as cinnarizine), and phenothiazines (such as prochlorperazine) are also used. Where possible, prochlorperazine should be reserved for the treatment of acute symptoms.

**Nausea caused by cytotoxic chemotherapy, palliative care, and migraine**

Antiemetics have a role in the management of nausea and vomiting induced by cytotoxic chemotherapy, in palliative care, and associated with migraine.

**Other drugs used for Nausea and labyrinth disorders**

Paracetamol with metoclopramide, p. 476 · Promethazine hydrochloride, p. 286
### Cyclizine

**INDICATIONS AND DOSE**
- Nausea or vomiting due to cause other than motion sickness
- Nausea and vomiting associated with vestibular disorders
- Vertigo

**ADULT: BY MOUTH**
- 25 mg up to 3 times daily, for motion sickness, take 1–2 hours before departure.
- Intravenous injection or by intramuscular injection
- 50 mg up to 3 times daily.

**CHILD: BY MOUTH OR BY INTRAVENOUS INJECTION**
- Child 1 month–5 years: 0.5–1 mg/kg up to 3 times daily (max. per dose 25 mg).
- Intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure.
- Child 6–11 years: 25 mg up to 3 times daily, intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure.
- Child 12–17 years: 50 mg up to 3 times daily, intravenous injection to be given over 3–5 minutes, for motion sickness, take 1–2 hours before departure.
- By continuous intravenous infusion, or by subcutaneous infusion
- Child 1–2 months: 3 mg/kg, dose to be given over 24 hours.
- Child 2–5 years: 50 mg, dose to be given over 24 hours.
- Child 6–11 years: 75 mg, dose to be given over 24 hours.
- Child 12–17 years: 150 mg, dose to be given over 24 hours.

**Nausea and vomiting in palliative care**
- Child 1–2 months: 3 mg/kg, dose to be given over 24 hours.
- Child 2–5 years: 50 mg, dose to be given over 24 hours.
- Child 6–11 years: 75 mg, dose to be given over 24 hours.
- Child 12–17 years: 150 mg, dose to be given over 24 hours.
- Adult: 150 mg, dose to be given over 24 hours.

**By mouth**
- Child 1 month–5 years: 0.5–1 mg/kg up to 3 times daily (max. per dose 25 mg).
- Child 6–11 years: 25 mg up to 3 times daily.
- Child 12–17 years: 50 mg up to 3 times daily.
- Adult: 50 mg up to 3 times daily.

**By intravenous injection**
- Child 1 month–5 years: 0.5–1 mg/kg up to 3 times daily (max. per dose 25 mg).
- Intravenous injection to be given over 3–5 minutes.
- Child 6–11 years: 25 mg up to 3 times daily, intravenous injection to be given over 3–5 minutes.
- Child 12–17 years: 50 mg up to 3 times daily, intravenous injection to be given over 3–5 minutes.

**By continuous intravenous infusion**
- Child 1–2 months: 3 mg/kg, dose to be given over 24 hours.
- Child 2–5 years: 50 mg, dose to be given over 24 hours.
- Child 6–11 years: 75 mg, dose to be given over 24 hours.
- Child 12–17 years: 150 mg, dose to be given over 24 hours.
- Adult: 150 mg, dose to be given over 24 hours.

**Specified side-effects**
- Rare or very rare: agitation (more common at high doses), angle closure glaucoma, depression.

**Special side-effects**
- With oral use: level of consciousness decreased.
- With parenteral use: Chills, consciousness impaired, injection site necrosis, pain, paralysis, sensation of pressure, thrombophlebitis.

**Pregnancy**
- Manufacturer advises avoid; however, there is no evidence of teratogenicity.

**Breast-feeding**
- No information available. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**Hepatic impairment**
- Manufacturer advises caution.

**Directions for administration**
- By mouth, tablets may be crushed.
- For administration by mouth, tablets may be crushed.
- For further information on the use of cyclizine in palliative care, see [www.medicinescomplete.com](http://www.medicinescomplete.com/)

**Prescribing and dispensing information**
- Palliative care: For further information on the use of cyclizine in palliative care, see [www.medicinescomplete.com](http://www.medicinescomplete.com/).
Nausea and labyrinth disorders 431

ANTIEMETICS AND ANTINAUSEANTS

CANNABINOIDS

Nabilone

INDICATIONS AND DOSE
Nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (preferably in hospital setting) (under close medical supervision)

BY MOUTH
• Adult: Initially 1 mg twice daily, increased if necessary to 2 mg twice daily throughout each cycle of cytotoxic therapy and, if necessary, for 48 hours after the last dose of each cycle, the first dose should be taken the night before initiation of cytotoxic treatment and the second dose 1–3 hours before the first dose of cytotoxic drug, daily dose maximum should be given in 3 divided doses; maximum 6 mg per day

CAUTIONS
Adverse effects on mental state can persist for 48–72 hours after stopping. Elderly, heart disease, history of psychiatric disorder, hypertension

INTERACTIONS
Appendix 1: nabilone

SIDE-EFFECTS
Abdominal pain, appetite decreased, concentration impaired, confusion, depression, dizziness, drowsiness, drug use disorders, dry mouth, euphoric mood, feeling of relaxation, hallucination, headache, hypotension, movement disorders, nausea, psychosis, sleep disorder, tachycardia, tremor, vertigo, visual impairment

SIDE-EFFECTS, FURTHER INFORMATION
Drowsiness and dizziness occur frequently with standard doses.

PREGNANCY
Avoid unless essential.

Breast Feeding
Avoid—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises avoid in severe impairment (primarily biliary excretion).

PATIENT AND CARER ADVICE
Behavioural effects. Patients should be made aware of possible changes of mood and other adverse behavioural effects.

Driving and skilled tasks
Drowsiness may affect performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including nabilone, see Drugs and driving under Guidance on prescribing p. 1.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

Capsule

CAUTIONARY AND ADVISORY LABELS
2

Nabilone (Non-proprietary)
Nabilone 250 microgram Nabilone 250 microgram capsules 20 capsule £150.00 DT = £150.00 CD

Nabilone 1 mg Nabilone 1 mg capsules 20 capsule £196.00 DT = £196.00 CD

DOMPERIDONE

10-Mar-2017

INDICATIONS AND DOSE
Relief of nausea and vomiting

BY MOUTH
• Child (body-weight up to 35 kg): 250 micrograms/kg up to 3 times a day; maximum 750 micrograms/kg per day
• Child 12-17 years (body-weight 35 kg and above): 10 mg up to 3 times a day; maximum 30 mg per day continued →
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Nervous system

HEPATIC IMPAIRMENT

BREAST FEEDING

▶ Uncommon

▶ Common or very common

SIDE-EFFECTS

CAUTIONS

CONTRA-INDICATIONS

INTERACTIONS

SIDE-EFFECTS

▶ Common or very common

Dry mouth

Uncommon

Anxiety - asthenia

breast abnormalities

diarrhoea - drowsiness - headache

lactation disorders - libido loss

Frequency not known

Arrhythmias - depression

gynaecomastia - menstrual cycle irregularities - movement disorders - oculogyric crisis - QT interval prolongation - seizure - sudden cardiac death - urinary retention

PREGNANCY

Use only if potential benefit outweighs risk.

BREAST FEEDING

Amount too small to be harmful.

HEPATIC IMPAIRMENT

Manufacturer advises avoid in moderate to severe impairment.

RENAL IMPAIRMENT

Dose adjustments

Reduce frequency.

PRESCRIBING AND DISPENSING INFORMATION

Palliative care

For further information on the use of domperidone in palliative care, see www.medicinescomplete.com/#/content/palliative/domperidone.

PATIENT AND CARER ADVICE

Arrhythmia

Patients and their carers should be told how to recognise signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncope develop.

Medicines for Children leaflet: Domperidone for gastro-oesophageal reflux www.medicinesforchildren.org.uk/domperidone-gastro-oesophageal-reflux

MEdICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Oral suspension

CAUTIONARY AND ADVISORY LABELS 22

Domperidone (Non-proprietary)

Domperidone 1 mg per 1 ml (20 ml) [P] £0.94 | 100 ml [P] £3.94 £0.04 DT = £3.13

Domperidone (as Domperidone maleate) 10 mg

Domperidone 10 mg tablets | 30 tablet [P] £2.71 DT = £0.94 | 100 tablet [P] £9.04 DT = £3.13

MOTILUM

(Motilium Zentiva)

Domperidone (as Domperidone maleate) 10 mg

Motilium 10 mg tablets | 30 tablet [P] £2.71 DT = £0.94 | 100 tablet [P] £9.04 DT = £3.13

Metoclopramide hydrochloride

INDICATIONS AND DOSE

Symptomatic treatment of nausea and vomiting including that associated with acute migraine | Delayed (but not acute) chemotherapy-induced nausea and vomiting | Radiotherapy-induced nausea and vomiting | Prevention of postoperative nausea and vomiting

BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION

Adult (body-weight up to 60 kg): Up to 500 micrograms/kg daily in 3 divided doses, when administered by slow intravenous injection, to be given over at least 3 minutes

Adult (body-weight 60 kg and above): 10 mg up to 3 times a day, when administered by slow intravenous injection, to be given over at least 3 minutes

Hiccups in palliative care

BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION

Adult: 10 mg every 6–8 hours

Nausea and vomiting in palliative care

BY MOUTH

Adult: 10 mg 3 times a day

BY SUBCUTANEOUS INFUSION

Adult: 30–100 mg/24 hours

Acute migraine

BY MOUTH, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

Adult: 10 mg for 1 dose, to be administered as soon as migraine symptoms develop; intravenous injection to be given over at least 3 minutes

www.getintopharma.com
Nausea and labyrinth disorders

Metoclopramide is used for the treatment of acute migraine, but is not licensed for this indication.

### IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE—METOCLOPRAMIDE: RISK OF NEUROLOGICAL ADVERSE EFFECTS—RESTRICTED DOSE AND DURATION OF USE (AUGUST 2013)

The benefits and risks of metoclopramide have been reviewed by the European Medicines Agency’s Committee on Medicinal Products for Human Use, which concluded that the risk of neurological effects such as extrapyramidal disorders and tardive dyskinesia outweigh the benefits in long-term or high-dose treatment. To help minimise the risk of potentially serious neurological adverse effects, the following restrictions to indications, dose, and duration of use have been made:

- **In adults over 18 years,** metoclopramide should only be used for prevention of postoperative nausea and vomiting, radiotherapy-induced nausea and vomiting, delayed (but not acute) chemotherapy-induced nausea and vomiting, and symptomatological treatment of nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics);
- **Metoclopramide should only be prescribed for short-term use (up to 5 days);**
- **Usual dose is 10 mg,** repeated up to 3 times daily; max. daily dose is 500 micrograms/kg;
- **Intravenous doses should be administered as a slow bolus over at least 3 minutes;**
- **Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy.**

This advice does not apply to unlicensed uses of metoclopramide (e.g. palliative care).

### CONTRA-INDICATIONS

- **3–4 days after gastrointestinal surgery,** gastro-intestinal haemorrhage, gastro-intestinal obstruction, gastro-intestinal perforation, phaeochromocytoma
- **Asthma,** atopic allergy, bradycardia, cardiac conduction disturbances, children, elderly, epilepsy, may mask underlying disorders such as cerebral irritation, Parkinson’s disease, uncorrected electrolyte imbalance—young adults (15–19 years old)

### INTERACTIONS

- Appendix 1: metoclopramide

### SIDE-EFFECTS

- **GENERAL SIDE-EFFECTS**
  - **Common or very common** Asthenia, depression, diarrhoea, drowsiness, hypotension, menstrual cycle irregularities, movement disorders, parkinsonism
  - **Uncommon** Arrhythmias, hallucination, hyperprolactinaemia, level of consciousness decreased
  - **Rare or very rare** Confusion, galactorrhoea, seizure, frequency not known, atrioventricular block, blood disorders, cardiac arrest, gynaecomastia, hypertension, neuroleptic malignant syndrome, QT interval prolongation, shock, syncope, tremor

### SPECIFIC SIDE-EFFECTS

- With parenteral use: anxiety, dizziness, dysphoria, oedema, skin reactions, visual impairment

**SIDE-EFFECTS**, **FURTHER INFORMATION**

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Small amount present in milk; avoid.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (risk of accumulation).

### Dose adjustments

- **Manufacturer advises dose reduction of 50% in severe impairment.**
- **RENAI IMPAIRMENT**
  - **Dose adjustments** Avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions.

### DIRECTIONS FOR ADMINISTRATION

Oral liquid preparation to be given via a graduated oral dosing syringe.

**PRESCRIBING AND DISPENSING INFORMATION**

**Palliative care** For further information on the use of metoclopramide hydrochloride in palliative care, see www.medicinescomplete.com/#/content/palliative/metoclopramide.

**PATIENT AND CARER ADVICE** Counselling on use of pipette advised with oral solution.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Solution for injection**

- **Metoclopramide hydrochloride (Non-proprietary)**
  - Metoclopramide hydrochloride 5 mg per 1 ml Metoclopramide 10mg/2ml solution for injection ampoules | 3 ampoule [£1.31-£15.00] 10 ampoule [£25.00 DT + £2.65]
  - **Maxolon** (Advanz Pharma)
    - Metoclopramide hydrochloride 5 mg per 1 ml Maxolon 10mg/2ml solution for injection ampoules | 12 ampoule [£21]
    - Maxolon High Dose 100mg/20ml solution for injection ampoules | 10 ampoule [£26.68]

**Oral solution**

- **Metoclopramide hydrochloride (Non-proprietary)**
  - Metoclopramide hydrochloride 1 mg per 1 ml Metoclopramide 5mg/5ml oral solution sugar free sugar-free | 150 ml [£19.77 DT + £19.77]

**Tablet**

- **Metoclopramide hydrochloride (Non-proprietary)**
  - Metoclopramide hydrochloride 10 mg Metoclopramide 10mg tablets | 28 tablet [£1.40 DT + £0.61]
  - **Maxolon** (Advanz Pharma)
    - Metoclopramide hydrochloride 10 mg Maxolon 10mg tablets | 84 tablet [£5.24]

**Combinations available:** Paracetamol with metoclopramide, p. 476

### ANTIEMETICS AND ANTINAUSEANTS

#### NEUROKININ RECEPTOR ANTAGONISTS

**Aprepitant**

**INDICATIONS AND DOSE**

Adjunct treatment to prevent nausea and vomiting associated with moderately and highly emetogenic chemotherapy

- **BY MOUTH**
  - Adult: Initially 125 mg, dose to be taken 1 hour before chemotherapy, then 80 mg once daily for 2 days, consult product literature for dose of concomitant dexamethasone and 5HT3-antagonist

**CONTRA-INDICATIONS**

Acute porphyrias p. 1058

**INTERACTIONS**

- Appendix 1: aprepitant

**SIDE-EFFECTS**

- **Common or very common** Appetite decreased, asthenia, constipation, gastrointestinal discomfort, headache, hiccup

- **Uncommon** Anaemia, anxiety, burping, dizziness, drowsiness, dry mouth, febrile neutropenia.
Nervous system

Rare or very rare

Uncommon

Common or very common

CONTRA-INDICATIONS

DRUG ACTION

Fosaprepitant

29-Aug-2018

INDICATIONS AND DOSE

Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

BY INTRAVENOUS INFUSION

Adult: 150 mg, dose to be administered over 20–30 minutes and given 30 minutes before chemotherapy on day 1 of cycle only, consult product literature for dose of concomitant corticosteroid and 5HT3-receptor antagonist

CONTRA-INDICATIONS

Acute porphyrias p. 1058

INTERACTIONS

Appendix J: fosaprepitant

SIDE-EFFECTS

Common or very common

Appetite decreased - asthena - constipation - gastrointestinal discomfort - headache - hiccups

Uncommon


Rare or very rare

Bradycardia - cardiovascular disorder - chest discomfort - cognitive disorder - conjunctivitis - cough - disorientation - euphoric mood - gait abnormal - hyperhidrosis - increased risk of infection - muscle spasms - muscle weakness - oedema - oropharyngeal pain - photosensitivity reaction - polydipsia - seborrhoea - severe cutaneous adverse reactions (SCARs) - sneezing - stomatitis - taste altered - throat irritation - tinnitus - weight decreased

Fosaprepitant is a prodrug of aprepitant.

Rolapitant

26-Oct-2017

INDICATIONS AND DOSE

Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing delayed nausea and vomiting associated with moderately and highly emetogenic chemotherapy

BY MOUTH

Adult: 180 mg as a single dose, dose should be administered up to 2 hours before chemotherapy. Interval between repeated doses must be at least 2 weeks, consult product literature for dose of concomitant corticosteroid and 5HT3-receptor antagonist

INTERACTIONS

Appendix J: rolapitant

SIDE-EFFECTS

Common or very common

Asthena - constipation - headache

Uncommon

Appetite decreased - concentration impaired - diarrhoea - dizziness - drowsiness - gastrointestinal discomfort - hiccups - increased risk of infection - insomnia - myalgia - nausea - neutropenia - stomatitis - taste altered

Rare or very rare


PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—limited information available.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

Manufacturer advises caution in concomitant treatment with an antiarrhythmic drug.

For intravenous infusion (Ivemend®), manufacturer advises give intermittently in Sodium chloride 0.9%; reconstitute each 150 mg vial with 5 mL sodium chloride 0.9% gently without shaking to avoid foaming, then dilute in 145 mL infusion fluid; give over 20–30 minutes.

The Scottish Medicines Consortium (SMC) decisions

SCMC No. 678/11

Scottish Medicines Consortium has advised (March 2011) that fosaprepitant (Ivemend®) is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy in adults.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Capsule

- Emend (Merck Sharp & Dohme Ltd)
  - Aprepitant 80 mg
  - Aprepitant 125 mg

Powder for solution for infusion

- Ivemend (Merck Sharp & Dohme Ltd)
  - Fosaprepitant (as Fosaprepitant dimeglumine) 150 mg

BY MOUTH

Aprepitant 125 mg (Merck Sharp & Dohme Ltd)

- Rolapitant 150 mg powder for solution for infusion vials 1 vial

Manufacturer advises caution in concomitant treatment with an antiarrhythmic drug.

Manufacturer advises avoid unless potential benefit outweighs risk—limited information available.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

Manufacturer advises avoid unless potential benefit outweighs risk—limited information available.

BREAST FEEDING

Avoid—present in milk in animal studies.

Manufacturer advises caution in concomitant treatment with an antiarrhythmic drug.

Manufacturer advises avoid—present in milk in animal studies.

Manufacturer advises caution in concomitant treatment with an antiarrhythmic drug.
Granisetron

**DRUG ACTION**
Granisetron is a specific SHT3-receptor antagonist which blocks SHT3 receptors in the gastrointestinal tract and in the CNS.

**INDICATIONS AND DOSE**
Nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used

- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: 1 mg, to be administered before induction of anaesthesia, dose to be diluted to 5 mL and given over 30 seconds

Treatment of postoperative nausea and vomiting

- BY INTRAVENOUS INJECTION
  - Adult: 1 mg, dose to be diluted to 5 mL and given over 30 seconds; maximum 3 mg per day

Management of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy

- BY MOUTH
  - Adult: 1–2 mg, to be taken within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses for up to 1 week following treatment, when intravenous route also used, maximum combined total dose 9 mg in 24 hours

- BY INTRAVENOUS INJECTION
  - Adult: 10–40 micrograms/kg (max. per dose 3 mg), to be given 5 minutes before start of treatment, dose may be repeated if necessary, further maintenance doses must not be given less than 10 minutes apart, for intravenous injection, each 1 mg granisetron diluted to 5 mL and given over not less than 30 seconds, for intravenous infusion, to be given over 5 minutes; maximum 9 mg per day

**CAUTIONS**
- Subacute intestinal obstruction - susceptibility to QT-interval prolongation (including electrolyte disturbances)
- Interactions
  - With intravenous use or oral use Diarrhoea - insomnia
  - With intravenous use or oral use Extrapyramidal symptoms - QT interval prolongation - serotonin syndrome
  - With transdermal use Appetite decreased - arthralgia - dry mouth - flushing - generalised oedema - vertigo
  - Rare or very rare
    - With transdermal use Dystonia
  - Pregnancy
    - Avoid - no information available.
  - Hepatic impairment
    - Manufacturer advises caution.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous infusion, give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute up to 3 mL in 20–50 mL infusion fluid; give over 5 minutes.

**PATIENT AND CARER ADVICE**
- With transdermal use Patients should be advised not to expose the site of the patch to sunlight during use and for 10 days after removal.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS: 3
- EXCIPIENTS: May contain Polysorbates
  - Varuby (Tosaro UK Ltd)
  - Rolapitant (as Rolapitant hydrochloride monohydrate)
  - 90 mg Varuby 90mg tablets | 2 tablet [PSt] £47.42

**ANTIEMETICS AND ANTINAUSEANTS**

**SEROTONIN (5HT3) RECEPTOR ANTAGONISTS**

**Granisetron**

**BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- Adult: 10–40 micrograms/kg (max. per dose 3 mg), to be given 5 minutes before start of treatment, dose may be repeated if necessary, further maintenance doses must not be given less than 10 minutes apart, for intravenous injection, each 1 mg granisetron diluted to 5 mL and given over not less than 30 seconds, for intravenous infusion, to be given over 5 minutes; maximum 9 mg per day

- **CAUSATIONS**
  - Subacute intestinal obstruction - susceptibility to QT-interval prolongation (including electrolyte disturbances)
  - **INTERACTIONS**
    - Appendix 1: granisetron
  - **SIDE-EFFECTS**
    - **GENERAL SIDE-EFFECTS**
      - Constipation - headache
  - **SPECIFIC SIDE-EFFECTS**
    - Constipation - headache
  - **DIRECTIONS FOR ADMINISTRATION**
    - With intravenous use For intravenous infusion, give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute up to 3 mL in 20–50 mL infusion fluid; give over 5 minutes.
  - **PATIENT AND CARER ADVICE**
    - With transdermal use Patients should be advised not to expose the site of the patch to sunlight during use and for 10 days after removal.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Granisetron (Non-proprietary)
  - Granisetron (as Granisetron hydrochloride) 1 mg per 1 mL Granisetron 3mg/3ml concentrate for solution for injection ampoules | 5 ampoule [PSt] £24.00–£30.00 | 10 ampoule [PSt] £48.00
  - Granisetron 1mg/1ml concentrate for solution for injection ampoules | 5 ampoule [PSt] £18.00–£10.00 | 10 ampoule [PSt] £36.00

**Tablet**

- Granisetron (Non-proprietary)
  - Granisetron (as Granisetron hydrochloride) 1 mg Granisetron 1mg tablets | 10 tablet [PSt] £51.20 DT = £40.79
  - Granisetron (as Granisetron hydrochloride) 2 mg Granisetron 2mg tablets | 5 tablet [PSt] £52.39
  - Kytril (Atnahs Pharma UK Ltd)
    - Granisetron (as Granisetron hydrochloride) 1 mg Kytril 1mg tablet | 10 tablet [PSt] £52.39 DT = £40.79
    - Kytril (as Granisetron hydrochloride) 2 mg Kytril 2mg tablets | 5 tablet [PSt] £52.39 DT = £52.39

**Transdermal patch**
- Sancuso (Kyowa Kirin Ltd)
  - Granisetron 3.1 mg per 24 hour Sancuso 3.1mg/24hours transdermal patches | 1 patch [PSt] £56.00 DT = £56.00

www.getintopharma.com
**DRUG ACTION** Ondansetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

**INDICATIONS AND DOSE**

**Moderately emetogenic chemotherapy or radiotherapy**
- **BY MOUTH**
  - Adult: Initially 8 mg, dose to be taken 1–2 hours before treatment, then 8 mg every 12 hours for up to 5 days
  - **BY RECTUM**
  - Adult: Initially 16 mg, dose to be taken 1–2 hours before treatment, then 16 mg daily for up to 5 days
  - **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 8 mg, dose to be administered immediately before treatment, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days
  - **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**
  - Elderly: Initially 8 mg, dose to be administered immediately before treatment, intravenous infusion to be given over at least 15 minutes, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**Severely emetogenic chemotherapy (consult product literature for dose of concomitant corticosteroid)**
- **BY MOUTH**
  - Adult: 24 mg, dose to be taken 1–2 hours before treatment, then 8 mg every 12 hours for up to 5 days
  - **BY RECTUM**
  - Adult: 16 mg, dose to be administered 1–2 hours before treatment, then 16 mg daily for up to 5 days
  - **INITIALLY BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 8 mg, dose to be administered immediately before treatment, followed by (by intramuscular injection or by slow intravenous injection) 8 mg every 4 hours if required for 2 doses, alternatively, followed by (by continuous intravenous infusion) 1 mg/hour for up to 24 hours, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days
  - **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: Initially 16 mg, immediately before treatment (over at least 15 minutes), followed by (by intramuscular injection or by slow intravenous injection) 8 mg every 4 hours if required for 2 doses, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days
  - Adult 65–74 years: Initially 8 mg, to be given immediately before treatment, followed by (by intramuscular injection) 8 mg every 4 hours if required for 2 doses, alternatively, followed by (by continuous intravenous infusion) 1 mg/hour for up to 24 hours, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

**Prevention of postoperative nausea and vomiting**
- **INITIALLY BY MOUTH**
- Adult: 16 mg, dose to be taken 1 hour before anaesthesia, alternatively (by intramuscular injection or by slow intravenous injection) 4 mg, dose to be administered at induction of anaesthesia

**TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING**
- **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
- Adult: 4 mg for 1 dose

**CONTRA-INDICATIONS** Congenital long QT syndrome

**CAUTIONS**
- Adenontsillar surgery, subacute intestinal obstruction, susceptibility to QT-interval prolongation (including electrolyte disturbances)

**INTERACTIONS**
- Appendix 1: ondansetron

**SIDE-EFFECTS**
- **Common or very common** Constipation, feeling hot, headache, sensation abnormal
- **Uncommon** Arrhythmias, chest pain, hiccup, hypotension, movement disorders, oculogyric crisis, seizure
- **Rare or very rare** Dizziness, QT interval prolongation, vision disorders

**PREGNANCY** No information available; avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Present in milk in animal studies—avoid

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment (decreased clearance). Dose adjustments Manufacturer advises maximum 8 mg daily in moderate to severe impairment.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous infusion (Zofran®), give continuously or intermittently in Glucose 5% or Glucose 5% with Potassium chloride 0.3% or Sodium chloride 0.9% or Sodium chloride 0.9% with Potassium chloride 0.3% or Mannitol 10% or Ringers solution; for intermittent infusion, dilute the required dose in 50–100 mL of infusion fluid and give over at least 15 minutes.
- With oral use Orodispersible films and lyophilisates should be placed on the tongue, allowed to disperse and swallowed.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include strawberry.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer orodispersible films and lyophilisates.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- **Ondansetron (Non-proprietary)**
  - **Ondansetron (as Ondansetron hydrochloride) 4 mg** Ondansetron 4mg tablets | 10 tablet (£0.81–£25.46 DT = £9.94) | 30 tablet (£3.15–£76.38)
  - **Ondansetron (as Ondansetron hydrochloride) 8 mg** Ondansetron 8mg tablets | 10 tablet (£4.79–£10.31)
- **Ondemet (Alliance Pharmaceuticals Ltd)**
  - **Ondansetron (as Ondansetron hydrochloride) 8 mg** Ondemet 8mg tablets | 10 tablet (£3.54–£10.31) (Hospital only)
- **Zofran (Novartis Pharmaceuticals UK Ltd)**
  - **Ondansetron (as Ondansetron hydrochloride) 4 mg** Zofran 4mg tablets | 30 tablet (£0.91–£10.75)
  - **Ondansetron (as Ondansetron hydrochloride) 8 mg** Zofran 8mg tablets | 10 tablet (£1.94–£10.31)

**Suppository**
- **Zofran (Novartis Pharmaceuticals UK Ltd)**
  - **Ondansetron 16 mg** Zofran 16mg suppositories | 1 suppository (£4.39)

Nervous System
Nausea and labyrinth disorders

Solution for injection

- Ondansetron (Non-proprietary)
  - Ondansetron (as Ondansetron hydrochloride) 2 mg per 1 ml Ondansetron 8mg/4ml solution for injection ampoules
  - 5 ampoule (Po) £11.80–£18.45 DT = £93.95
  - Ondansetron 4mg/2ml solution for injection ampoules
  - 5 ampoule (Po) £5.00–£29.97 DT = £22.97
  - 10 ampoule (Po) £15.00

- Zofer Flexi-amp (Novartis Pharmaceuticals UK Ltd)
  - Ondansetron (as Ondansetron hydrochloride) 2 mg per 1 ml Zofer Flexi-amp 8mg/4ml solution for injection
  - 5 ampoule (Po) £9.35 DT = £93.95
  - Zofer Flexi-amp 4mg/2ml solution for injection
  - 5 ampoule (Po) £29.97 DT = £22.97

Oral solution

- Ondansetron (Non-proprietary)
  - Ondansetron (as Ondansetron hydrochloride) 800 microgram
  - 1 ml Ondansetron 4mg/5ml oral solution sugar-free sugar-free
  - 50 ml (Po) £38.11 DT = £38.10

- Zofer (Novartis Pharmaceuticals UK Ltd)
  - Ondansetron (as Ondansetron hydrochloride) 800 microgram
  - 1 ml Zofer 4mg/5ml syrup sugar-free
  - 50 ml (Po) £35.97 DT = £38.10

Orodispersible film

- Setofilm (Norgine Pharmaceuticals Ltd)
  - Ondansetron 4 mg Setofilm 4mg orodispersible films sugar-free
  - 10 film (Po) £28.50 DT = £28.50

- Ondansetron 8 mg Setofilm 8mg orodispersible films sugar-free
  - 10 film (Po) £57.00 DT = £57.00

Oral lyophilisate

- EXCIPENTS: May contain Aspartame

- Zofer Melt (Novartis Pharmaceuticals UK Ltd)
  - Ondansetron 4 mg Zofer Melt 4mg oral lyophilisates sugar-free
  - 10 tablet (Po) £35.97 DT = £35.97

- Ondansetron 8 mg Zofer Melt 8mg oral lyophilisates sugar-free
  - 10 tablet (Po) £71.94 DT = £71.94

Orodispersible tablet

- Ondansetron (Non-proprietary)
  - Ondansetron 4 mg Ondansetron 4mg orodispersible tablets
  - 10 tablet (Po) £43.46 DT = £43.46

- Ondansetron 8 mg Ondansetron 8mg orodispersible tablets
  - 10 tablet (Po) £85.43 DT = £85.43

Palonosetron

- **DRUG ACTION** Palonosetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

- **INDICATIONS AND DOSE**
  - **Moderately emetogenic chemotherapy**
    - **INITIALLY BY MOUTH**
    - Adult: 500 micrograms, dose to be taken 1 hour before treatment, alternatively (by intravenous injection) 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment
  - **Severely emetogenic chemotherapy**
    - **BY INTRAVENOUS INJECTION**
    - Adult: 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment

- **CAUTIONS** History of constipation - intestinal obstruction - susceptibility to QT-interval prolongation (including electrolyte disturbances)

- **INTERACTIONS**
  - Appendix 1: palonosetron

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common Constipation - headache
  - **SPECIFIC SIDE-EFFECTS**
    - With intravenous use Diarrhoea - dizziness - electrolyte imbalance - metabolic disorder

- **INDICATIONS AND DOSE**
  - **Moderately emetogenic chemotherapy**
  - **Highly emetogenic cisplatin-based chemotherapy**
    - **BY MOUTH**
      - Adult: 1 capsule, to be taken approximately 1 hour before the start of each chemotherapy cycle

- **CAUTIONS**
  - Patients over 75 years

- **INTERACTIONS**
  - Appendix 1: netupitant - palonosetron

- **SIDE-EFFECTS**
  - Common or very common Asthenia - constipation - headache

- **UNCOMMON**
  - Alopecia - cardiac conduction disorders - cardiomyopathy - diarrhoea - dizziness - flatulence - gastrointestinal discomfort - hiccups - hypertension - increased leucocytes - neutropenia - QT interval prolongation - sleep disorders - urticaria - vertigo

- **RARE or very rare**
  - Acute psychosis - arrhythmias - conjunctivitis - cystitis - dizziness - euphoria - feeling hot - hypokalaemia - hypertension - leucopenia - mirtal valve incompetence - mood altered - myocardial ischaemia - numbness - pain - tongue coated - vision blurred

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer recommends exclude pregnancy before treatment in females of childbearing age; ensure effective contraception during treatment and for one month after treatment.

Palonosetron with netupitant

The properties listed below are those particular to the different medicines containing the same drug.

- **NETUPITANT**
  - **Palonosetron (Non-proprietary)**
    - Palonosetron (as Palonosetron hydrochloride) 50 microgram per 1 ml Palonosetron 250micrograms/5ml solution for injection vials
      - 1 vial (Po) £53.10–£55.89
      - 10 vial (Po) £561.10
    - Palonosetron (as Palonosetron hydrochloride) 50 microgram per 1 ml Palonosetron 250micrograms/5ml solution for injection vials
      - 1 vial (Po) £55.89
    - **Capsule**
      - Palonosetron (as Palonosetron hydrochloride) 500 microgram
        - 1 capsule (Po) £55.89

www.getintopharma.com
**Antihistamines**

**Cinnarizine**

- **Indications and dose**
  - Relief of symptoms of vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière’s disease
  - **By mouth**
    - Child 5–11 years: 15 mg 3 times a day
    - Child 12–17 years: 30 mg 3 times a day
    - Adult: 30 mg 3 times a day

- **Motion sickness**
  - **By mouth**
    - Child 5–11 years: Initially 15 mg, dose to be taken 2 hours before travel, then 7.5 mg every 8 hours if required, dose to be taken during journey
    - Child 12–17 years: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey
    - Adult: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey

- **Contra-indications**
  - Avoid in Acute porphyrias p. 1058

- **Cautions**
  - Epilepsy, glaucoma (in children), Parkinson’s disease (in adults), prostatic hypertrophy (in adults), pyloroduodenal obstruction, susceptibility to angle-closure glaucoma (in adults), urinary retention

- **Interactions**
  - Appendix 1: antihistamines, sedating

- **Side-effects**
  - Common or very common: Drowsiness, gastrointestinal discomfort, nausea, weight increased

- **Frequency not known**
  - Dry mouth, gastrointestinal disorder, headache, jaundice cholestatic, movement disorders, muscle rigidity, parkinsonism, skin reactions, subacute cutaneous lupus erythematosus, tremor

- **Pregnancy**
  - Manufacturer advises avoid; however, there is no evidence of teratogenicity. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

- **Breast feeding**
  - Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**Promethazine teoclate**

- **Indications and dose**
  - Nausea or vomiting, Labyrinthine disorders
  - **By mouth**
    - Child 5–9 years: 12.5–37.5 mg daily
    - Child 10–17 years: 25–75 mg daily; maximum 100 mg per day
    - Adult: 25–75 mg daily; maximum 100 mg per day

  - **Motion sickness prevention (acts longer than promethazine hydrochloride)**
    - **By mouth**
      - Child 5–9 years: 12.5 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel
      - Child 10–17 years: 25 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel
      - Adult: 25 mg once daily, dose to be taken at bedtime on night before travel or 1–2 hours before travel

  - **Motion sickness treatment (acts longer than promethazine hydrochloride)**
    - **By mouth**
      - Child 5–9 years: 12.5 mg, dose to be taken at onset of motion sickness, then 12.5 mg daily for 2 days, dose to be taken at bedtime
PATIENT AND CARER ADVICE

RENAL IMPAIRMENT

Child 10-17 years: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime

Adult: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009) OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN

Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

CAUTIONS

Asthma • bronchiectasis • bronchitis • epilepsy • prostatic hypertrophy (in adults) • pyloroduodenal obstruction • Reye’s syndrome • severe coronary artery disease • susceptibility to angle-closure glaucoma • urinary retention

INTERACTIONS → Appendix 1: antihistamines, sedating

SIDE-EFFECTS

Anticholinergic syndrome • anxiety • appetite decreased • arrhythmia • blood disorder • bronchial secretion viscosity increased • confusion • dizziness • drowsiness • dry mouth • epigastric discomfort • fatigue • haemolytic anaemia • headache • hypotension • jaundice • movement disorders • muscle spasms • nightmare • palpitations • photosensitivity reaction • urinary retention • vision blurred

SIDE-EFFECTS, FURTHER INFORMATION

Elderly patients are more susceptible to anticholinergic side-effects. In children paradoxical stimulation may occur, especially with high doses.

PREGNANCY

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitation, and tremor.

BREAST FEEDING

Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

RENAL IMPAIRMENT

Use with caution.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2

Avonite (Manx Healthcare Ltd)

Promethazine teoclacte 25 mg Avonite 25mg tablets 10 tablet £1.13 | 28 tablet £3.13 DT = £3.13

Veritolin (Manx Healthcare Ltd)

Promethazine teoclacte 25 mg Veritogen 25mg tablets 28 tablet £3.13 DT = £3.13

ANTIMUSCARINICS

Hyoscine hydrobromide

(Scopolamine hydrobromide)

INDICATIONS AND DOSE

Motion sickness

→ BY MOUTH

Child 4-9 years: 75–150 micrograms, dose to be taken up to 30 minutes before the start of journey, then

75–150 micrograms every 6 hours if required; maximum 450 micrograms per day

Child 10-17 years: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day

Adult: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day

BY TRANSDERMAL APPLICATION

Child 10-17 years: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear

Adult: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear

Hypersalivation associated with clozapine therapy

→ BY MOUTH

Adult: 300 micrograms up to 3 times a day; maximum 900 micrograms per day

Excessive respiratory secretion in palliative care

→ BY SUBCUTANEOUS INJECTION

Adult: 400 micrograms every 4 hours as required, hourly use is occasionally necessary, particularly in excessive respiratory secretions

→ BY CONTINUOUS SUBCUTANEOUS INFUSION

Adult: 1.2–2 mg/24 hours

Bowel colic in palliative care

→ BY MOUTH USING SUBLINGUAL TABLETS

Adult: 300 micrograms 3 times a day, as Kwells®

Premedication

→ BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

Adult: 200–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia

UNLICENSED USE

Not licensed for hypersalivation associated with clozapine therapy.

IMPORTANT SAFETY INFORMATION

Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

CAUTIONS

Epilepsy

CAUTIONS, FURTHER INFORMATION

Anticholinergic syndrome

In adults In some patients, especially the elderly, hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

In children In some children hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

INTERACTIONS → Appendix 1: hyoscine

SIDE-EFFECTS

→ Common or very common

With transdermal use Eye disorders • eyelid irritation

www.getintopharma.com
Nervous system

PATIENT AND CARER ADVICE

PRESCRIBING AND DISPENSING INFORMATION

With transdermal use in children

HEPATIC IMPAIRMENT

BREAST FEEDING

PREGNANCY

With transdermal use

Use with caution.

Use only if potential bene

DRUG ACTION

Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

INDICATIONS AND DOSE

Prevention and treatment of postoperative nausea and vomiting

BY INTRAVENOUS INJECTION

Adult: 0.625–1.25 mg, dose to be given 30 minutes before end of surgery, then 0.625–1.25 mg every 6 hours as required

Elderly: 625 micrograms, dose to be given 30 minutes before end of surgery, then 625 micrograms every 6 hours as required

Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia (PCA)

BY INTRAVENOUS INJECTION

Adult: 15–50 micrograms of droperidol for every 1 mg of morphine in PCA, reduce dose in elderly; maximum 5 mg per day

CONTRA-INDICATIONS

Bradycardia · CNS depression · comatose states · hypokalaemia · hypomagnesaemia · phaeochromocytoma · QT-interval prolongation

CAUTIONS

Chronic obstructive pulmonary disease · electrolyte disturbances · history of alcohol abuse · respiratory failure

INTERACTIONS

Appendix 1: droperidol

SIDE-EFFECTS

Uncommon Anxiety · oculogyration

Rare or very rare Blood disorder · cardiac arrest · confusion · dysphoria

Frequency not known Coma · epilepsy · hallucination · oligomenorhoea · respiratory disorders · SIADH · syncpe

BREAST FEEDING

Limited information available—avoid repeated administration.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

Dose adjustments

When used for Prevention and treatment of postoperative nausea and vomiting Manufacturer advises maximum 625 micrograms repeated every 6 hours as required.

When used for Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia Manufacturer advises dose reduction (no information available).

RENAL IMPAIRMENT

Dose adjustments

In postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required.

For nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose.

MONITORING REQUIREMENTS

Continuous pulse oximetry required if risk of ventricular arrhythmia—continue for 30 minutes following administration.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2

Kwells (Bayer Plc)

Hyoscine hydrobromide 150 microgram Kwells Kids 150microgram tablets | 12 tablet [P] £1.84 DT = £1.84

Hyoscine hydrobromide 300 microgram Kwells 300microgram tablets | 12 tablet [P] £1.84 DT = £1.84

Travel Calm (The Boots Company Plc)

Hyoscine hydrobromide 300 microgram Travel Calm 300microgram tablets | 12 tablet [P] £1.84 DT = £1.84

Solution for injection

Hyoscine hydrobromide (Non-proprietary)

Hyoscine hydrobromide 400 microgram per 1 ml Hyoscine hydrobromide 400micrograms/1ml solution for injection ampoules | 10 ampoule [P] £25.00–£47.21 DT = £47.21

Hyoscine hydrobromide 600 microgram per 1 ml Hyoscine hydrobromide 600micrograms/1ml solution for injection ampoules | 10 ampoule [P] £55.93 DT = £55.93

Transdermal patch

CAUTIONARY AND ADVISORY LABELS 19

Scopoderm (GlaxoSmithKline Consumer Healthcare)

Hyoscine 1 mg per 72 hour Scopoderm 1.5mg patches | 2 patch [P] £12.87 DT = £12.87

Chewable tablet

CAUTIONARY AND ADVISORY LABELS 2, 24

Joy-Rides (Teva UK Ltd)

Hyoscine hydrobromide 150 microgram Joy-rides 150microgram chewable tablets sugar-free | 12 tablet [P] £1.55 DT = £1.55

ANTIPSYCHOTICS

FIRST-GENERATION

Droperidol

BNF 78
**Levomepromazine**

*(Methotrimeprazine)*

- **INDICATIONS AND DOSE**
  - Pain in palliative care (reserved for distressed patients with severe pain unresponsive to other measures)
  - Restlessness and confusion in palliative care
  - Nausea and vomiting in palliative care

- **CAUTIONS**
  - Restlessness and confusion in palliative care
  - Gastrointestinal discomfort

- **CONTRA-INDICATIONS**
  - CNS depression
  - Comatose states
  - Phaeochromocytoma

- **SIDE-EFFECTS**
  - Common or very common: Asthenia, heat stroke
  - Rare or very rare: Cardiac arrest, hepatic disorders

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises consider avoiding.

- **RENAL IMPAIRMENT**
  - Dose adjustments: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

- **DIRECTIONS FOR ADMINISTRATION**
  - With subcutaneous use in children: For administration by subcutaneous injection; dilute with a suitable volume of Sodium Chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Prolonged use: For further information on the use of levomepromazine in palliative care, see www.medicinescomplete.com/#!/content/palliative/levomepromazine.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution.

- **Solution for injection**
  - Levomepromazine maleate 25 mg
  - 1 ml levomepromazine 25 mg/ml solution for injection ampoules

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Levomepromazine hydrochloride 25 mg per 1 ml
  - 10 ampoules

- **Solution for injection**
  - Levomepromazine maleate 25 mg
  - 84 tablet

- **Solution for injection**
  - Levomepromazine maleate 25 mg
  - 84 tablet

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**5.1 Ménière’s disease**

**HISTAMINE ANALOGUES**

- **Betahistine dihydrochloride**
  - **INDICATIONS AND DOSE**
    - Vertigo, tinnitus and hearing loss associated with Ménière’s disease
  - **CAUTIONS**
    - Phaeochromocytoma
  - **INTERACTIONS**
    - Appendix 1: betahistine
  - **SIDE-EFFECTS**
    - Common or very common: Gastrointestinal discomfort
  - **PREGNANCY**
    - Avoid unless clearly necessary—no information available.
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 21
  - Betahistine dihydrochloride (Non-proprietary)
    - Betahistine dihydrochloride 8 mg
    - 84 tablet

- **Tablet**
  - Betahistine dihydrochloride 16 mg
  - 84 tablet

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**BNF 78**

**www.getintopharma.com**
Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen or aspirin is usually continued for about 24 to 72 hours.

Temporomandibular dysfunction can be related to anxiety in some patients who may clench or grind their teeth (bruxism) during the day or night. The muscle spasm (which appears to be the main source of pain) may be treated empirically with an overlay appliance which provides a free sliding occlusion and may also interfere with grinding. In addition, diazepam p. 343, which has muscle relaxant as well as anxiolytic properties, may be helpful but it should only be prescribed on a short-term basis during the acute phase. Analgesics such as aspirin or ibuprofen may also be required.

**Nervous system**

Benzydamine hydrochloride mouthwash or spray p. 120 (and other NSAIDs), are particularly suitable for pain in mucosal conditions, whereas the opioid analgesics are more suitable for moderate to severe pain, particularly of visceral origin.

**Pain in sickle-cell disease**

The pain of mild sickle-cell crises is managed with paracetamol, a NSAID, codeine phosphate p. 454, or dihydrocodeine tartrate p. 456. Severe crises may require the use of morphine p. 463 or diamorphine hydrochloride p. 455; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used. Pethidine hydrochloride p. 470 should be avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine hydrochloride necessitates frequent injections.

**Dental and orofacial pain**

Analgesics should be used judiciously in dental care as a temporary measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpitis, apical infection, localised osteitis or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures, and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpitis, intra-osseous infection or abscesses, reliance on analgesics alone is usually inappropriate. Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by paracetamol or diclofenac sodium p. 1135, and aspirin.

Paracetamol has analgesic and antipyretic effects but no anti-inflammatory effect. Opioid analgesics such as dihydrocodeine tartrate act on the central nervous system and are traditionally used for moderate to severe pain. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant. Paracetamol, ibuprofen, or aspirin are adequate for most cases of dental pain and an opioid is rarely required.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

**Analgesics**

**Pain relief**

The non-opioid drugs, paracetamol p. 444 and aspirin p. 121 (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics are more suitable for moderate to severe pain, particularly of visceral origin.

Aspirin is indicated for headache, transient musculoskeletal pain, dysmenorrhoea, and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAID which may be better tolerated and more convenient for the patient. Aspirin is used increasingly for its antiplatelet properties. Aspirin tablets or dispersible aspirin tablets are adequate for most purposes as they act rapidly.

Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain). Aspirin interacts significantly with a number of other drugs and its interaction with warfarin sodium p. 140 is a special hazard.

Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly. Overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days.

Nefopam hydrochloride p. 446 may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics. It causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.

**Non-steroidal anti-inflammatory analgesics (NSAIDs)** are particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation. Some of them are also used in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred, particularly in the elderly. They are also suitable for the relief of pain in dysmenorrhoea and to treat pain caused by secondary bone tumours, many of which produce lysis of bone and release prostaglandins. Selective inhibitors of cyclo-oxgenase-2 may be used in preference to non-selective NSAIDs for patients at risk of developing serious gastro-intestinal side-effects. Several NSAIDs are also used for postoperative analgesia.
A non-opioid analgesic administered by intrathecal infusion (ziconotide (Prialt®), available from Eisai) is licensed for the treatment of chronic severe pain; ziconotide can be used by a hospital specialist as an adjunct to opioid analgesics.

**Compound analgesic preparations**

Compound analgesic preparations that contain a simple analgesic (such as aspirin or paracetamol p. 444) with an opioid component reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol or aspirin p. 121 with a low dose of an opioid analgesic (e.g. 8 mg of codeine phosphate p. 454 per compound tablet) are commonly used, but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of overdosage yet may not provide significant additional relief of pain.

A full dose of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations effectively augments the analgesic activity but is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration).

**Important:** the elderly are particularly susceptible to opioid side-effects and should receive lower doses.

In general, when assessing pain, it is necessary to weigh up carefully whether there is a need for a non-opioid and an opioid analgesic to be taken simultaneously.

**Caffeine** is a weak stimulant that is often included, in small doses, in analgesic preparations. It is claimed that the addition of caffeine may enhance the analgesic effect, but the alerting effect, mild habit-forming effect and possible provocation of headache may not always be desirable. Moreover, in excessive dosage or on withdrawal caffeine may itself induce headache.

**Co-proxamol** tablets (dextropropoxyphene in combination with paracetamol) are no longer licensed because of safety concerns, particularly toxicity in overdose. Co-proxamol tablets [unlicensed] may still be prescribed for patients who find it difficult to change, because alternatives are not effective or suitable.

**Opioid analgesics and dependence**

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the patient should be assessed at regular intervals.

**Strong opioids**

Morphine p. 463 remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of severe pain in palliative care. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations).

Buprenorphine p. 447 has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone hydrochloride p. 1369.

Dipipanone hydrochloride used alone is less sedating than morphine but the only preparation available contains an antiemetic and is therefore not suitable for regular regimens in palliative care.

**Diamorphine hydrochloride** p. 456 (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In *palliative care* the greater solubility of diamorphine hydrochloride allows effective doses to be injected in smaller volumes and this is important in the emaciated patient.

Alfentanil p. 1343, fentanyl p. 458 and remifentanil p. 1344 are used by injection for intra-operative analgesia; fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Methadone hydrochloride p. 502 is less sedating than morphine and acts for longer periods. In prolonged use, methadone hydrochloride should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone hydrochloride may be used instead of morphine in the occasional patient who experiences excitation (or exacerbation of pain) with morphine.

Oxycodone hydrochloride p. 466 has an efficacy and side-effect profile similar to that of morphine. It is commonly used as a second-line drug if morphine is not tolerated or does not control the pain.

Papaveretum p. 469 is rarely used; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pentazocine p. 469 has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on other opioids. By injection it is more potent than dihydrocodeine tartrate p. 456 or codeine phosphate, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine hydrochloride p. 470 produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour; however, other opioids, such as morphine or diamorphine hydrochloride, are often preferred for obstetric pain.

Tapentadol p. 471 produces analgesia by two mechanisms. It is an opioid-receptor agonist and it also inhibits noradrenaline reuptake. Nausea, vomiting, and constipation are less likely to occur with tapentadol than with other strong opioid analgesics.

Tramadol hydrochloride p. 471 produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

**Weak opioids**

Codeine phosphate can be used for the relief of mild to moderate pain where other painkillers such as paracetamol or ibuprofen p. 1141 have proved ineffective.

Dihydrocodeine tartrate has an analgesic efficacy similar to that of codeine phosphate. Higher doses may provide some additional pain relief but this may be at the cost of more nausea and vomiting.

Meptazinol p. 463 is claimed to have a low incidence of respiratory depression. It has a reported length of action of 2 to 7 hours with onset within 15 minutes.

**Postoperative analgesia**

A combination of opioid and non-opioid analgesics is used to treat postoperative pain. The use of intra-operative opioids affects the prescribing of postoperative analgesics. A
postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression.

Morphine is used most widely. Tramadol hydrochloride is not as effective in severe pain as other opioid analgesics. Buprenorphine may antagonise the analgesic effect of previously administered opioids and is generally not recommended. Pethidine hydrochloride is generally not recommended for postoperative pain because it is metabolised to norpethidine which may accumulate, particularly in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with morphine p. 463. Patient-controlled analgesia (PCA) can be used to relieve postoperative pain—consult individual hospital protocols.

Pain management and opioid dependence
Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need. Treatment with opioid analgesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special licence to prescribe opioid analgesics to patients with opioid dependence for relief of pain due to organic disease or injury.

Patient-controlled analgesia (PCA) can be used to relieve postoperative pain—consult individual hospital protocols.

### Pain management and opioid dependence

**Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need.** Treatment with opioid analgesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special licence to prescribe opioid analgesics to patients with opioid dependence for relief of pain due to organic disease or injury.

- **Frequency not known** Consciousness impaired - disorientation - dissociation - hypoxia - nystagmus - renal failure - vomiting
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with hypersensitivity to fluorinated anaesthetics.
- **PREGNANCY** Manufacturer advises use with caution—limited information available.
- **BREAST FEEDING** Manufacturer advises use with caution—limited information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure).
- **RENAL IMPAIRMENT** Manufacturer advises avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** The manufacturer of Penthrox® has provided an Administration Checklist and an Administration Guide for healthcare professionals.
- **HANDLING AND STORAGE** Manufacturer advises exposure of healthcare professionals to methoxyflurane should be minimised—risk of serious side-effects.
- **PATIENT AND CARER ADVICE** Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and drowsiness.

### Methoxyflurane

**INDICATIONS AND DOSE**

**Moderate to severe pain associated with trauma (under close medical supervision)**

- **BY INHALATION**
  - Adult: 3–6 mL as required, avoid administration on consecutive days; administer using inhaler device; maximum 15 mL per week

**IMPORTANT SAFETY INFORMATION**

Manufacturer advises methoxyflurane should only be self-administered under the supervision of personnel experienced in its use, using a hand-held Penthrox® inhaler device.

- **CONTRA-INDICATIONS** Cardiovascular disease · history of liver damage associated with use of methoxyflurane or other halogenated anaesthetics · impaired consciousness · respiratory depression · susceptibility to malignant hyperthermia
- **CAUTIONS** Elderly—increased risk of hypotension—repeated administration more than once every 3 months—increased risk of hepatic injury · risk factors for hepatic impairment · risk factors for renal impairment
- **INTERACTIONS** → Appendix 1: volatile halogenated anaesthetics
- **SIDE-EFFECTS**
  - Common or very common Anxiety · cough · depression · dizziness · drowsiness · dry mouth · dysarthria · headache · hyperhidrosis · hypotension · memory loss · mood altered · nausea · neuropathy sensory · taste altered
  - Uncommon Appetite increased · chills · fatigue · oral discomfort · paraesthesia · vision disorders
  - Rare or very rare Hepatic disorders

**ANALGESICS > NON-OPIOID**

**Paracetamol**

*(Acetaminophen)*

**INDICATIONS AND DOSE**

**Mild to moderate pain** | **Pyrexia**

- **BY MOUTH**
  - Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day

- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 50 kg): 15 mg/kg every 4–6 hours, dose to be administered over 15 minutes; maximum 60 mg/kg per day
  - Adult (body-weight 50 kg and above): 1 g every 4–6 hours, dose to be administered over 15 minutes; maximum 4 g per day

- **BY RECTUM**
  - Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day

**Mild to moderate pain in patients with risk factors for hepatotoxicity** | **Pyrexia in patients with risk factors for hepatotoxicity**

- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 50 kg): 15 mg/kg every 4–6 hours, dose to be administered over 15 minutes; maximum 60 mg/kg per day
  - Adult (body-weight 50 kg and above): 1 g every 4–6 hours, dose to be administered over 15 minutes; maximum 3 g per day

**Pain** | **Pyrexia with discomfort**

- **BY MOUTH**
  - Child 3–5 months: 60 mg every 4–6 hours; maximum 4 doses per day
INTERACTIONS

POST-IMMUNISATION PYREXIA IN INFANTS
BY MOUTH
Child 2-3 months: 60–125 mg every 4–6 hours as required; maximum 4 doses per day
Child 4–6 months: 125–250 mg every 4–6 hours as required; maximum 4 doses per day
Child 6 months onwards: 250–500 mg every 4–6 hours as required; maximum 4 doses per day
Child 12–17 years: 500 mg every 4–6 hours

ACUTE MIGRAINE
BY MOUTH
Adult: 1 g for 1 dose, to be taken as soon as migraine symptoms develop

UNLICENSED USE
In children Paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years. Not licensed for use as prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine.

CAUTIONS
Before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours. Body weight under 50 kg, chronic alcohol consumption, chronic dehydration, chronic malnutrition, hepatocellular insufficiency, long-term use (especially in those who are malnourished).

CAUTIONS, FURTHER INFORMATION
Some patients may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body weight under 50 kg and those with risk factors for hepatotoxicity. Clinical judgement should be used to adjust the dose of oral and intravenous paracetamol in these patients.

Co-administration of enzyme-inducing antiepileptic medications may increase toxicity; doses should be reduced.

INTERACTIONS
Appendix 1: paracetamol

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
Rare or very rare: Thrombocytopenia
SPECIFIC SIDE-EFFECTS
Common or very common
With rectal use: Anorectal erythema
Rare or very rare
With intravenous use: Hypersensitivity, hypotension, leucopenia, malaise, neutropenia
With rectal use: Angioedema, liver injury, skin reactions
Frequency not known
With intravenous use: Flushing, skin reactions, tachycardia

With oral use: Agranulocytosis, bronchospasm, hepatic function abnormal, rash, severe cutaneous adverse reactions (SCARs)
With rectal use: Agranulocytosis, blood disorder, severe cutaneous adverse reactions (SCARs)

OVERDOSE
Liver damage and less frequently renal damage can occur following overdose.
Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis.

For specific details on the management of poisoning, see Paracetamol, under Emergency treatment of poisoning, p. 1359.

PREGNANCY
Not known to be harmful.

BREAST FEEDING
Amount too small to be harmful.

HEPATIC IMPAIRMENT
Dose-related toxicity—avoid large doses.

RENAL IMPAIRMENT
Dose adjustments
In adults Increase infusion dose interval to every 6 hours if eGFR less than 30 mL/minute/1.73 m².
In children Increase infusion dose interval to every 6 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
With intravenous use For intravenous infusion (Perfalgal®), give in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of not less than 1 mg/mL and use within an hour; may also be given undiluted. For children under 33 kg, use 50 mL.vial.

PRESCRIBING AND DISPENSING INFORMATION
BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Paracetamol for mild-to-moderate pain www.medicinesforchildren.org.uk/paracetamol-mild-moderate-pain

PROFESSIONAL INFORMATION
Dental practitioners’ formulary
Paracetamol Tablets may be prescribed.
Paracetamol Soluble Tablets 500 mg may be prescribed.
Paracetamol Oral Suspension may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY
Paracetamol capsules or tablets can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository, powder.

Tablet
CAUTIONARY AND ADVISORY LABELS 29, 30
Paracetamol (Non-proprietary)
Paracetamol 500 mg Paracetamol 500mg caplets | 100 tablet £3.05 DT = £1.81
Paracetamol 500mg tablets | 100 tablet £2.13 DT = £1.81 | 1000 tablet £15.94–£18.10
Paracetamol 1 gram Paracetamol 1g tablets | 100 tablet £2.49
Paracetamol 500 mg Mandanol 500mg caplets | 100 tablet £1.17 DT = £1.81
Mandanol 500mg tablets | 100 tablet £1.17 DT = £1.81
Paravict (Ecogen Europe Ltd) Paracetamol 500 mg Paravict 500mg tablets | 100 tablet £1.62 DT = £1.81
Suppository

CAUTIONARY AND ADVISORY LABELS 30

- Paracetamol (Non-proprietary)

Paracetamol 80 mg Paracetamol 80mg suppositories | 10 suppository (£ 10.00)

Paracetamol 120 mg Paracetamol 120mg suppositories | 10 suppository (£ 12.39 DT = £12.39)

Paracetamol 125 mg Paracetamol 125mg suppositories | 10 suppository (£ 13.80 DT = £13.80)

Paracetamol 240 mg Paracetamol 240mg suppositories | 10 suppository (£ 22.01 DT = £22.01)

Paracetamol 250 mg Paracetamol 250mg suppositories | 10 suppository (£ 27.60 DT = £27.60)

Paracetamol 500 mg Paracetamol 500mg suppositories | 10 suppository (£ 36.50 DT = £36.50)

Paracetamol 1 gram Paracetamol 1g suppositories | 10 suppository (£ 50.00 DT = £50.00)

- Alvedon (Intranspharm Laboratories Ltd)

Paracetamol 60 mg Alvedon 60mg suppositories | 10 suppository (£ 11.95 DT = £11.95)

Paracetamol 125 mg Alvedon 125mg suppositories | 10 suppository (£ 13.80 DT = £13.80)

Paracetamol 250 mg Alvedon 250mg suppositories | 10 suppository (£ 27.60 DT = £27.60)

Oral suspension

CAUTIONARY AND ADVISORY LABELS 30

- Paracetamol (Non-proprietary)

Paracetamol 24 mg per 1 ml Paracetamol 120mg/5ml oral solution paediatric sugar free sugar-free | 100 ml (£ 1.23-£1.50 | 500 ml (£ 5.75-£6.13 DT = £5.13)

Paracetamol 120mg/5ml oral solution paediatric sugar free sugar-free | 100 ml (£ 1.19 DT = £1.19 sugar-free | 200 ml (£ 2.38 sugar-free | 500 ml (£ 5.95 sugar-free | 1000 ml (£ 11.90

Paracetamol 50 mg per 1 ml Paracetamol 250mg/5ml oral suspension | 100 ml (£ 1.40-£1.75 DT = £1.75 | 500 ml (£ 7.00-£8.75

Paracetamol 250mg/5ml oral suspension sugar free sugar-free | 100 ml (£ 1.17-£1.19 sugar-free | 200 ml (£ 2.23 DT = £2.24 sugar-free | 500 ml (£ 5.83-5.85 sugar-free | 1000 ml (£ 11.65

Paracetamol 100 mg per 1 ml Paracetamol 500mg/5ml oral suspension sugar free sugar-free | 150 ml (£ 24.00 DT = £24.00

- Calpol (McNeil Products Ltd)

Paracetamol 24 mg per 1 ml Calpol Infant 120mg/5ml oral suspension | 200 ml (£ 3.78

Calpol Infant 120mg/5ml oral suspension sugar free sugar-free | 200 ml (£ 3.78

Paracetamol 50 mg per 1 ml Calpol Six Plus 250mg/5ml oral suspension | 200 ml (£ 4.40

Calpol Six Plus 250mg/5ml oral suspension sugar free sugar-free | 100 ml (£ 2.64 sugar-free | 200 ml (£ 4.40 DT = £2.34

Effervescent tablet

CAUTIONARY AND ADVISORY LABELS 29, 30

- Paracetamol (Non-proprietary)

Paracetamol 500 mg Paracetamol 500mg soluble tablets | 100 tablet (£ 16.79

Paracetamol 500mg effervescent tablets | 24 tablet (£ 1.72 | 60 tablet (£ 4.30 | 100 tablet (£ 8.25

- Altrixdexamol (Trion Pharma Ltd)

Paracetamol 1 gram Altrixdexamol 1000mg effervescent tablets sugar-free | 50 tablet (£ 16.59

Solution for infusion

- Paracetamol (Non-proprietary)

Paracetamol 10 mg per 1 ml Paracetamol 500mg/50ml solution for infusion bottles | 10 bottle (£ 11.00 (Hospital only)

Paracetamol 500mg/50ml solution for infusion vials | 10 vial (£ 14.40

Paracetamol 1g/100ml solution for infusion bottles | 10 bottle (£ 12.00-£15.60 DT = £12.00 | 20 vial (£ 24.00

Paracetamol 100mg/10ml solution for infusion ampoules | 20 ampoule (£ 22.00

- Perifalan (Bristol-Myers-Squibb Pharmaceuticals Ltd)

Paracetamol 10 mg per 1 ml Perifalan 1g/100ml solution for infusion vials | 12 vial (£ 14.96

Perifalan 500mg/50ml solution for infusion vials | 12 vial (£ 13.60

Oral solution

CAUTIONARY AND ADVISORY LABELS 30

- Paracetamol (Non-proprietary)

Paracetamol 24 mg per 1 ml Paracetamol 120mg/5ml oral solution paediatric sugar free sugar-free | 2000 ml (£ 23.80 DT = £23.80

Paracetamol 100 mg per 1 ml Paracetamol 500mg/5ml oral solution sugar free sugar-free | 150 ml (£ 24.00 sugar-free | 200 ml (£ 18.00 DT = £18.00

Powder

- Paracetamol (Non-proprietary)

Paracetamol 650 mg Paracetamol 650mg oral powder sachets | 10 sachet (£ 5.90

Capsule

CAUTIONARY AND ADVISORY LABELS 29, 30

- Paracetamol (Non-proprietary)

Paracetamol 500 mg Paracetamol 500mg capsules | 32 capsule (£ 6.88–£7.32 DT = £6.98 | 100 capsule (£ 13.06 DT = £13.06

Orodispensible tablet

CAUTIONARY AND ADVISORY LABELS 30

- Calpol Fastmelts (McNeil Products Ltd)

Paracetamol 250 mg Calpol Six Plus Fastmelts 250mg tablets sugar-free | 24 tablet (£ 4.12 DT = £4.12

Combinations available: Co-codamol, p. 453 - Dihydrocodeine with paracetamol, p. 457

ANALGESICS > NON-OPIOID, CENTRALLY ACTING

Nefopam hydrochloride

- INDICATIONS AND DOSE

Moderate pain

> BY MOUTH

- Adult: Initially 60 mg 3 times a day, adjusted according to response; usual dose 30–90 mg 3 times a day

- Elderly: Initially 30 mg 3 times a day, adjusted according to response; usual dose 30–90 mg 3 times a day

- CONTRA-INDICATIONS Convulsive disorders - not indicated for myocardial infarction

- CAUTIONS Elderly - urinary retention

- INTERACTIONS > Appendix 1: nefopam

- SIDE-EFFECTS

  > Uncommon Coma - drowsiness - headache - hyperhidrosis - insomnia - tachycardia - vision blurred - vomiting

  > Rare or very rare Urine red

  > Frequency not known Abdominal pain - angioedema - confusion - diarrhoea - dizziness - dry mouth - gastrointestinal disorder - hallucination - hypeension - nausea - nervousness - palpitations - paraesthesia - seizure - syncope - tremor - urinary retention

- PREGNANCY No information available—avoid unless no safer treatment.

- HEPATIC IMPAIRMENT Manufacturer advises caution.

- RENAL IMPAIRMENT Caution.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
ANALGESICS > NON-Steroidal Anti-INFLAMMATORY DRUGS

Aspirin with codeine

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 121, codeine phosphate p. 454.

- **INDICATIONS AND DOSE**
  - Mild to moderate pain / Pyrexia
  - **BY MOUTH**
  - Adult: 1–2 tablets every 4–6 hours as required, dose to be dispensed in water; maximum 8 tablets per day

- **INTERACTIONS** → Appendix 1: aspirin - opioids
- **PRESCRIBING AND DISPENSING INFORMATION** When co-codaprin tablets or dispersible tablets are prescribed and no strength is stated, tablets or dispersible tablets, respectively, containing codeine phosphate 8 mg and aspirin 400 mg should be dispensed.
- **LESS SUITABLE FOR PRESCRIBING** Aspirin with codeine is less suitable for prescribing.
- **EXCEPTIONS TO LEGAL CATEGORY** Aspirin with codeine can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Dispersible tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 13, 21, 32
  - **Aspirin with codeine (Non-proprietary)**
    - Codeine phosphate 8 mg, Aspirin 400 mg
    - **Codaprin 8 mg/400 mg** dispersible tablets | 100 tablet [US] £97.55 DT = £93.41 [GB]
    - **Codis** (Reckitt Benckiser Healthcare (UK) Ltd)
      - **Codine phosphate 8 mg, Aspirin 500 mg** Codis 50 dispersible tablets sugar-free | 32 tablet [P] £3.23 [GB]
  - **Tablet**
    - **Aspirin with codeine (Non-proprietary)**
      - Codeine phosphate 8 mg, Aspirin 400 mg
      - Aspirin and Codeine tablets | 32 tablet [P] £0.95

ANALGESICS > OPIOIDS

Opioids

- **CONTRA-INDICATIONS** Acute respiratory depression - comatose patients - head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment) - raised intracranial pressure (opioid analgesics interfere with pupillary responses vital for neurological assessment) - risk of paralytic ileus

- **CAUTIONS** Adrenocortical insufficiency (reduced dose is recommended) - asthma (avoid during an acute attack) - convulsive disorders - debilitated patients (reduced dose is recommended) (in adults) - diseases of the biliary tract - elderly (reduced dose is recommended) - hypotension - hypothyroidism (reduced dose is recommended) - impaired respiratory function (avoid in chronic obstructive pulmonary disease) - inflammatory bowel disorders - myasthenia gravis - obstructive bowel disorders - prostatic hypertrophy (in adults) - shock - urethral stenosis (in adults)

**CAUTIONS, FURTHER INFORMATION**

- Dependence Repeat use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence.

- **SIDE-EFFECTS**
  - **Common or very common** Arrhythmias - confusion - constipation - dizziness - drowsiness - dry mouth - euphoric mood - flushing - hallucination - headache - hyperhidrosis - hypotension (with high doses) - miosis - nausea (more common on initiation) - palpitations - respiratory depression (with high doses) - skin reactions - urinary retention - vertigo - visual impairment - vomiting (more common on initiation) - withdrawal syndrome (in adults)

- **Uncommon** Drug dependence - dysphoria

**SIDE EFFECTS, FURTHER INFORMATION**

**Respiratory depression** Respiratory depression is a major concern with opioid analgesics and it may be treated by artificial ventilation or be reversed by naloxone.

**Dependence and withdrawal** Psychological dependence rarely occurs when opioids are used therapeutically (e.g. for pain relief), but tolerance can develop during long-term treatment.

**Overdose** Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. For details on the management of poisoning, see Opioids, under Emergency treatment of poisoning p. 1359 and consider the specific antidote, naloxone hydrochloride.

**PREGNANCY** Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

**TREATMENT CESSATION** Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

**PRESCRIBING AND DISPENSING INFORMATION** The Faculty of Pain Medicine has produced resources for healthcare professionals around opioid prescribing: www.fpm.ac.uk/ faculty-of-pain-medicine/opioids-aware

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including opioids, see Drugs and driving under Guidance on prescribing p. 1.

**Buprenorphine**

**DRUG ACTION** Buprenorphine is an opioid-receptor partial agonist (it has opioid agonist and antagonist properties).

**INDICATIONS AND DOSE**

**Moderate to severe pain**

- **BY SUBLINGUAL ADMINISTRATION**
  - Child (body-weight 16–25 kg): 100 micrograms every 6–8 hours
  - Child (body-weight 25–37.5 kg): 100–200 micrograms every 6–8 hours
  - Child (body-weight 37.5–50 kg): 200–300 micrograms every 6–8 hours
  - Child (body-weight 50 kg and above): 200–400 micrograms every 6–8 hours
  - Adult: 200–400 micrograms every 6–8 hours

- **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - Child 6 months–11 years: 3–6 micrograms/kg every 6–8 hours (max. per dose 9 micrograms/kg)
Nervous system

Adult:

BY TRANSDERMAL APPLICATION USING PATCHES

Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic—If necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

PHARMACOKINETICS

For Buprenorphine®: It may take approximately 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

BUPLAST®

Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic—Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic

BY TRANSDERMAL APPLICATION USING PATCHES

Adult: Initially 35 micrograms/hour up to every 96 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

PHARMACOKINETICS

For Buplast®: It may take approximately 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

BUPRAMYL®

Moderate, non-malignant pain unresponsive to non-opioid analgesics—Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic—Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic

BY TRANSDERMAL APPLICATION USING PATCHES

Adult: The initial dose should be based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

PHARMACOKINETICS

For Bupramyl®: It may take approximately 12 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.
Moderate, non-malignant pain unresponsive to non-opioid analgesics

**BY TRANSDERMAL APPLICATION USING PATCHES**

- **Adult:** Initially 5 micrograms/hour up to every 7 days, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

**PHARMACOKINETICS**

- For **Bute®:** It may take approximately 12 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**BUVIDAL®**

**Adjunct in the treatment of opioid dependence**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** (consult product literature)

**PHARMACOKINETICS**

- Weekly **Buvidal®** has a terminal half-life ranging from 3 to 5 days.
- Monthly **Buvidal®** has a terminal half-life ranging from 19 to 25 days.

**HAPOCATIN®**

Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic

- **Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic**

  **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** Initially 35 micrograms/hour up to every 72 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually.

**Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic**

- **Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic**

  **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** The initial dose should be based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually.

**PHARMACOKINETICS**

- For **Hapocatin®:** It may take approximately 25 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**PANITAZ®**

Moderate, non-malignant pain unresponsive to non-opioid analgesics

- **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** Initially 5 micrograms/hour up to every 7 days, dose adjustments—when starting, analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of at least 3 days using a patch of the next strength or a combination of 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

**PHARMACOKINETICS**

- For **Panitaz®:** It may take approximately 12 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**PRENOTRIX®**

Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic

- **Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic**

  **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** Initially 35 micrograms/hour up to every 72 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

**PRENOTRIX®**

Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic

- **Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic**

  **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** The initial dose should be based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.

**PHARMACOKINETICS**

- For **Prenotrix®:** It may take approximately 25 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**RELETRANS®**

Moderate, non-malignant pain unresponsive to non-opioid analgesics

- **BY TRANSDERMAL APPLICATION USING PATCHES**

  - **Adult:** Initially 5 micrograms/hour up to every 7 days, dose adjustments—when starting, analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of at least 3 days using a patch of the next strength or a combination of 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time.
PHARMACOKINETICS
- For Reletrans®: It may take approximately 12 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

RELEVTEC®
Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic: Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic
- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: Initially 35 micrograms/hour up to every 96 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

Moderate to severe chronic cancer pain in patients who have previously received strong opioid analgesic: Severe pain unresponsive to non-opioid analgesics in patients who have previously received strong opioid analgesic
- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: The initial dose should be based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

PHARMACOKINETICS
- For Relevtec®: It may take approximately 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

SEVODYNE®
Moderate, non-malignant pain unresponsive to non-opioid analgesics
- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: Initially 5 micrograms/hour up to every 7 days, dose adjustments—when starting, analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of at least 3 days using a patch of the next strength or a combination of 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

PHARMACOKINETICS
- For Sevodyne®: It may take approximately 12 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

TRANSCTEC®
Moderate to severe chronic cancer pain in patients who have not previously received strong opioid analgesic: Severe pain unresponsive to non-opioid analgesics in patients who have not previously received strong opioid analgesic
- BY TRANSDERMAL APPLICATION USING PATCHES
  - Adult: Initially 35 micrograms/hour up to every 96 hours, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

PHARMACOKINETICS
- For Transtec®: It may take approximately 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

UNLICENSED USE

IMPORTANT SAFETY INFORMATION
- With transdermal use in adults
  Do not confuse the formulations of transdermal patches which are available as 72-hourly, 96-hourly and 7-day patches, see Prescribing and dispensing information.

- CAUTIONS
  - GENERAL CAUTIONS: Impaired consciousness
  - SPECIFIC CAUTIONS
    - With transdermal use: Fever or external heat - other opioids should not be administered within 24 hours of patch removal (long duration of action)
    - When used for adjunct in the treatment of opioid dependence: Hepatitis B infection - hepatitis C infection - pre-existing liver enzyme abnormalities
  - CAUTIONS, FURTHER INFORMATION
    - Fever or external heat
    - With transdermal use: Manufacturer advises monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption).
  - BUVIDAL®: Susceptibility to QT-interval prolongation

- SIDE-EFFECTS
  - GENERAL SIDE-EFFECTS
    - Common or very common: Anxiety (in adults) - appetite decreased (in adults) - depression (in adults) - diarrrhoea (in adults) - dysphoria (in adults) - syncope (in adults) - tremor (in adults)
  - SPECIFIC SIDE-EFFECTS
    - Common or very common: With parenteral use: Arthralgia (in adults) - asthenia (in adults) - asthma (in adults) - behaviour abnormal (in adults) - chest pain (in adults) - chills (in adults) - cough (in adults) - dysmenorrhoea (in adults) - eye disorders (in adults) - fever (in adults) - gastrointestinal discomfort (in adults)
adults) - gastrointestinal disorders (in adults) - hypnoticsensitivity - increased risk of infection (in adults) - insomnia (in adults) - lymphadenopathy (in adults) - malaise (in adults) - migraine (in adults) - muscle complaints (in adults) - muscle tone increased (in adults) - pain (in adults) - parasthesia (in adults) - peripheral oedema (in adults) - speech disorder (in adults) - thinking abnormal (in adults) - vasodilation (in adults) - withdrawal syndrome neonatal - yawning (in adults)

- With sublingual use: Fatigue - sleep disorders
- With transdermal use: Astenia - gastrointestinal discomfort - muscle weakness - oedema - sleep disorders
- Uncommon
- With parenteral use: Procedural dizziness (in adults)
- Rare or very rare
- With sublingual use: Angioedema - bronchospasm
- With transdermal use: Angina pectoris - asthma exacerbated - dehydration - dysphagia - ear pain - eyelid oedema - increased risk of infection - influenza like illness - muscle contractions involuntary - psychotic disorder - vasodilation
- Frequency not known
- With parenteral use: Angioedema - bronchospasm - death (in adults) - hepatic disorders - hepatic encephalopathy (in adults) - psychotic disorder - vision blurred
- With sublingual use: Cerebrospinal fluid pressure increased - circulation impaired - haemorrhagic diathesis - hepatic disorders - oral disorders
- With transdermal use: Biliary colic - depersonalisation - seizure - withdrawal syndrome neonatal

Overdose
The effects of buprenorphine are only partially reversed by naloxone.

Breast feeding
Present in low levels in breast milk.

Monitoring
Neonates should be monitored for drowsiness, adequate weight gain, and developmental milestones.

Hepatic impairment
Manufacturer advises caution; avoid in severe impairment (limited information available).

For transdermal patch, manufacturer advises consider avoiding in severe impairment.

Dose adjustments
- In adults: For oral lyophilisate, manufacturer advises initial dose reduction in mild to moderate impairment.
- Renal impairment
Avoid use or reduce dose; opioid effects increased and prolonged; increased cerebral sensitivity.

Pre-treatment screening
Documentation of viral hepatitis status is recommended before commencing therapy for opioid dependence.

Monitoring requirements
Monitor liver function; when used in opioid dependence baseline liver function test is recommended before commencing therapy, and regular liver function tests should be performed throughout treatment.

Directions for administration
- In children: Sublingual tablets may be halved.
- In adults: Manufacturer advises oral lyophilisate should be placed on the tongue and allowed to dissolve. Patients should be advised not to swallow for 2 minutes and not to consume food or drink for at least 5 minutes after administration.

Butrans
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after 7 days and sitting replacement patch on a different area (avoid same area for at least 3 weeks).

Prenotrix
Manufacturer advises apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 72 hours and sitting replacement patch on a different area (avoid same area for at least 7 days).

Hapocasin
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 72 hours and sitting replacement patch on a different area (avoid same area for at least 7 days).

Butech, Bupramyl, Panitaz, Reletrans
Manufacturer advises apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and sitting replacement patch on a different area (avoid same area for at least 7 days).

Transtec
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and sitting replacement patch on a different area (avoid same area for at least 7 days).

Prescribing and dispensing information
Transdermal buprenorphine patches are not suitable for acute pain in or those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Transdermal patches are available as 72-hourly, 96-hourly and 7-day formulations; prescribers and dispensers must ensure that the correct preparation is prescribed and dispensed. Preparations that should be applied up to every 72 hours include Hapocasin and Prenotrix. Preparations that should be applied up to every 96 hours include Bupeaze, Buplast, Relevec, and Transtec. Preparations that should be applied up to every 7 days include Bupranyl, Butech, BuTrans, Panitaz, Reletrans and Sevodyne. Esprano oral lyophilisate has different bioavailability to other buprenorphine products and is not interchangeable with them—consult product literature before switching between products.

Patient and carer advice
Patients or carers should be given advice on how to administer buprenorphine products.

National funding/access decisions
NICE decisions
- Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TAI4
- In adults Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

Scottish Medicines Consortium (SMC) decisions
- In adults The Scottish Medicines Consortium has advised (June 2017) that buprenorphine oral lyophilisate (Esprano®) is accepted for restricted use within NHS Scotland as substitution treatment for opioid dependence for patients in whom methadone is not suitable. This
advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**BUTEC®**

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium has advised (January 2017) that buprenorphine transdermal patches (Buteed®) are accepted for restricted use within NHS Scotland for the treatment of chronic non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia in elderly patients (over 65 years).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Temosic** (Indivior UK Ltd)
  - Buprenorphine (as Buprenorphine hydrochloride)
    - 36 microgram per 1 ml Temgesic 30micrograms/1ml solution for injection ampoules | 5 ampoule [PMS] £2.46 [03]

**Sublingual tablet**

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<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 2, 26</th>
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<tbody>
<tr>
<td><strong>Buprenorphine</strong> (as Buprenorphine hydrochloride)</td>
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<td>400 microgram</td>
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<th><strong>Natzon</strong> (Morningside Healthcare Ltd)</th>
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<th><strong>Prefelix</strong> (Sandoz Ltd)</th>
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<th><strong>Tepheen</strong> (Sandoz Ltd)</th>
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<td>200 microgram</td>
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**Transdermal patch**

**CAUTIONARY AND ADVISORY LABELS 2**

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<th><strong>BuTRANS</strong> (Napp Pharmaceuticals Ltd)</th>
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<td>Buprenorphine 5 microgram per 1 hour</td>
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<td>Buprenorphine 10 microgram per 1 hour</td>
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<td>Buprenorphine 15 microgram per 1 hour</td>
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<td>Buprenorphine 20 microgram per 1 hour</td>
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<tr>
<th><strong>Bupeaze</strong> (Dr Reddy’s Laboratories (UK) Ltd)</th>
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<td>Buprenorphine 35 microgram per 1 hour</td>
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<td>Buprenorphine 52.5 microgram per 1 hour</td>
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<th><strong>Butec</strong> (Qdem Pharmaceuticals Ltd)</th>
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<th><strong>Hapoctacin</strong> (Actavis UK Ltd)</th>
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<td>Buprenorphine 52.5 microgram per 1 hour</td>
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<td>Buprenorphine 70 microgram per 1 hour</td>
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<tr>
<th><strong>Panitaz</strong> (Dr Reddy’s Laboratories (UK) Ltd)</th>
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<td>Buprenorphine 5 microgram per 1 hour</td>
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<td>Buprenorphine 10 microgram per 1 hour</td>
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<tr>
<th><strong>Relatrans</strong> (Sandoz Ltd)</th>
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<td>Buprenorphine 5 microgram per 1 hour</td>
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Buprenorphine 10 microgram per 1 hour
Reletrans
10micrograms/hour transdermal patches | 4 patch [POM] £14.20 DT = £31.55 [BD]
Buprenorphine 15 microgram per 1 hour
Reletrans
15micrograms/hour transdermal patches | 4 patch [POM] £22.12 DT = £49.15 [BD]
Buprenorphine 20 microgram per 1 hour
Reletrans
20micrograms/hour transdermal patches | 4 patch [POM] £25.86 DT = £57.46 [BD]

Relevec (Sandoz Ltd)
Buprenorphine 35 microgram per 1 hour
Relevec
35micrograms/hour transdermal patches | 4 patch [POM] £11.06 DT = £23.71 [BD]
Buprenorphine 52.5 microgram per 1 hour
Relevec
52.5micrograms/hour transdermal patches | 4 patch [POM] £16.60 DT = £33.11 [BD]
Buprenorphine 70 microgram per 1 hour
Relevec
70micrograms/hour transdermal patches | 4 patch [POM] £22.12 DT = £31.60 [BD]

Sevodyne (Aspire Pharma Ltd)
Buprenorphine 5 microgram per 1 hour
Sevodyne
5micrograms/hour transdermal patches | 4 patch [POM] £7.92 DT = £17.66 [BD]
Buprenorphine 10 microgram per 1 hour
Sevodyne
10micrograms/hour transdermal patches | 4 patch [POM] £14.20 DT = £33.11 [BD]
Buprenorphine 20 microgram per 1 hour
Sevodyne
20micrograms/hour transdermal patches | 4 patch [POM] £25.86 DT = £57.46 [BD]

Transec (Napp Pharmaceuticals Ltd)
Buprenorphine 35 microgram per 1 hour
Transec
35micrograms/hour transdermal patches | 4 patch [POM] £11.06 DT = £23.71 [BD]
Buprenorphine 52.5 microgram per 1 hour
Transec
52.5micrograms/hour transdermal patches | 4 patch [POM] £16.60 DT = £33.11 [BD]
Buprenorphine 70 microgram per 1 hour
Transec
70micrograms/hour transdermal patches | 4 patch [POM] £22.12 DT = £31.60 [BD]

Oral lyophilisate
CAUTIONARY AND ADVISORY LABELS 2
EXCIPIENTS: May contain Aspartame, gelatin

Espranor (Martindale Pharmaceuticals Ltd)
Buprenorphine (as Buprenorphine hydrochloride) 2 mg
Espranor
2mg oral lyophilisates sugar-free | 7 tablet [POM] £6.35 DT = £6.35 [BD]

Buprenorphine (as Buprenorphine hydrochloride) 8 mg
Espranor
8mg oral lyophilisates sugar-free | 7 tablet [POM] £19.05 DT = £19.05 [BD]

Prolonged-release solution for injection
Buvidal (Camurus AB)
Buprenorphine 50 mg per 1 ml
Buvidal 16mg/0.32ml prolonged-release solution for injection pre-filled syringes | 1 pre-filled disposable injection [POM] £55.93 [BD]
Buvidal 8mg/0.10ml prolonged-release solution for injection pre-filled syringes | 1 pre-filled disposable injection [POM] £26.31 [BD]
Buvidal 32mg/0.64ml prolonged-release solution for injection pre-filled syringes | 1 pre-filled disposable injection [POM] £86.24 [BD]
Buvidal 8mg/0.32ml prolonged-release solution for injection pre-filled syringes | 1 pre-filled disposable injection [POM] £23.97 [BD]

Co-codamol
The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 444.

- **INDICATIONS AND DOSE**
  - **Moderate pain (using co-codamol 8/500 preparations only)**
    - **BY MOUTH**
      - Adult: 8/500–16/1000 mg every 4–6 hours as required; maximum 64/4000 mg per day
  - **Moderate pain (using co-codamol 15/500 preparations only)**
    - **BY MOUTH**
      - Adult: 15/500–30/1000 mg every 4–6 hours as required; maximum 120/4000 mg per day
  - **Moderate to severe pain (using co-codamol 30/500 preparations only)**
    - **BY MOUTH**
      - Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

- **KAPAKE 15/500**
  - **Mild to moderate pain**
    - **BY MOUTH**
      - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

- **SOLPADOL® CAPLETS**
  - **Severe pain**
    - **BY MOUTH**
      - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

- **SOLPADOL® CAPSULES**
  - **Severe pain**
    - **BY MOUTH USING EFFERVESCENT TABLETS**
      - Adult: 2 tablets every 4–6 hours as required, tablets to be dispersed in water; maximum 8 tablets per day

- **CONTRA-INDICATIONS**
  - Acute ulcerative colitis - antibiotic-associated colitis - conditions where inhibition of peristalsis should be avoided - known ultra-rapid codeine metabolisers

- **CAUTIONS**
  - Acute abdomen - alcohol dependence - avoid abrupt withdrawal after long-term treatment - cardiac arrhythmias - chronic alcoholism - chronic dehydration - chronic malnutrition - convulsive disorders - gallstones - hepatocellular insufficiency

- **CAUTIONS, FURTHER INFORMATION**
  - Variation in metabolism - The capacity to metabolise codeine to morphine can vary considerably between individuals; there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers.

- **INTERACTIONS**
  - Appendix 1: opioids - paracetamol

- **SIDE-EFFECTS**
  - Abdominal pain - addiction - agranulocytosis - blood disorder - irritability - pancreatitis - restlessness - severe cutaneous adverse reactions (SCARs) - thrombocytopenia

- **OVERDOSE**
  - Liver damage (and less frequently renal damage) following overdosage with paracetamol.

- **BREAST FEEDING**
  - Avoid — although amount of codeine usually too small to be harmful, mothers vary considerably...
in their capacity to metabolise codeine—risk of morphine overdose in infant.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
- **Dose adjustments** Manufacturer advises consider dose reduction in mild to moderate impairment.
- **RENA L IMPAIRMENT** Reduce dose or avoid codeine; increased and prolonged effect; increased cerebral sensibility.

- **PRESCRIBING AND DISPENSING INFORMATION** Co-codamol is a mixture of codeine phosphate and paracetamol; the proportions are expressed in the form x:y, where x and y are the strengths in milligrams of codeine phosphate and paracetamol respectively.

  When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and no strength is stated, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and paracetamol 500 mg should be dispensed.

  The Drug Tariff allows tablets of co-codamol labelled 'dispersible' to be dispensed against an order for 'effervescent' and vice versa.

- **LESS SUITABLE FOR PRESCRIBING** Co-codamol is less suitable for prescribing.

- **EXCEPTIONS TO LEGAL CATEGORY** Co-codamol 8/500 can be sold to the public in certain circumstances; for exemptions see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Tablet**

  | CAUTIONARY AND ADVISORY LABELS | 2 (does not apply to the 8/500 tablet), 29, 30 |
  | Co-codamol (Non-proprietary) | |
  | Codeine phosphate 8 mg, Paracetamol 500 mg | Co-codamol 8mg/500mg tablets | 100 tablet (P) £7.20 DT = £7.20 (G5) |
  | | 500 tablet (P) £13.50 DT = £13.50 (G5) |
  | Codeine phosphate 15 mg, Paracetamol 500 mg | Co-codamol 15mg/500mg tablets | 100 tablet (P) £15.00 DT = £14.12 (G5) |
  | Codeine phosphate 30 mg, Paracetamol 500 mg | Co-codamol 30mg/500mg caplets | 100 tablet (P) £3.90 DT = £3.63 (G5) |
  | | Co-codamol 30mg/500mg tablets | 30 tablet (P) £1.17 DT = £1.09 (G5) |
  | | 100 tablet (P) £7.53 DT = £7.63 (G5) |
  | Codeine phosphate 60 mg, Paracetamol 1 gram | Co-codamol 60mg/1000mg tablets | 100 tablet (P) £11.85 (G5) |
  | Codepar (Advanz Pharma) | Co-codamol 15mg, Paracetamol 500 mg Codpar 15mg/500mg tablets | 100 tablet (P) £8.25 DT = £8.14 (G5) |
  | | Emcozin (M & A Pharmacem Ltd) |
  | Codeine phosphate 30 mg, Paracetamol 500 mg Emcozin 30mg/500mg tablets | 100 tablet (P) £2.55 DT = £2.63 (G5) |
  | Kapake (Galen Ltd) |
  | Codeine phosphate 30 mg, Paracetamol 500 mg Kapake 30mg/500mg tablets | 100 tablet (P) £7.10 DT = £7.63 (G5) |
  | Migraleve Yellow (McNeil Products Ltd) |
  | Codeine phosphate 8 mg, Paracetamol 500 mg Migraleve Yellow tablets | 16 tablet (P) £6.05 (G5) |
  | Panadol Ultra (GlaxoSmithKline Consumer Healthcare) |
  | Codeine phosphate 12.8 mg, Paracetamol 500 mg Panadol Ultra 12.8mg/500mg tablets | 20 tablet (P) £2.61 DT = £3.63 (G5) |
  | Solpadeine Max (Omega Pharma Ltd) |
  | Codeine phosphate 12.8 mg, Paracetamol 500 mg Solpadeine Max 12.8mg/500mg tablets | 20 tablet (P) £3.61 DT = £3.61 (G5) |
  | | 30 tablet (P) £4.65 DT = £4.65 (G5) |
  | Solpado (Sanofi) |
  | Codeine phosphate 30 mg, Paracetamol 500 mg Solpado 30mg/500mg caplets | 30 tablet (P) £2.02 DT = £1.09 (G5) |
  | | 100 tablet (P) £6.74 DT = £6.63 (G5) |
  | Zapain (Advanz Pharma) |
  | Codeine phosphate 30 mg, Paracetamol 500 mg Zapain 30mg/500mg tablets | 100 tablet (P) £3.11 DT = £3.63 (G5) |

**Codeine phosphate**

- **INDICATIONS AND DOSE**
  - **Acute diarrhoea**
    - **BY MOUTH**
      - Child 12-17 years: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day
      - Adult: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day
    - **BY INTRAMUSCULAR INJECTION**
      - Child 12-17 years: 30–60 mg every 6 hours if required for maximum 3 days; maximum 240 mg per day
  - **Mild to moderate pain**
    - **BY MOUTH**
      - Adult: 30–60 mg every 4 hours if required; maximum 240 mg per day
    - **BY INTRAMUSCULAR INJECTION**
      - Child 12-17 years: 30–60 mg every 6 hours if required for maximum 3 days; maximum 240 mg per day
Dry or painful cough

- BY MOUTH USING LINCTUS
- Adult: 15–30 mg 3–4 times a day

### IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE (JULY 2013) CODEINE FOR ANALGESIA: RESTRICTED USE IN CHILDREN DUE TO REPORTS OF MORPHINE TOXICITY**

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone. A significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy:

- in children aged 12–18 years, the maximum daily dose of codeine should not exceed 240 mg. Doses may be taken up to four times a day at intervals of no less than 6 hours. The lowest effective dose should be used and duration of treatment should be limited to 3 days
- codeine is contra-indicated in all children (under 18 years) who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea
- codeine is not recommended for use in children whose breathing may be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, respiratory infections, multiple trauma or extensive surgical procedures
- codeine is contra-indicated in patients of any age who are known to be ultra-rapid metabolisers of codeine (CYP2D6 ultra-rapid metabolisers)
- codeine should not be used in breast-feeding mothers because it can pass to the baby through breast milk
- parents and carers should be advised on how to recognise signs and symptoms of morphine toxicity, and to stop treatment and seek medical attention if signs or symptoms of toxicity occur (including reduced consciousness, lack of appetite, somnolence, constipation, respiratory depression, ‘pin-point’ pupils, nausea, vomiting)

**MHRA/CHM ADVICE (APRIL 2015) CODEINE FOR COUGH AND COLD: RESTRICTED USE IN CHILDREN**

Do not use codeine in children under 12 years as it is associated with a risk of respiratory side effects. Codeine is not recommended for adolescents (12–18 years) who have problems with breathing. When prescribing or dispensing codeine-containing medicines for cough and cold, consider that codeine is contra-indicated in:

- children younger than 12 years old
- patients of any age known to be CYP2D6 ultra-rapid metabolisers
- breastfeeding mothers

### CONTRA-INDICATIONS

- Acute ulcerative colitis
- antibiotic-associated colitis
- children under 18 years who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea
- conditions where abdominal distension develops
- conditions where inhibition of peristalsis should be avoided
- known ultra-rapid codeine metabolisers

### CAUTIONS

- Acute abdomen
- cardiac arrhythmias
- gallstones
- not recommended for adolescents aged 12–18 years with breathing problems

### CAUTIONS, FURTHER INFORMATION

- Variation in metabolism: The capacity to metabolise codeine to morphine can vary considerably between individuals; there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers.

### INTERACTIONS

- Appendix 1: opioids

### SIDE-EFFECTS

#### GENERAL SIDE-EFFECTS

- Biliary spasm
- hypothermia
- mood altered
- sexual dysfunction
- urethral spasm

#### SPECIFIC SIDE-EFFECTS

- With oral use:
  - Abdominal cramps
  - addiction
  - appetite decrease
  - depression
  - drug reaction with eosinophilia and systemic symptoms (DRESS)
  - dyskinesia
  - dysphoria
  - face oedema
  - fatigue
  - fever
  - hypergastrinaemia
  - hypersensitivity
  - intracranial pressure increased
  - lymphadenopathy
  - malaise
  - muscle rigidity (with high doses)
  - nightmare
  - panic reaction
  - restless lessness
  - seizure
  - splenomegaly
  - urinary disorders
  - vision disorders
- With parenteral use
  - Dysuria

#### BREAST FEEDING

Avoid—although amount usually too small to be harmful, mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant.

#### HEPATIC IMPAIRMENT

- With oral use
  - Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
- With intravenous use
  - Manufacturer advises avoid.

#### DOSAGE ADJUSTMENTS

- With oral use
  - Manufacturer advises dose reduction in mild to moderate impairment.

#### RENAL IMPAIRMENT

Avoid
- Avoid or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

#### PRESCRIBING AND DISPENSING INFORMATION

- BP directs that when Diabetic Codeine Linctus is prescribed, Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled 'Diabetic Codeine Linctus', shall be dispensed or supplied.

#### PATIENT AND CARER ADVICE

- Medicines for Children leaflet: Codeine phosphate for pain
  - www.medicinesforchildren.org.uk/codeine-phosphate-pain

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection

#### TABLET

- **CAUTIONARY AND ADVISORY LABELS**
  - 2
- **Codeine phosphate (Non-proprietary)**
  - Codeine phosphate 15 mg Codeine 15 mg tablets | 28 tablet | £1.40 DT = £0.83 (D53) | 100 tablet | £2.96 DT = £2.04 (D53)
  - Codeine phosphate 30 mg Codeine 30 mg tablets | 28 tablet | £1.59 DT = £0.93 (D53) | 100 tablet | £5.68 DT = £3.32 (D53) | 500 tablet | £16.60 (D53)
  - Codeine phosphate 60 mg Codeine 60 mg tablets | 28 tablet | £1.89 DT = £1.53 (D53)

#### Solution for injection

- **Codeine phosphate (Non-proprietary)**
  - Codeine phosphate 60 mg per 1 ml Codeine 60 mg/1 ml solution for injection ampoules | 10 ampoule | £24.10–£24.15 DT = £24.19 (D52)

#### Oral solution

- **CAUTIONARY AND ADVISORY LABELS**
  - 2
- **Codeine phosphate (Non-proprietary)**
  - Codeine phosphate 3 mg per 1 ml Codeine 15 mg/5 ml linctus sugar free sugar-free | 200 ml | £1.90 DT = £1.62 (D53) | 2000 ml | £11.20 (D53)
  - Codeine 15 mg/5 ml linctus | 28 tablet | £1.73–£1.90 DT = £1.90 (D53)
  - Codeine phosphate 5 mg per 1 ml Codeine 25 mg/5 ml oral solution | 500 ml | £6.64 DT = £6.64 (D53)
- **Galcodine** (Thornton & Ross Ltd)
  - Codeine phosphate 3 mg per 1 ml Galcodine 15 mg/5 ml linctus sugar-free | 2000 ml | £3.90 (D53)

Combinations available: **Aspirin with codeine**, p. 447
Diamorphine hydrochloride (Heroin hydrochloride)

**INDICATIONS AND DOSE**

**Acute pain**
- By intramuscular injection, or by subcutaneous injection
  - Adult: 5 mg every 4 hours if required
  - By slow intravenous injection
  - Adult: 1.25–2.5 mg every 4 hours if required

**Acute pain (heavier, well-muscled patients)**
- By intramuscular injection, or by subcutaneous injection
  - Adult: Up to 10 mg every 4 hours if required
  - By slow intravenous injection
  - Adult: 2.5–5 mg every 4 hours if required

**Chronic pain not currently treated with a strong opioid analgesic**
- By subcutaneous injection, or by intramuscular injection
  - Adult: Initially 2.5–5 mg every 4 hours, adjusted according to response
  - By subcutaneous infusion
  - Adult: Initially 5–10 mg, adjusted according to response, dose to be administered over 24 hours

**Acute pulmonary oedema**
- By slow intravenous injection
  - Adult: 2.5–5 mg, dose to be administered at a rate of 1 mg/minute

**Myocardial infarction**
- By slow intravenous injection
  - Adult: 5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute
  - Elderly: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Myocardial infarction (frail patients)**
- By slow intravenous injection
  - Adult: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Contra-indications**
- Delayed gastric emptying • phaeochromocytoma

**Cautions**
- CNS depression • severe cor pulmonary • severe diarrhoea • toxic psychosis

**Interactions**
- Appendix 1: opioids

**Side-effects**
- Biliary spasm • circulatory depression • intracranial pressure increased • mood altered

**Breast Feeding**
- Therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring.

**Hepatic Impairment**
- Manufacturer advises caution.

**Renal Impairment**
- Avoid use or reduce dose; opioid effects increased and prolonged; increased cerebral sensitivity.

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Powder for solution for injection**
- Diamorphine hydrochloride (Non-proprietary)
  - Diamorphine hydrochloride 5 mg: Diamorphine 5 mg powder for solution for injection ampoules | 5 ampoule £11.36–£14.95 DT = £13.76 (C02)

  - Diamorphine hydrochloride 10 mg: Diamorphine 10 mg powder for solution for injection ampoules | 5 ampoule £16.36–£16.95 DT = £14.49 (C02)
Dihydrocodeine tartrate (Non-proprietary)  
Dihydrocodeine tartrate 30 mg | Dihydrocodeine 30mg tablets | 28 tablet (PS) £0.99 DT = £0.36 (CT) | 30 tablet (PS) £0.99–£1.56 (CT) | 100 tablet (PS) £3.89 DT = £3.36 (CT) | 500 tablet (PS) £16.80 (CT)  
DF 118 (Martindale Pharmaceuticals Ltd)  
Dihydrocodeine tartrate 40 mg | DF 118 Forte 40mg tablets | 100 tablet (PS) £11.51 DT = £11.51 (CT)  

Solution for injection  
Dihydrocodeine tartrate (Non-proprietary)  
Dihydrocodeine tartrate 50 mg per 1 ml | Dihydrocodeine 50mg/1ml solution for injection ampoules | 10 ampoule (PS) £115.80 DT = £115.80 (CT)  

Oral solution  
Dihydrocodeine tartrate (Non-proprietary)  
Dihydrocodeine tartrate 2 mg per 1 ml | Dihydrocodeine 10mg/5ml oral solution | 150 ml (PS) £9.83 DT = £9.83 (CT)  

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 444.

**INDICATIONS AND DOSE**

**Mild to moderate pain (using 10/500 preparations only)**  
**BY MOUTH**  
Adult: 10/500–20/1000 mg every 4–6 hours as required; maximum 80/4000 mg per day  

**Severe pain (using 20/500 preparations only)**  
**BY MOUTH**  
Adult: 20/500–40/1000 mg every 4–6 hours as required; maximum 160/4000 mg per day  

**Severe pain (using 30/500 preparations only)**  
**BY MOUTH**  
Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day  

**DOSE EQUIVALENCE AND CONVERSION**  
A mixture of dihydrocodeine tartrate and paracetamol; the proportions are expressed in the form x/ y, where x and y are the strengths in milligrams of dihydrocodeine and paracetamol respectively.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: DIHYDROCODEINE WITH PARACETAMOL (CO-DYDRAMOL): PRESCRIBE AND DISPENSE BY STRENGTH TO MINIMISE RISK OF MEDICATION ERROR (JANUARY 2018)

The MHRA has advised that dihydrocodeine with paracetamol preparations are prescribed and dispensed by strength to minimise dispensing errors and the risk of accidental opioid overdose—see Prescribing and dispensing information.

**CAUTIONS**  
Alcohol dependence - before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours - chronic alcoholism - chronic dehydration - chronic malnutrition - hepatocellular insufficiency - pancreatitis - severe cor pulmonale  

**INTERACTIONS**  
Appendix 1: opioids - paracetamol  

**SIDE-EFFECTS**  
Abdominal pain - blood disorder - leucopenia - malaise - neutropenia - pancreatitis - paraesthesia - paralytic ileus - severe cutaneous adverse reactions (SCARs) - thrombocytopenia  

**OVERDOSE**  
Lever damage (and less frequently renal damage) following overdosage with paracetamol.

**BREAST FEEDING**  
Amount of dihydrocodeine too small to be harmful but use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT**  
Manufacturer advises consider avoiding in mild to moderate impairment; avoid in severe impairment.

**Dose adjustments**  
Manufacturer advises dose reduction in mild to moderate impairment, if used.

**RENAL IMPAIRMENT**  
Reduce dose or avoid dihydrocodeine; increased and prolonged effect; increased cerebral sensitivity.

**PRESCRIBING AND DISPENSING INFORMATION**  
The MHRA advises when prescribing dihydrocodeine with paracetamol, the tablet strength and dose must be clearly indicated; when dispensing dihydrocodeine with paracetamol, ensure the prescribed strength is supplied—contact the prescriber if in doubt.

The BP defines Co-dyramol Tablets as containing dihydrocodeine tartrate 10 mg and paracetamol 500 mg.

**LESS SUITABLE FOR PRESCRIBING**  
Dihydrocodeine with paracetamol is less suitable for prescribing.

**MEDICINAL FORMS**  
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrocodeine with paracetamol (Co-Dyramol)</td>
<td>PRESCRIBE AND DISPENSE BY STRENGTH TO MINIMISE RISK OF MEDICATION ERROR (JANUARY 2018)</td>
</tr>
</tbody>
</table>

**CAUTIONARY AND ADVISORY LABELS 2, 29, 30**

**Dihydrocodeine with paracetamol (Non-proprietary)  
Dihydrocodeine tartrate 10 mg, Paracetamol 500 mg**  

- **Dihydrocodeine 10mg/500mg tablets**  
  - 30 tablet (PS) £0.68 DT = £0.79 (CT) | 100 tablet (PS) £1.48 DT = £2.63 (CT) | 112 tablet (PS) £1.13 (CT)  
  - Co-dyramol 10mg/500mg tablets | 30 tablet (PS) £0.68 DT = £0.79 (CT) | 100 tablet (PS) £1.48 DT = £2.63 (CT)  
  - Co-dyramol 20mg/500mg tablets | 56 tablet (PS) £5.57–£5.87 (CT) | 112 tablet (PS) £11.13 (CT)  

**Dihydrocodeine tartrate 20 mg, Paracetamol 500 mg**  

- **Dihydrocodeine tartrate 20mg/500mg tablets**  
  - 56 tablet (PS) £6.82 DT = £6.82 (CT)  
  - Erosot (M & A Pharmachen Ltd)  
    - **Dihydrocodeine 20mg/500mg tablets**  
      - 100 tablet (PS) £0.68 DT = £0.79 (CT) | 112 tablet (PS) £1.13 (CT) | 12 tablet (PS) £2.26 (CT) | 32 tablet (PS) £4.52 (CT)  
  - Paramol (SSL International Plc)  
    - **Dihydrocodeine 20mg/500mg tablets**  
      - 12 tablet (PS) £2.26 (CT) | 24 tablet (PS) £3.88 (CT) | 32 tablet (PS) £4.52 (CT)  
  - Remedene (Crescent Pharma Ltd)  
    - **Dihydrocodeine 20mg/500mg tablets**  
      - 56 tablet (PS) £5.87 (CT) | 112 tablet (PS) £11.13 (CT) | 56 tablet (PS) £6.82 DT = £6.82 (CT)  

**Dihydrocodeine tartrate 30 mg, Paracetamol 500 mg**  

- **Erosot (M & A Pharmachen Ltd)**  
  - **Dihydrocodeine 30mg/500mg tablets**  
    - 56 tablet (PS) £6.82 DT = £6.82 (CT)  
  - **Erosot (M & A Pharmachen Ltd)**  
  - **Dihydrocodeine 30mg/500mg tablets**  
    - 56 tablet (PS) £6.82 DT = £6.82 (CT)  
  - **Erosot (M & A Pharmachen Ltd)**  
  - **Dihydrocodeine 30mg/500mg tablets**  
    - 112 tablet (PS) £11.13 (CT) | 56 tablet (PS) £6.82 DT = £6.82 (CT) | 56 tablet (PS) £6.82 DT = £6.82 (CT)  

**Dipipanone hydrochloride with cyclizine**

**INDICATIONS AND DOSE**

**Acute pain**  
**BY MOUTH**  
Adult: Initially 1 tablet every 6 hours, then increased if necessary up to 3 tablets every 6 hours, dose to be increased gradually

**CAUTIONS**  
Diabetes mellitus - palliative care (not recommended) - phaeochromocytoma

**INTERACTIONS**  
Appendix 1: antihistamines, sedating - opioids

**SIDE-EFFECTS**  

www.getintopharma.com
Fentanyl

**INDICATIONS AND DOSE**

**Chronic intractable pain not currently treated with a strong opioid analgesic**

- **BY TRANSDERMAL APPLICATION**
  - **Child 16-17 years:** Initially 12 micrograms/hour every 72 hours, alternatively initially 25 micrograms/hour every 72 hours, when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application, dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually)
  - **Adult:** Initially 12 micrograms/hour every 72 hours, alternatively initially 25 micrograms/hour every 72 hours, when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application, dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually)

**Chronic intractable pain currently treated with a strong opioid analgesic**

- **BY TRANSDERMAL APPLICATION**
  - **Child 2-17 years:** Initial dose based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see under Chronic intractable pain not currently treated with a strong opioid analgesic, for conversion from long term oral morphine to transdermal fentanyl, see Pain management with opioids under Prescribing in palliative care p. 25.
  - **Adult:** Initial dose based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see under Chronic intractable pain not currently treated with a strong opioid analgesic, for conversion from long term oral morphine to transdermal fentanyl, see Pain management with opioids under Prescribing in palliative care p. 25.

**DOSE EQUIVALENCE AND CONVERSION**

- Fentanyl films are not bioequivalent to other fentanyl preparations.
- Fentanyl preparations for the treatment of breakthrough pain are not interchangeable; if patients...
are switched from another fentanyl-containing preparation, a new dose titration is required.

DOSES AT EXTREMES OF BODY-WEIGHT
- To avoid excessive dosage in obese patients, weight-based doses may need to be calculated on the basis of ideal bodyweight.

ABSTRAL®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY MOUTH USING SUBLINGUAL TABLETS
  - Adult: Initially 100 micrograms, then 100 micrograms after 15–30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units 15–30 minutes apart, for each pain episode; max. 800 micrograms per episode of breakthrough pain; leave at least 2 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

EFFENTORA®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY MOUTH USING BUCAL TABLET
  - Adult: Initially 100 micrograms, then 100 micrograms after 30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units for each pain episode; max. 800 micrograms per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain during titration

INSTANYL®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY INTRANASAL ADMINISTRATION
  - Adult: Initially 50 micrograms, dose to be administered into one nostril, then 50 micrograms after 10 minutes if required, dose to be adjusted according to response, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

PECEFENT®
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain
- BY INTRANASAL ADMINISTRATION
  - Adult: Initially 100 micrograms, adjusted according to response, dose to be administered into one nostril only, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: TRANSDERMAL FENTANYL PATCHES: LIFE-THREATENING AND FATAL OPIOID TOXICITY FROM ACCIDENTAL EXPOSURE, PARTICULARLY IN CHILDREN (OCTOBER 2018)
Accidental exposure to transdermal fentanyl can occur if a patch is swallowed or transferred to another individual. Always fully inform patients and their carers about directions for safe use of fentanyl patches, including the importance of:
- not exceeding the prescribed dose;
- following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application;
- not cutting patches and avoiding exposure of patches to heat including via hot water;
- ensuring that old patches are removed before applying a new one;

- following instructions for safe storage and properly disposing of used patches or those which are not needed.

Patients and carers should be advised to seek immediate medical attention if overdose is suspected—see Side-effects and Patient and carer advice for further information.

- CAUTIONS
  - GENERAL CAUTIONS
    - Cerebral tumour - diabetes mellitus (with Actiq® and Cynril® lozenges) - impaired consciousness
  - SPECIFIC CAUTIONS
    - With buccal use mucusitis—absorption from oral preparations may be increased, caution during dose titration (in adults)

- CAUTIONS, FURTHER INFORMATION
  - With transdermal use Transdermal fentanyl patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients.
  - With intravenous use Repeated intra-operative doses should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive.

- INTERACTIONS
  - Appendix 1: opioids

- SIDE-EFFECTS
  - Common or very common
    - With parenteral use Apnoea - hypertension - movement disorders - muscle rigidity - post procedural complications - respiratory disorders - vascular pain
    - With sublingual use Asthenia - dyspnoea - oral disorders
    - With transdermal use Anxiety - appetite decreased - asthena - depression - diarrhoea - dyspnoea - gastrointestinal discomfort - hypertension - insomnia - malaise - muscle complaints - peripheral oedema - sensation abnormal - temperature sensation altered - tremor
  - Uncommon
    - With parenteral use Airway complication of anaesthesia - chills - hiccup - hypothermia
    - With transdermal use Consciousness impaired - cyanosis - fever - gastrointestinal disorders - influenza like illness - memory loss - respiratory disorders - seizures - sexual dysfunction - vision blurred
  - Rare or very rare
    - With transdermal use Apnoea
  - Frequency not known
with intranasal use. Diarrhoea, epistaxis, fatigue, fever, hot flush, insomnia, malaise, motion sickness, myoclonus, nasal complaints, peripheral oedema, seizure, sensation abnormal, stomatitis, taste altered, throat irritation.

- With sublingual use. Addiction, consciousness impaired, diarrhoea, fall, fever, hot flush, peripheral oedema, seizure, withdrawal syndrome neonatal

- With transdermal use. Myoclonus, withdrawal syndrome neonatal

**SIDE-EFFECTS, FURTHER INFORMATION**

**Muscle rigidity**

Intravenous administration of fentanyl can cause muscle rigidity, which may involve the thoracic muscles. Manufacturer advises administration by slow intravenous injection to avoid; higher doses may require premedication with benzodiazepines and muscle relaxants.

**Transdermal use**

Monitor patients using patches for increased side-effects if fever is present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption).

**BREAST FEEDING**

- With buccal or intranasal use or sublingual use. Manufacturer advises avoid during treatment and for 5 days after last administration—present in milk.
- With intravenous use. Manufacturer advises avoid during treatment and for 24 hours after last administration—present in milk.
- With transdermal use. Manufacturer advises avoid during treatment and for 72 hours after removal of patch—present in milk.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution (risk of accumulation).

**Dose adjustments**

Manufacturer advises cautious dose titration.

**RENAL IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**DIRECTIONS FOR ADMINISTRATION**

- With transdermal use. For patches, apply to dry, non-irritated, non-irradiated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patch on a different area (avoid using the same area for several days).
- With intravenous use in adults. For intravenous infusion (Sublimaze), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%.
- With buccal use in adults. For buccal films, moisten mouth, place film on inner lining of cheek (pink side to cheek), hold for at least 5 seconds until it sticks, and leave to dissolve (15–30 minutes); if more than 1 film required do not overlap, but use another area of the mouth. Avoid liquids for 5 minutes after application; avoid food until the film has dissolved.
- With buccal use. Patients should be advised to place the lozenge in the mouth against the cheek and move it around the mouth using the applicator; each lozenge should be sucked over a 15 minute period. In patients with a dry mouth, water may be used to moisten the buccal mucosa. Patients with diabetes should be advised each lozenge contains approximately 2 g glucose.
- With buccal use. Patient should sit or stand during administration.

**EFFENTORA®**

Place tablet between cheek and gum and leave to dissolve; if more than 1 tablet required, place second tablet on the other side of the mouth; tablet may alternatively be placed under the tongue (sublingually).

**PRESCRIBING AND DISPENSING INFORMATION**

With transdermal use. Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write ‘(Fentanyl 25 micrograms per hour)’. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. ‘one patch to be applied every 72 hours’. The total quantity of patches to be supplied should be written in words and figures.

**PATIENT AND CARER ADVICE**

- With transdermal use. Patients and carers should be informed about safe use, including correct administration and disposal, strict adherence to dosage instructions, and the symptoms and signs of opioid overdose. Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or impaired speech, and patients and carers should seek prompt medical attention.
- In adults. Patients or carers should be given advice on how to administer fentanyl buccal films or fentanyl lozenges. Patients or carers should be given advice on how to administer fentanyl nasal spray.

**PNSCH**

Avoid concomitant use of other nasal preparations.

**INSTANYL®**

Avoid concomitant use of other nasal preparations.

**EFFENTORA®**

Patients or carers should be given advice on how to administer Effentora® buccal tablets.

Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed with a glass of water. Patients with a dry mouth should be advised to drink water to moisten the buccal mucosa before administration of the tablets; if appropriate, effervescence does not occur, a switch of therapy may be advised.

**ABSTAL®**

Patients should be advised not to eat or drink until the tablet is completely dissolved. In patients with a dry mouth, the buccal mucosa may be moistened with water before administration of tablet.

**NATIONAL FUNDING/ACCESS DECISIONS**

**PECFENT®**

The Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2008) that PecFent® nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**INSTANYL®**

The Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised that Instanyl® nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**EFFENTORA®**

The Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised that Effentora® buccal tablets should be restricted for the management of breakthrough pain in adult patients using

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opioid therapy for chronic cancer pain, when other short acting opioids are unsuitable.

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium has advised (January 2009) that Abstral® sublingual tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short acting opioids are unsuitable.

### Medicinal Forms

There can be variation in the licensing of different manufacturers using the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion

#### Solution for injection

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<thead>
<tr>
<th>Drug Name</th>
<th>Dose</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml</td>
<td>Fentanyl 100 micrograms/2ml solution for injection ampoules</td>
<td>10 ampoule (PK), £7.00–£14.33 DT = £14.32 (CD)</td>
</tr>
<tr>
<td>Fentanyl (as Fentanyl citrate) 100 microgram per 1 dose</td>
<td>Fentanyl 500 micrograms/1ml solution for injection ampoules</td>
<td>10 ampoule (PK), £15.60–£16.15 (CD)</td>
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#### Sublingual spray

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<th>Drug Name</th>
<th>Dose</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml</td>
<td>Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml</td>
<td>5 ampoule (PK), £6.25 (CD)</td>
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#### Buccal tablet

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<th>Dose</th>
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<tbody>
<tr>
<td>Fentanyl (as Fentanyl citrate) 100 microgram</td>
<td>Fentanyl (as Fentanyl citrate) 100 microgram</td>
<td>4 tablet (PK), £19.96 (CD)</td>
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<tr>
<td>Fentanyl (as Fentanyl citrate) 200 microgram</td>
<td>Fentanyl (as Fentanyl citrate) 200 microgram</td>
<td>4 tablet (PK), £19.96 (CD)</td>
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#### Solution for infusion

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<th>Drug Name</th>
<th>Dose</th>
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<tr>
<td>Fentanyl (as Fentanyl citrate) 50 microgram per 1 ml</td>
<td>Fentanyl 2.5mg/50ml solution for infusion vials</td>
<td>1 vial (PK), £5.50 (CD)</td>
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#### Sublingual tablet

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<th>Drug Name</th>
<th>Dose</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>Abstral (Kyowa Kirin Ltd)</td>
<td>Abstral 100 microgram</td>
<td>10 tablet (PK), £49.99 DT = £49.99 (CD) sugar-free</td>
</tr>
<tr>
<td>Fentanyl (as Fentanyl citrate) 200 microgram</td>
<td>Fentanyl 100 micrograms/2ml solution for injection ampoules</td>
<td>10 ampoule (PK), £49.99 (CD) sugar-free</td>
</tr>
<tr>
<td>Fentanyl (as Fentanyl citrate) 300 microgram</td>
<td>Fentanyl 100 micrograms/2ml solution for injection ampoules</td>
<td>10 ampoule (PK), £49.99 (CD) sugar-free</td>
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</table>

### Nervous System

#### Transderm patch

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<tr>
<th>Drug Name</th>
<th>Dose</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Abstral (Kyowa Kirin Ltd)</td>
<td>Abstral 100 microgram</td>
<td>10 patch (PK), £12.59 DT = £12.59 (CD)</td>
</tr>
<tr>
<td>Fentanyl 25 microgram per 1 hour</td>
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</table>
Hydromorphone hydrochloride

**INDICATIONS AND DOSE**

Severe pain in cancer

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain
  - Adult: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 12-17 years: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain
  - Adult: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain

**CONTRA-INDICATIONS**

- Acute abdomen
- Pancreatitis - toxic psychosis

**SIDE-EFFECTS**

- Common or very common Abdominal pain - anxiety - appetite decreased - asthenia - sleep disorders
- Uncommon Depression - diarrhoea - dyspnoea - erectile dysfunction - malaise - movement disorders - paraesthesia - peripheral oedema - taste altered - tremor
- Frequency not known Hyperalgesia - paralytic ileus - seizure - withdrawal syndrome neonatal

**BREAST FEEDING**

Avoid — no information available

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid

**RENAL IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs

**DIRECTIONS FOR ADMINISTRATION**

For immediate-release capsules, swallow whole capsule or sprinkle contents on soft food. For modified-release capsules, swallow whole or open capsule and sprinkle contents on soft cold food (swallow the pellets within the capsule whole; do not crush or chew).

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer hydromorphone hydrochloride capsules and modified-release capsules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS**

**462 Pain**

<table>
<thead>
<tr>
<th>Opioid (RX Farma)</th>
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<tr>
<td>Fentanyl 12 microgram per 1 hour transdermal patches</td>
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<tr>
<td>Fentanyl 100 microgram per 1 hour transdermal patches</td>
</tr>
</tbody>
</table>

**Lozenge**

**CAUTIONARY AND ADVISORY LABELS**

**Excipients:** May contain Propylene glycol

- **Fentanyl (as Fentanyl citrate) 200 microgram** Cynril 200microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
- **Fentanyl (as Fentanyl citrate) 400 microgram** Cynril 400microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
- **Fentanyl (as Fentanyl citrate) 600 microgram** Cynril 600microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
- **Actiq (Teva Ltd)**
  - **Fentanyl (as Fentanyl citrate) 200 microgram** Actiq 200microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
  - **Fentanyl (as Fentanyl citrate) 400 microgram** Actiq 400microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
  - **Fentanyl (as Fentanyl citrate) 600 microgram** Actiq 600microgram lozenges with integral oromucosal applicator | 3 lozenge (Pkt) £21.05 DT + £21.05 (CD) | 30 lozenge (Pkt) £210.41 DT + £210.41 (CD)
**Meptazinol**

**INDICATIONS AND DOSE**

Moderate to severe pain, including post-operative pain and renal colic

- **BY MOUTH**
  - Adult: 200 mg every 3–6 hours as required
  - Adult: 75–100 mg every 2–4 hours if required
  - Adult: 50–100 mg every 2–4 hours if required

**Contra-indications**

- Myocardial infarction - phaeochromocytoma

**INTERACTIONS** → Appendix 1: opioids

**SIDE-EFFECTS**

- Common or very common Diarrhoea, gastrointestinal discomfort

**Overdose**

Effects only partially reversed by naloxone.

**Contraindications**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Meptid (Almirall Ltd)**
  - Meptazinol (as Meptazinol hydrochloride) 100 mg per 1 ml Meptid 100mg/1ml solution for injection ampoules | 10 ampoule<br> 15.21
  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 2
    - **Meptid (Almirall Ltd)**
      - Meptazinol (as Meptazinol hydrochloride) 200 mg Meptid 200mg tablets | 112 tablet 15.11 DT = 15.11

**Morphine**

**INDICATIONS AND DOSE**

**Pain**

- **BY SUBCUTANEOUS INJECTION**
  - Child 1 year: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response
  - Child 6 months-1 year: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response

- **BY MOUTH**
  - Adult: 200 mg every 3–6 hours as required
  - Adult: 75–100 mg every 2–4 hours if required
  - Adult: 50–100 mg every 2–4 hours if required

- **CONTRA-INDICATIONS**
  - Myocardial infarction - phaeochromocytoma

- **INTERACTIONS** → Appendix 1: opioids

- **SIDE-EFFECTS**
  - Common or very common Diarrhoea, gastrointestinal discomfort

- **Overdose**
  - Effects only partially reversed by naloxone.

- **Contraindications**
  - Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Meptid (Almirall Ltd)**
  - Meptazinol (as Meptazinol hydrochloride) 100 mg per 1 ml Meptid 100mg/1ml solution for injection ampoules | 10 ampoule<br> 15.21

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 2
  - **Meptid (Almirall Ltd)**
    - Meptazinol (as Meptazinol hydrochloride) 200 mg Meptid 200mg tablets | 112 tablet 15.11 DT = 15.11

**Pain**

- **Child 6 months-11 years:** 100 micrograms/kg every 4 hours, adjusted according to response, dose to be administered over at least 5 minutes, alternatively (by intravenous injection) initially 100 micrograms/kg, dose to be administered over at least 5 minutes, followed by (by continuous intravenous infusion) 20–30 micrograms/kg/hour, adjusted according to response
  - Child 12-17 years: 5 mg every 4 hours, adjusted according to response, dose to be administered over at least 5 minutes, alternatively (by intravenous injection) initially 5 mg, dose to be administered over at least 5 minutes, followed by (by continuous intravenous infusion) 20–30 micrograms/kg/hour, adjusted according to response

  - **By mouth, or by rectum**
    - Child 1 year: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response
    - Child 3–5 years: 100–150 micrograms/kg every 4 hours, adjusted according to response
    - Child 6–11 years: 200 micrograms/kg every 4 hours, adjusted according to response
    - Child 12–17 years: Initially 5–10 mg every 4 hours, adjusted according to response

**Acute pain**

- **By mouth, or by subcutaneous injection, or by intramuscular injection**
  - Adult: Initially 10 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration, use dose for elderly in frail patients
  - Elderly: Initially 5 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration

- **By slow intravenous injection**
  - Adult: Initially 5 mg every 4 hours, adjusted according to response, dose can be adjusted more frequently during titration, reduced dose recommended in frail and elderly patients

**Chronic pain**

- **By mouth, or by subcutaneous injection, or by intramuscular injection**
  - Adult: Initially 5–10 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients
  - Adult: Initially 50–100 micrograms/kg every 4 hours, adjusted according to response

**Pain (with modified-release 12-hourly preparations)**

- **By mouth using modified-release medicines**
  - Adult: Every 12 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered

**Pain (with modified-release 24-hourly preparations)**

- **By mouth using modified-release medicines**
  - Adult: Every 24 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered

**Pain management in palliative care (starting dose for opioid-naive patients)**

- **By mouth**
  - Adult: 20–30 mg daily in divided doses, using immediate-release preparation 4-hourly or a 12-hourly modified-release preparation, for
management of breakthrough pain and other general advice, see Pain management with opioids under Prescribing in palliative care p. 25.

Pain management in palliative care (starting dose for patients being switched from a regular weak opioid)

- **BY MOUTH**
  - Adult: 40–60 mg daily in divided doses, using immediate-release preparation 4-hourly or 12-hourly modified-release preparation, for management of breakthrough pain and other general advice, see Pain management with opioids under Prescribing in palliative care p. 25.

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: Usual dose 100 mg every 12 hours; up to 600 mg every 12 hours, higher dose may be required for some patients (occasionally more is needed); for management of breakthrough pain and other general advice, see Pain management with opioids under Prescribing in palliative care p. 25.

**Cough in palliative care**
- **BY MOUTH**
  - Adult: Initially 5 mg every 4 hours

**Premedication**
- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: Up to 10 mg, dose to be administered 60–90 minutes before operation

**Patient controlled analgesia (PCA)**
- **BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

**Myocardial infarction**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, followed by 5–10 mg if required, dose to be administered at a rate of 1–2 mg/minute, use dose for elderly in frail patients
  - Elderly: 2.5–5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Acute pulmonary oedema**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 5–10 mg, dose to be administered at a rate of 2 mg/minute, use dose for elderly in frail patients
  - Elderly: 2.5–5 mg, dose to be administered at a rate of 2 mg/minute

**Dyspnoea at rest in palliative care**
- **BY MOUTH**
  - Adult: Initially 5 mg every 4 hours, to be given in carefully titrated doses

**DOSE EQUIVALENCE AND CONVERSION**
- The doses stated refer equally to morphine hydrochloride and sulfate.

- With rectal use in children Suppositories are not licensed for use in children.

**IMPORTANT SAFETY INFORMATION**
Do not confuse modified-release 12-hourly preparations with 24-hourly preparations, see Prescribing and dispensing information.

- **CONTRA-INDICATIONS** Acute abdomen · delayed gastric emptying · heart failure secondary to chronic lung disease · phaeochromocytoma

- **CAUTIONS** Cardiac arrhythmias · pancreatitis · severe cor pulmonale

- **INTERACTIONS** → Appendix 1: opioids

- **SIDE-EFFECTS**
  - Common or very common
  - With oral use Appetite decreased · asthenic conditions · gastrointestinal discomfort · insomnia · neuromuscular dysfunction
  - Uncommon
  - With oral use Agitation · bronchospasm · ileus · mood altered · myoclonus · peripheral oedema · pulmonary oedema · seizure · sensation abnormal · syncope · taste altered

- **Frequency not known**
  - With oral use Amenorrhoea · biliary pain · cough decreased · hyperalgesia · hypertension · pancreatitis exacerbated · sexual dysfunction · thinking abnormal · ureteral spasm
  - With parenteral use Alertness decreased · bile duct disorders · mood altered · myoclonus · sexual dysfunction · ureteral spasm · urinary disorders · vision disorders

- **BREAST FEEDING** Therapeutic doses unlikely to affect infant.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
  - Avoid oral preparations in acute impairment; for injectable preparations—consult product literature.

- **DOSE ADJUSTMENTS** Manufacturer advises consider dose reduction—consult product literature.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged; increased cerebral sensitivity.

- **MONITORING REQUIREMENTS** Possible association between acute chest syndrome in patients with sickle cell disease treated with morphine during a vaso-occlusive crisis—manufacturer advises close monitoring for acute chest syndrome symptoms during treatment.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children For continuous intravenous infusion, dilute with Glucose 5% or 10% or Sodium Chloride 0.9%.
  - With oral use For modified release capsules—swallow whole or open capsule and sprinkle contents on soft food.

**PRESCRIBING AND DISPENSING INFORMATION**
Modified-release preparations are available as 12-hourly or 24-hourly formulations; prescribers must ensure that the correct preparation is prescribed. Preparations that should be given 12-hourly include Filmarine® SR, MST Continus®, Morphgesic® SR and Zomorph®. Preparations that should be given 24-hourly include MXL®.

Prescriptions must specify the ‘form’.

- With rectal use Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber.

**Palliative care** For further information on the use of morphine in palliative care, see www.medicinescomplete.com/#/content/palliative/morphine.

**PATIENT AND CARER ADVICE**
- With oral use Patients or carers should be given advice on how to administer morphine modified-release capsules.
Medicines for Children leaflet: Morphine for pain
www.medicinesforchildren.org.uk/morphine-pain

EXCEPTIONS TO LEGAL CATEGORY
Morphine Oral Solutions Prescription-only medicines or schedule 2 controlled drug. The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes a schedule 2 controlled drug. It is usual to adjust the strength so that the dose volume is 5 or 10 mL. Oral solutions of morphine can be prescribed by writing the formula:
Morphine hydrochloride 5 mg
Chloroform water to 5 mL.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from specialist-order manufacturers include: capsule, oral solution, solution for injection, infusion, solution for infusion, suppository

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 2, 25
- MST Continus (Napp Pharmaceuticals Ltd) Morphine sulfate 5 mg MST Continus 5mg tablets | 60 tablet [Pharm £13.29 DT = £3.92 (C02)] Morphine sulfate 10 mg MST Continus 10mg tablets | 60 tablet [Pharm £15.20 DT = £5.05 (C02)] Morphine sulfate 15 mg MST Continus 15mg tablets | 60 tablet [Pharm £19.10 DT = £6.01 (C02)] Morphine sulfate 30 mg MST Continus 30mg tablets | 60 tablet [Pharm £22.47 DT = £7.13 (C02)] Morphine sulfate 60 mg MST Continus 60mg tablets | 60 tablet [Pharm £43.80 DT = £13.05 (C02)] Morphine sulfate 100 mg MST Continus 100mg tablets | 60 tablet [Pharm £106.80 DT = £31.55 (C02)]

Morphine sulphate SR (Advanz Pharma) Morphine sulfate 10 mg Morphine SR 10mg tablets | 60 tablet [Pharm £3.85 DT = £5.42 (C02)] Morphine sulfate 30 mg Morphine SR 30mg tablets | 60 tablet [Pharm £9.24 DT = £11.47 (C02)] Morphine sulfate 60 mg Morphine SR 60mg tablets | 60 tablet [Pharm £18.04 DT = £27.33 (C02)] Morphine sulfate 100 mg Morphine SR 100mg tablets | 60 tablet [Pharm £39.34 DT = £33.30 (C02)]

Tablet
CAUTIONARY AND ADVISORY LABELS 2
- Sevedrol (Napp Pharmaceuticals Ltd) Morphine sulfate 10 mg Sevedrol 10mg tablets | 56 tablet [Pharm £5.31 DT = £5.31 (C02)] Morphine sulfate 20 mg Sevedrol 20mg tablets | 56 tablet [Pharm £10.61 DT = £10.61 (C02)] Morphine sulfate 50 mg Sevedrol 50mg tablets | 56 tablet [Pharm £16.02 DT = £16.02 (C02)]

Suppository
CAUTIONARY AND ADVISORY LABELS 2
- Morphine (Non-proprietary) Morphine sulfate 10 mg Morphine sulfate 10mg suppositories | 12 suppository [Pharm £13.45 DT = £13.45 (C02)]

Solution for injection
- Morphine (Non-proprietary) Morphine sulfate 1 mg per 1 ml Morphine sulfate 5mg/5ml solution for injection ampoules | 10 ampoule [Pharm £4.00 DT = £4.00 (C02)] Morphine sulfate 1mg/1ml solution for injection ampoules | 10 ampoule [Pharm £3.10 DT = £3.10 (C02)] Morphine sulfate 10mg/10ml solution for injection ampoules | 10 ampoule [Pharm £11.00 DT = £11.00 (C02)] Morphine sulfate 10 mg per 1 ml Morphine sulfate 10mg/1ml solution for injection ampoules | 10 ampoule [Pharm £12.96 DT = £12.96 (C02)] Morphine sulfate 15 mg per 1 ml Morphine sulfate 15mg/1ml solution for injection ampoules | 10 ampoule [Pharm £15.00 DT = £15.00 (C02)] Morphine sulfate 20 mg per 1 ml Morphine sulfate 20mg/1ml solution for injection ampoules | 10 ampoule [Pharm £18.03 DT = £18.03 (C02)]

Morphine sulfate 30 mg per 1 ml Morphine sulfate 30mg/1ml solution for injection ampoules | 10 ampoule [Pharm £14.02 DT = £14.02 (C02)] Morphine sulfate 60 mg/2ml solution for injection ampoules | 5 ampoule [Pharm £10.07 DT = £10.07 (C02)]

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 2
- MXL (Napp Pharmaceuticals Ltd) Morphine sulfate 30 mg MXL 30mg capsules | 28 capsule [Pharm £10.91 (C02)] Morphine sulfate 60 mg MXL 60mg capsules | 28 capsule [Pharm £14.95 (C02)] Morphine sulfate 90 mg MXL 90mg capsules | 28 capsule [Pharm £22.04 DT = £22.04 (C02)] Morphine sulfate 120 mg MXL 120mg capsules | 28 capsule [Pharm £29.15 DT = £29.15 (C02)] Morphine sulfate 150 mg MXL 150mg capsules | 28 capsule [Pharm £36.43 DT = £36.43 (C02)] Morphine sulfate 200 mg MXL 200mg capsules | 28 capsule [Pharm £46.15 (C02)]
- Zomorph (Ethypharm UK Ltd) Morphine sulfate 10 mg Zomorph 10mg modified-release capsules | 60 capsule [Pharm £3.47 DT = £3.47 (C02)] Morphine sulfate 30 mg Zomorph 30mg modified-release capsules | 60 capsule [Pharm £6.30 DT = £6.30 (C02)] Morphine sulfate 60 mg Zomorph 60mg modified-release capsules | 60 capsule [Pharm £16.20 DT = £16.20 (C02)]

Morphine sulfate 100 mg Zomorph 100mg modified-release capsules | 60 capsule [Pharm £21.80 DT = £21.80 (C02)] Morphine sulfate 200 mg Zomorph 200mg modified-release capsules | 60 capsule [Pharm £43.60 DT = £43.60 (C02)]

Solution for infusion
- Morphine (Non-proprietary) Morphine sulfate 1 mg per 1 ml Morphine sulfate 50mg/50ml solution for infusion vials | 1 vial [Pharm £15.00 DT = £15.00 (C02)] Morphine sulfate 2 mg per 1 ml Morphine sulfate 100mg/50ml solution for infusion vials | 1 vial [Pharm £36.40 DT = £36.40 (C02)]

Oral solution
CAUTIONARY AND ADVISORY LABELS 2
- Morphine (Non-proprietary) Morphine sulfate 2 mg per 1 ml Morphine sulfate 10mg/5ml oral solution | 100 ml [Pharm £1.69 (C02)] | 300 ml [Pharm £6.54 DT = £6.54 (C02)] Morphine sulfate 4 mg per 1 ml Morphine sulfate 20mg/5ml oral solution | 100 ml [Pharm £1.69 (C02)] | 300 ml [Pharm £6.54 DT = £6.54 (C02)]

Oramorph (Boehringer Ingelheim Ltd) Oramorph 2 mg per 1 ml Oramorph 20mg/ml oral solution | 100 ml [Pharm £1.80 (C02)] | 300 ml [Pharm £5.45 DT = £5.45 (C02)] | 500 ml [Pharm £8.50 (C02)]

Morphine sulfate 20 mg per 1 ml Oramorph 20mg/ml concentrated oral solution sugar-free | 120 ml [Pharm £19.50 DT = £19.50 (C02)]

Modified-release granules
CAUTIONARY AND ADVISORY LABELS 2, 13
- MST Continus (Napp Pharmaceuticals Ltd) Morphine sulfate 20 mg MST Continus suspension 20mg granules packets sugar-free | 30 sachet [Pharm £24.58 DT = £24.58 (C02)] Morphine sulfate 30 mg MST Continus suspension 30mg granules packets sugar-free | 30 sachet [Pharm £25.54 (C02)] Morphine sulfate 60 mg MST Continus suspension 60mg granules packets sugar-free | 30 sachet [Pharm £51.09 DT = £51.09 (C02)]

Morphine sulfate 100 mg MST Continus suspension 100mg granules packets sugar-free | 30 sachet [Pharm £85.15 DT = £85.15 (C02)]
- Morphine 200 mg MST Continus suspension 200mg granules packets sugar-free | 30 sachet [Pharm £170.30 DT = £170.30 (C02)]
Morphine with cyclizine

The properties listed below are those particular to the combination only. For the properties of the components please consider, morphine p. 463, cyclizine p. 430.

**INDICATIONS AND DOSE**

**CYCLIMORPH-10®**

- Moderate to severe pain (short-term use only)
  - By subcutaneous injection, or by intramuscular injection, or by intravenous injection
  - Adult: 1 mL, do not repeat dose more often than every 4 hours; maximum 3 doses per day

**CYCLIMORPH-15®**

- Moderate to severe pain (short-term use only)
  - By subcutaneous injection, or by intramuscular injection, or by intravenous injection
  - Adult: 1 mL, do not repeat dose more often than every 4 hours; maximum 3 doses per day

**CAUTIONS**

- Myocardial infarction (cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids) - not recommended in palliative care

**INTERACTIONS** → Appendix 1: antihistamines, sedating opioids

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Cyclimorph** (Advanz Pharma)
  - Morphine tartrate 15 mg per 1 mL, Cyclizine tartrate 50 mg per 1 mL Cyclimorph 15 solution for injection 1 mL ampoules | 5 ampoule | £9.12(10)
  - Morphine tartrate 10 mg per 1 mL, Cyclizine tartrate 50 mg per 1 mL Cyclimorph 10 solution for injection 1 mL ampoules | 5 ampoule | £8.77(10)

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**Oxycodone hydrochloride**

**INDICATIONS AND DOSE**

**Postoperative pain | Severe pain**

- By mouth using immediate-release medicines
  - Adult: Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day

- By mouth using modified-release medicines
  - Adult: Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose, use 12-hourly modified-release preparations for this dose; see Prescribing and dispensing information

- By slow intravenous injection
  - Adult: 1–10 mg every 4 hours as required

- By intravenous infusion
  - Adult: Initially 2 mg/hour, adjusted according to response

- By subcutaneous injection
  - Adult: Initially 5 mg every 4 hours as required

- By intravenous infusion
  - Adult: Initially 7.5 mg/24 hours, adjusted according to response

**Patient controlled analgesia (PCA)**

- By intravenous infusion
  - Adult: (consult local protocol)

**Moderate to severe pain in palliative care**

- By mouth using immediate-release medicines
  - Adult: Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain,
**PRESCRIBING AND DISPENSING INFORMATION**

Modified-release preparations are available as 12-hourly or 24-hourly formulations. Preparations that should be given 12-hourly include Abtard®, Carexil®, Ixyldone®, Leveraxo®, Longtec®, Oxeltra®, OxyCon®in, Oxynorm®, Oxylan®, Reltebon®, and Rencon®. Preparations that should be given 24-hourly include Onevita® XL.

**BREAST FEEDING**

With parenteral use:
- Max. initial dose:
- Dose adjustments:
- Avoid if eGFR less than 10 mL/minute/1.73 m².
- Max. initial dose 2.5 mg every 6 hours in patients not currently treated with an opioid with mild to moderate impairment.

**PAIN**

Pain severity can be classified as mild, moderate, or severe. Pain severity is determined by the pain intensity, duration, and impact on daily activities.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special order manufacturers include: oral solution, solution for infusion.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (October 2004 and November 2010) that OxyNorm® injection is restricted for use within NHS Scotland for patients with cancer who have difficulty in tolerating morphine or diamorphine.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use
- With intravenous infusion (Oxynorm®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of 1 mg/mL.

**PRESCRIBING AND DISPENSING INFORMATION**

- Modified-release preparations are available as 12-hourly or 24-hourly formulations. Preparations that should be given 12-hourly include Abtard®, Carexil®, Ixyldone®, Leveraxo®, Longtec®, Oxeltra®, OxyCon®, Oxynorm®, Oxylan®, Reltebon®, and Rencon®. Preparations that should be given 24-hourly include Onevita® XL.
- Palliative care: For further information on the use of oxycodone in palliative care, see www.medicinescomplete.com/#/content/palliative/oxycodone.
- Longtec® (Odem Pharmaceuticals Ltd)
- Oxeltra® (Oxeltra Ltd)
- Onevita® XL (Aspire Pharma Ltd)
- OxyCon®in (Nap Pharmaceuticals Ltd)
- Ixyldone® (Morningside Healthcare Ltd)
- Leveraxo® (Mylan)
- Carexil® (Sandoz Ltd)
- Carexil® (Sanofi-Aventis)
- Oxeltra® (Oxeltra UK Ltd)
- Oxylan® (Oxylan Medical Ltd)
- Reltebon® (Reltebon Medical Ltd)
- Oxynorm® (Oxynorm Medical Ltd)
- OxyCon®in (Nap Pharmaceuticals Ltd)
- Ixyldone® (Morningside Healthcare Ltd)
- Oxeltra® (Oxeltra Ltd)
- Onevita® XL (Aspire Pharma Ltd)
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- Carexil® (Sanofi-Aventis)
- Oxeltra® (Oxeltra UK Ltd)
- Oxylan® (Oxylan Medical Ltd)
- Reltebon® (Reltebon Medical Ltd)
- Oxynorm® (Oxynorm Medical Ltd)
- OxyCon®in (Nap Pharmaceuticals Ltd)
- Ixyldone® (Morningside Healthcare Ltd)
- Oxeltra® (Oxeltra Ltd)
- Onevita® XL (Aspire Pharma Ltd)
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- Carexil® (Sanofi-Aventis)
- Oxeltra® (Oxeltra UK Ltd)
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- Oxeltra® (Oxeltra UK Ltd)
- Oxylan® (Oxylan Medical Ltd)
- Reltebon® (Reltebon Medical Ltd)
- Oxynorm® (Oxynorm Medical Ltd)
- OxyCon®in (Nap Pharmaceuticals Ltd)
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### Solution for injection

- **Oxycodone hydrochloride (Non-proprietary)**
  - **Oxycodone hydrochloride 10 mg per 1 ml** Oxycodone 20mg/2ml solution for injection ampoules | 5 ampoule (Pb) £16.00 DT + £16.00 DT | 10 ampoule (Pb) £30.00 DT
  - **Oxycodone hydrochloride 15 mg per 1 ml** Oxycodone 30mg/3ml solution for injection ampoules | 5 ampoule (Pb) £18.00 DT + £18.00 DT | 10 ampoule (Pb) £36.00 DT
  - **Oxycodone hydrochloride 20 mg per 1 ml** Oxycodone 40mg/4ml solution for injection ampoules | 5 ampoule (Pb) £20.00 DT + £20.00 DT | 10 ampoule (Pb) £40.00 DT
  - **Oxycodone hydrochloride 30 mg per 1 ml** Oxycodone 60mg/6ml solution for injection ampoules | 5 ampoule (Pb) £32.00 DT + £32.00 DT | 10 ampoule (Pb) £64.00 DT
  - **Oxycodone hydrochloride 40 mg per 1 ml** Oxycodone 80mg/8ml solution for injection ampoules | 5 ampoule (Pb) £44.00 DT + £44.00 DT | 10 ampoule (Pb) £88.00 DT

- **Oxycodone hydrochloride 10 mg per 1 ml** Oxycodone 20mg/2ml solution for injection ampoules | 5 ampoule (Pb) £16.00 DT + £16.00 DT | 10 ampoule (Pb) £30.00 DT
  - **Oxycodone hydrochloride 15 mg per 1 ml** Oxycodone 30mg/3ml solution for injection ampoules | 5 ampoule (Pb) £18.00 DT + £18.00 DT | 10 ampoule (Pb) £36.00 DT
  - **Oxycodone hydrochloride 20 mg per 1 ml** Oxycodone 40mg/4ml solution for injection ampoules | 5 ampoule (Pb) £20.00 DT + £20.00 DT | 10 ampoule (Pb) £40.00 DT
  - **Oxycodone hydrochloride 30 mg per 1 ml** Oxycodone 60mg/6ml solution for injection ampoules | 5 ampoule (Pb) £32.00 DT + £32.00 DT | 10 ampoule (Pb) £64.00 DT
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  - **Oxycodone hydrochloride 40 mg per 1 ml** Oxycodone 80mg/8ml solution for injection ampoules | 5 ampoule (Pb) £44.00 DT + £44.00 DT | 10 ampoule (Pb) £88.00 DT

### Oral solution

#### CAUTIONARY AND ADVISORY LABELS 2

- **Oxycodone hydrochloride (Non-proprietary)**
  - **Oxycodone hydrochloride 1 mg per 1 ml** Oxycodone 5mg/5ml oral solution sugar free sugar-free | 250 ml (Pb) £3.91 DT + £3.91 DT
  - **Oxycodone hydrochloride 10 mg per 1 ml** Oxycodone 10mg/ml oral solution sugar free sugar-free | 120 ml (Pb) £4.63 DT + £4.63 DT

- **Oxycodone hydrochloride 1 mg per 1 ml** Oxycodone 5mg/5ml oral solution sugar free sugar-free | 250 ml (Pb) £3.91 DT + £3.91 DT

- **Oxycodone hydrochloride 10 mg per 1 ml** Oxycodone 10mg/ml oral concentrate oral solution sugar-free | 120 ml (Pb) £4.63 DT + £4.63 DT

- **Oxycodone hydrochloride 1 mg per 1 ml** Shortec liquid 5mg/5ml oral solution sugar-free | 250 ml (Pb) £3.91 DT + £3.91 DT

### Capsule

#### CAUTIONARY AND ADVISORY LABELS 2

- **Lynlor (Actavis UK Ltd)**
  - **Oxycodone hydrochloride 5 mg** Lynlor 5mg capsules | 56 capsule (Pb) £6.86 DT + £11.43 DT
  - **Oxycodone hydrochloride 10 mg** Lynlor 10mg capsules | 56 capsule (Pb) £11.72 DT + £22.86 DT

- **Oxycodone hydrochloride 5 mg** Oxycodone 5mg capsules | 56 capsule (Pb) £6.86 DT + £11.43 DT
  - **Oxycodone hydrochloride 10 mg** Oxycodone 10mg capsules | 56 capsule (Pb) £11.72 DT + £22.86 DT

- **Oxycodone hydrochloride 5 mg** Shortec 5mg capsules | 56 capsule (Pb) £6.86 DT + £11.43 DT
  - **Oxycodone hydrochloride 10 mg** Shortec 10mg capsules | 56 capsule (Pb) £11.72 DT + £22.86 DT

- **Oxycodone hydrochloride 5 mg** Shortec 5mg capsules | 56 capsule (Pb) £6.86 DT + £11.43 DT
  - **Oxycodone hydrochloride 10 mg** Shortec 10mg capsules | 56 capsule (Pb) £11.72 DT + £22.86 DT
Oxycodone with naloxone

The properties listed below are those particular to the combination only. For the properties of the components please consider, oxycodone hydrochloride p. 466, naloxone hydrochloride p. 1369.

- **INDICATIONS AND DOSE**
  
  **Severe pain requiring opioid analgesia in patients not currently treated with opioid analgesics**
  
  - **BY MOUTH**
    - Adult: Initially 10/5 mg every 12 hours (max. per dose 40/20 mg every 12 hours), dose to be increased according to response; patients already receiving opioid analgesics can start with a higher dose.
  
  **Second-line treatment of symptomatic severe to very severe idiopathic restless legs syndrome after failure of dopamine therapy**
  
  - **BY MOUTH**
    - Adult: Initially 5/2.5 mg every 12 hours, adjusted weekly according to response, usual dose 10/5 mg every 12 hours; maximum 60/30 mg per day.

- **DOSE EQUIVALENCE AND CONVERSION**
  
  Dose quantities are expressed in the form x/y where x and y are the strengths in milligrams of oxycodone and naloxone respectively.

- **INTERACTIONS** → Appendix 1: opioids

- **MEDIcINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension.

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS** 2, 25

- Targinact (Napp Pharmaceuticals Ltd)

<table>
<thead>
<tr>
<th>Oxycodone with naloxone</th>
<th>Naloxone</th>
<th><strong>Dose</strong></th>
<th><strong>Children</strong></th>
<th><strong>Adult</strong></th>
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<tr>
<td>5 mg Targinact 5mg/2.5mg modified-release tablets</td>
<td>25</td>
<td>£21.16 DT + £21.16 (C2)</td>
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</table>

Papaveretum

- **INDICATIONS AND DOSE**

  **Postoperative analgesia | Severe chronic pain**
  
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Adult: 7.7–15.4 mg every 4 hours if required
    - Elderly: Initially 7.7 mg every 4 hours if required
  
  - **BY INTRAVENOUS INJECTION**
    - Adult: Use 25 to 50% of the corresponding subcutaneous/intramuscular dose.

- **PREMEDICATION**

  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Adult: 7.7–15.4 mg
    - Elderly: 7.7 mg

**Pain**

- **SIDE-EFFECTS** Biliary spasm · dysuria · hypothermia · mood altered · sexual dysfunction · urethral spasm

- **BREAST FEEDING** Therapeutic doses unlikely to affect infant.

- **HEPATIC IMPAIRMENT** Manufacturer advises consider avoiding.

- **DOSE adjustments** Manufacturer advises dose reduction, if used.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

- **PRESCRIBING AND DISPENSING INFORMATION** The name Omnopon® was formerly used for papaveretum preparations.

  Papaveretum is a mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride.

- **LESS SUITABLE FOR PRESCRIBING** Papaveretum is less suitable for prescribing.

- **MEDIcINAL FORMS** Forms available from special-order manufacturers include: solution for injection

Pentazocine

- **INDICATIONS AND DOSE**

  **Moderate to severe pain**
  
  - **BY MOUTH**
    - Adult: 50 mg every 3–4 hours, dose to be taken preferably after food, usual dose 25–100 mg every 3–4 hours; maximum 600 mg per day

  **Moderate pain**
  
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 30 mg every 3–4 hours as required; maximum 360 mg per day

  **Severe pain**
  
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 45–60 mg every 3–4 hours as required; maximum 360 mg per day

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 · heart failure secondary to chronic lung disease · patients dependent on opioids (can precipitate withdrawal)

- **CAUTIONS** Arterial hypertension · cardiac arrhythmias · myocardial infarction · pancreatitis · phaeochromocytoma · pulmonary hypertension

- **INTERACTIONS** → Appendix 1: opioids

- **SIDE-EFFECTS** Biliary spasm · blood disorder · chills · circulatory depression · face oedema · facial plethora · generalised tonic-clonic seizure · hypertension · hypothermia · intracranial pressure increased · mood altered · myalgia · paraesthesia · sexual dysfunction · sleep disorders · syncope · toxic epidermal necrolysis · tremor · urogenital spasm

- **OVERDOSE** Effects only partially reversed by naloxone.

- **BREAST FEEDING** Use with caution—limited information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (risk of increased bioavailability).

- **DOSE adjustments** Manufacturer advises consider dose reduction in severe impairment.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

- **LESS SUITABLE FOR PRESCRIBING** Pentazocine is less suitable for prescribing.

**IMPORTANT SAFETY INFORMATION**

Do not confuse with papaverine.

- **CONTRA-INDICATIONS** Heart failure secondary to chronic lung disease · phaeochromocytoma

- **CAUTIONS** Supraventricular tachycardia

- **INTERACTIONS** → Appendix 1: opioids

www.getintopharma.com
Pethidine hydrochloride
(Meperidine)

**INDICATIONS AND DOSE**

**Acute pain**
- **BY MOUTH**
  - Adult: 50–150 mg every 4 hours
  - By subcutaneous injection, or by intramuscular injection
    - Adult: 25–100 mg, then 25–100 mg after 4 hours, for debilitated patients use dose described for elderly patients
    - Elderly: Initially 25 mg, then 25–100 mg after 4 hours
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 25–50 mg, then 25–50 mg after 4 hours, for debilitated patients use dose described for elderly patients
  - Elderly: Initially 25 mg, then 25–50 mg after 4 hours

**Obstetric analgesia**
- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 50–100 mg, then 50–100 mg after 1–3 hours if required; maximum 400 mg per day

**Premedication**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 25–100 mg, dose to be given 1 hour before operation, for debilitated patients use dose described for elderly patients
  - Elderly: 25 mg, dose to be given 1 hour before operation

**Postoperative pain**
- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 25–100 mg every 2–3 hours if required, for debilitated patients use dose described for elderly patients
  - Elderly: Initially 25 mg every 2–3 hours if required

**CONTRA-INDICATIONS** Phaeochromocytoma

**CAUTIONS** Accumulation of metabolites may result in neurotoxicity · cardiac arrhythmias · not suitable for severe continuing pain · severe cor pulmonale

**INTERACTIONS** → Appendix 1: opioids

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Biliary spasm · dysuria · hypothermia

**SPECIFIC SIDE-EFFECTS**
- With oral use: Agitation · mood altered · muscle rigidity · sexual dysfunction · ureteral spasm
- With parenteral use: Anxiety · asthenia · coordination abnormal · delirium · seizure · syncope · tremor

**Overdose** Convulsions reported in overdosage.

**BREAST FEEDING** Present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**Dose adjustments** Manufacturer advises dose reduction in mild to moderate impairment.

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 2, 21
  - **Pentazocine (Non-proprietary)**
    - Pentazocine hydrochloride 25 mg · Pentazocine 25 mg tablets
    - 28 tablet (P) £25.36 DT + £24.99 (O)

**Capsule**
- CAUTIONARY AND ADVISORY LABELS 2, 21
  - **Pentazocine (Non-proprietary)**
    - Pentazocine hydrochloride 50 mg · Pentazocine 50 mg capsules
    - 28 capsule (P) £29.78 DT + £28.50 (O)

**Solution for injection**
- **Pentazocine hydrochloride (Non-proprietary)**
  - Pentazocine hydrochloride 50 mg/
  - 50 tablet (P) £49.92 DT + £69.92 (O)
  - Pentazocine 50 mg tablets
  - Pentazocine hydrochloride 50 mg per 1 ml
  - Solution for injection ampoules
    - 10 ampoule (P) £5.11 DT = £5.11 (O)

Sufentanil

**INDICATIONS AND DOSE**

**Acute moderate-to-severe post-operative pain**
- **BY SUBLINGUAL ADMINISTRATION**
  - Adult: (Specialist supervision in hospital): 15 micrograms every 20 minutes if required for a maximum of 72 hours

**CAUTIONS** Brain tumour · head injury · history of bradycardiac episodes (increased risk of bradycardia) · increased susceptibility to cerebral effects of CO₂ retention (including increased intracranial pressure and impaired consciousness)

**INTERACTIONS** → Appendix 1: opioids

**SIDE-EFFECTS**

- **Common or very common** Dyspepsia · fever · muscle Complaints
- **Uncommon** Apnoea · asthenia · chills · paraesthesia
- **Frequency not known** Apathy · biliary spasm · coma · movement disorders · nervousness · reflexes increased · respiratory arrest · seizure

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—risk of opioid effects or toxicity in the infant.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment (limited information available).

**RENAL IMPAIRMENT** Manufacturer advises caution and close monitoring in severe impairment—limited information available.

**DIRECTIONS FOR ADMINISTRATION** Manufacturer advises doses should be administered using patient controlled analgesia administration device—consult product literature.

**PATIENT AND CARER ADVICE** Manufacture advises patients should avoid eating and drinking, and minimise talking, for 10 minutes after each dose. Patients should be instructed on appropriate use of the patient controlled analgesia administration device—consult product literature.

**Driving and skilled tasks** Manufacturer advises patients should be counselled on the effects on driving and skilled tasks—increased risk of dizziness and visual disturbances.
Tapentadol

**INDICATIONS AND DOSE**

**Moderate to severe acute pain which can be managed only with opioid analgesics**

- **By mouth using immediate-release medicines**
  - Adults: Initially 50 mg every 4–6 hours, adjusted according to response, on the first day of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose; maximum 700 mg in the first 24 hours; maximum 600 mg per day

**Severe chronic pain**

- **By mouth using modified-release medicines**
  - Adults: Initially 50 mg every 12 hours, adjusted according to response; maximum 500 mg per day

**INDICATIONS AND DOSE**

**Moderate to severe pain**

- **By mouth using immediate-release medicines**
  - Adults: 20 mg every 1–2 hours; maximum 160 mg/24 hours

**Severe chronic pain**

- **By mouth using modified-release medicines**
  - Adults: Initially 50 mg every 12 hours, adjusted according to response; maximum 600 mg per day

**INDICATIONS AND DOSE**

**Moderate to severe pain**

- **By mouth using immediate-release medicines**
  - Adults: Initially 20 mg every 4–6 hours; maximum 240 mg every 24 hours

**Severe chronic pain**

- **By mouth using modified-release medicines**
  - Adults: Initially 50 mg every 12 hours, adjusted according to response; maximum 600 mg per day

**INDICATIONS AND DOSE**

**Moderate to severe pain**

- **By mouth using immediate-release medicines**
  - Adults: Initially 20 mg up to every 8 hours; for oral solution, initiate at 25 mg up to every 8 hours; for modified-release tablets, initiate at 50 mg up to every 24 hours

**RENAI IMPAIRMENT**

- Manufacturer advises avoid in severe impairment (no information available).
**Moderate to severe pain (with modified-release 12-hourly preparations)**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 12-17 years: 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, doses exceeding the usual maximum not generally required; Usual maximum 400 mg/24 hours
  - Adult: 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, doses exceeding the usual maximum not generally required; Usual maximum 400 mg/24 hours

**Moderate to severe pain (with modified-release 24-hourly preparations)**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 12-17 years: Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours
  - Adult: Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily; Usual maximum 400 mg/24 hours

**ZYDOL ® XL Moderate to severe pain**

- **BY MOUTH USING MODIFIED-RELEASE TABLETS**
  - Child 12-17 years: Initially 150 mg once daily, increased if necessary up to 400 mg once daily
  - Adult: Initially 150 mg once daily, increased if necessary up to 400 mg once daily

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**IMPORTANT SAFETY INFORMATION**

Do not confuse modified-release 12-hourly preparations with 24-hourly preparations, see Prescribing and dispensing information.

- **CONTRA-INDICATIONS** Acute intoxication with alcohol - acute intoxication with analgesics - acute intoxication with hypnotics - acute intoxication with opioids - compromised respiratory function (in children) - not suitable for narcotic withdrawal treatment - uncontrolled epilepsy

- **CAUTIONS** Excessive bronchial secretions - history of epilepsy - use tramadol only if compelling reasons - impaired consciousness - not suitable as a substitute in opioid-dependent patients - not suitable in some types of general anaesthesia - postoperative use (in children) - susceptibility to seizures - use tramadol only if compelling reasons - variation in metabolism

- **CAUTIONS, FURTHER INFORMATION**
  - General anaesthesia Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported).
  - Variation in metabolism The capacity to metabolise tramadol can vary considerably between individuals; there is a risk of developing side-effects of opioid toxicity in patients who are ultra-rapid tramadol metabolisers (CYP2D6 ultra-rapid metabolisers) and the therapeutic effect may be reduced in poor tramadol metabolisers.
  - Postoperative use Manufacturer advises extreme caution when used for postoperative pain relief in children - reports of rare, but life threatening adverse events after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea; if used, monitor closely for symptoms of opioid toxicity.

- **INTERACTIONS** → Appendix 1: opioids

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common Fatigue
    - Rare or very rare Dyspnoea - epileptiform seizure - respiratory disorders - sleep disorders - vision blurred
    - Frequency not known Asthma exacerbated - hypoglycaemia

  - **SPECIFIC SIDE-EFFECTS**
    - Uncommon
      - With parenteral use Circulatory collapse - gastrointestinal discomfort
    - Rare or very rare
      - With parenteral use Angioedema - appetite change - behaviour abnormal - cognitive disorder - dysuria - hypersensitivity - mood altered - movement disorders - muscle weakness - perception disorders - psychiatric disorder - sensation abnormal
    - Frequency not known
      - With oral use Anxiety - blood disorder - gastrointestinal disorder - hyperkinesia - hypertension - paraesthesia - syncope - tremor - urinary disorder

- **PREGNANCY** Embryotoxic in animal studies—manufacturers advise avoid.

- **BREAST FEEDING** Amount probably too small to be harmful, but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturers advise caution (risk of delayed elimination); some oral preparations should be avoided in severe impairment—consult product literature.

- **DOSE ADJUSTMENTS** Manufacturers advise consider increasing dosage interval.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs. Caution (avoid for oral drops) in severe impairment.

- **TREATMENT CESSATION** Manufacturer advises consider tapering the dose gradually to prevent withdrawal symptoms.

- **DIRECTIONS FOR ADMINISTRATION** Tramadol hydrochloride orodispersible tablets should be sucked and then swallowed. May also be dispersed in water. Some tramadol hydrochloride modified-release capsule preparations may be opened and the contents swallowed immediately without chewing—check individual preparations.

  For intravenous infusion, dilute in Glucose 5% or Sodium Chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION** Modified-release preparations are available as 12-hourly or 24-hourly formulations. Non-proprietary preparations of modified-release tramadol may be available as either 12-hourly or 24-hourly formulations; prescribers and dispensers must ensure that the correct formulation is prescribed and dispensed. Branded preparations that should be given 12-hourly include Invodol ® SR, Mabron ®, Manco ®, Maril ®, Moxitrax ® SR, Oldaram ®, Tilodol ® SR, Tramquiel ® SR, Zamadol ® SR, Zerodame ® SR and Zydol SR ®. Preparations that should be given 24-hourly include Tradorec XL ®, Zamadol ™ 24hr, and Zydol XR ®.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer tramadol hydrochloride orodispersible tablets.

  Medicines for Children leaflet: Tramadol for pain www.medicinesforchildren.org.uk/tramadol-pain

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension Modified-release tablet

  CAUTIONARY AND ADVISORY LABELS 2, 25

- **BRIMISOL PR (Bristol Laboratories Ltd)**
  - Tramadol hydrochloride 100 mg Brimisol PR 100mg tablets | 60 tablet (rrp £18.00 (C))

- **INVODOL SR (Ennogen Healthcare Ltd)**
  - Tramadol hydrochloride 100 mg Invodol SR 100mg tablets | 60 tablet (rrp £5.25 (C))
  - Tramadol hydrochloride 150 mg Invodol SR 150mg tablets | 60 tablet (rrp £8.31 (C))
Tramadol hydrochloride 200 mg Invovel SR 200mg tablets | 60 tablet [(Pd) £11.35 (C03)]
- **Mabron** (Morningside Healthcare Ltd, Teva UK Ltd)
- **Mabron** hydrochloride 100 mg Mabron 100mg modified-release tablets | 60 tablet [(Pd) £15.92 (C03)]
- **Mabron** hydrochloride 150 mg Mabron 150mg modified-release tablets | 60 tablet [(Pd) £23.28 (C03)]
- **Mabron** hydrochloride 200 mg Mabron 200mg modified-release tablets | 60 tablet [(Pd) £31.94 (C03)]

- **Maneo** (Mylan)
- **Maneo** hydrochloride 100 mg Maneo 100mg modified-release tablets | 60 tablet [(Pd) £6.95 (C03)]
- **Maneo** hydrochloride 150 mg Maneo 150mg modified-release tablets | 60 tablet [(Pd) £10.40 (C03)]
- **Maneo** hydrochloride 200 mg Maneo 200mg modified-release tablets | 60 tablet [(Pd) £14.20 (C03)]

- **Marol** (Teva UK Ltd)
- **Marol** hydrochloride 100 mg Marol 100mg modified-release tablets | 60 tablet [(Pd) £6.94 (C03)]
- **Marol** hydrochloride 150 mg Marol 150mg modified-release tablets | 60 tablet [(Pd) £10.49 (C03)]
- **Marol** hydrochloride 200 mg Marol 200mg modified-release tablets | 60 tablet [(Pd) £14.19 (C03)]

- **Tilodol SR** (Sandoz Ltd)
- **Tilodol SR** hydrochloride 100 mg Tilodol SR 100mg tablets | 60 tablet [(Pd) £15.52 (C03)]
- **Tilodol SR** hydrochloride 150 mg Tilodol SR 150mg tablets | 60 tablet [(Pd) £23.28 (C03)]
- **Tilodol SR** hydrochloride 200 mg Tilodol SR 200mg tablets | 60 tablet [(Pd) £31.04 (C03)]

- **Tradorec XL** (Endo Ventures Ltd)
- **Tradorec XL** hydrochloride 100 mg Tradorec XL 100mg tablets | 30 tablet [(Pd) £14.10 (C03)]
- **Tradorec XL** hydrochloride 200 mg Tradorec XL 200mg tablets | 30 tablet [(Pd) £14.98 (C03)]
- **Tradorec XL** hydrochloride 300 mg Tradorec XL 300mg tablets | 30 tablet [(Pd) £22.47 (C03)]

- **Tramulief SR** (Advanz Pharma)
- **Tramulief SR** hydrochloride 100 mg Tramulief SR 100mg tablets | 60 tablet [(Pd) £6.98 (C03)]
- **Tramulief SR** hydrochloride 150 mg Tramulief SR 150mg tablets | 60 tablet [(Pd) £10.46 (C03)]
- **Tramulief SR** hydrochloride 200 mg Tramulief SR 200mg tablets | 60 tablet [(Pd) £14.26 (C03)]

- **Zamadol 24hr** (Meda Pharmaceuticals Ltd)
- **Zamadol 24hr** hydrochloride 150 mg Zamadol 24hr 150mg modified-release tablets | 28 tablet [(Pd) £10.70 (C03)]
- **Zamadol 24hr** hydrochloride 200 mg Zamadol 24hr 200mg modified-release tablets | 28 tablet [(Pd) £14.24 (C03)]
- **Zamadol 24hr** hydrochloride 300 mg Zamadol 24hr 300mg modified-release tablets | 28 tablet [(Pd) £21.39 (C03)]
- **Zamadol 400mg** hydrochloride 400 mg Zamadol 40hr 400mg modified-release tablets | 28 tablet [(Pd) £28.51 (C03)]

- **Zeridame SR** (Actavis UK Ltd)
- **Zeridame SR** hydrochloride 100 mg Zeridame SR 100mg tablets | 60 tablet [(Pd) £17.21 (C03)]
- **Zeridame SR** hydrochloride 150 mg Zeridame SR 150mg tablets | 60 tablet [(Pd) £25.82 (C03)]
- **Zeridame SR** hydrochloride 200 mg Zeridame SR 200mg tablets | 60 tablet [(Pd) £34.43 (C03)]

- **Zydol SR** (Grunenthal Ltd)
- **Zydol SR** hydrochloride 50 mg Zydol SR 50mg tablets | 60 tablet [(Pd) £4.60 DT = £4.60 (C03)]
- **Zydol SR** hydrochloride 100 mg Zydol SR 100mg tablets | 60 tablet [(Pd) £11.72 (C03)]
- **Zydol SR** hydrochloride 150 mg Zydol SR 150mg tablets | 60 tablet [(Pd) £25.83 (C03)]
- **Zydol SR** hydrochloride 200 mg Zydol SR 200mg tablets | 60 tablet [(Pd) £34.40 (C03)]

- **Zydol XL** (Grunenthal Ltd)
- **Zydol XL** hydrochloride 150 mg Zydol XL 150mg tablets | 30 tablet [(Pd) £12.18 (C03)]
- **Zydol XL** hydrochloride 200 mg Zydol XL 200mg tablets | 30 tablet [(Pd) £17.98 (C03)]
- **Zydol XL** hydrochloride 300 mg Zydol XL 300mg tablets | 30 tablet [(Pd) £24.94 (C03)]
- **Zydol XL** hydrochloride 400 mg Zydol XL 400mg tablets | 30 tablet [(Pd) £32.47 (C03)]

- **Zytram SR** (Qdem Pharmaceuticals Ltd)
- **Zytram SR** hydrochloride 100 mg Zytram SR 100mg tablets | 60 tablet [(Pd) £6.94 (C03)]
- **Zytram SR** hydrochloride 150 mg Zytram SR 150mg tablets | 60 tablet [(Pd) £10.49 (C03)]
- **Zytram SR** hydrochloride 200 mg Zytram SR 200mg tablets | 60 tablet [(Pd) £14.19 (C03)]

**Soluteable tablet**

CAUTIONARY AND ADVISORY LABELS 2, 13

- **Zydol** (Grunenthal Ltd)
- **Zydol** hydrochloride 50 mg Zydog 50mg soluble tablets sugar-free | 20 tablet [(Pd) £2.79 (C03)]
- **Zydol** hydrochloride 100 mg Zydog 100mg soluble tablets | 10 tablet [(Pd) £3.33 DT = £13.33 (C03)]

**Solution for injection**

- **Tramadol hydrochloride (Non-proprietary)**
- **Tramadol hydrochloride 50 mg per 1 ml** Tramadol 100mg/2ml solution for injection ampoules | 5 ampoule [(Pd) £4.90 DT = £6.00 (C03)]
- **Zamadol** (Meda Pharmaceuticals Ltd)
- **Zamadol hydrochloride 50 mg per 1 ml** Zamadol 100mg/2ml solution for injection ampoules | 5 ampoule [(Pd) £3.59 DT = £4.99 (C03)]

**Modified-release capsule**

CAUTIONARY AND ADVISORY LABELS 2, 25

- **Maxitrax SR** (Chiesi Ltd)
- **Maxitrax SR** hydrochloride 50 mg Maxitrax SR 50mg capsules | 60 capsule [(Pd) £4.55 DT = £7.24 (C03)]
- **Maxitrax SR** hydrochloride 100 mg Maxitrax SR 100mg capsules | 60 capsule [(Pd) £12.14 DT = £14.47 (C03)]
- **Maxitrax SR** hydrochloride 150 mg Maxitrax SR 150mg capsules | 60 capsule [(Pd) £18.21 DT = £21.71 (C03)]
- **Zamadol SR** (Meda Pharmaceuticals Ltd)
- **Zamadol SR** hydrochloride 150 mg Zamadol SR 150mg capsules | 60 capsule [(Pd) £21.71 DT = £21.71 (C03)]

**Oral drops**

CAUTIONARY AND ADVISORY LABELS 2, 13

- **Tramadol hydrochloride (Non-proprietary)**
- **Tramadol hydrochloride 100 mg per 1 ml** Tramadol 100mg/ml oral drops | 10 ml [(Pd) £3.50 DT = £3.50 (C03)]

**Capsule**

CAUTIONARY AND ADVISORY LABELS 2

- **Tramadol hydrochloride (Non-proprietary)**
- **Tramadol hydrochloride 50 mg** Tramadol 50mg capsules | 30 capsule [(Pd) £1.39 DT = £1.39 (C03)]
- **Tramadol hydrochloride 150 mg** Tramadol 150mg capsules | 60 capsule [(Pd) £2.84 DT = £2.84 (C03)]

**Orodispensible tablet**

CAUTIONARY AND ADVISORY LABELS 2

- **Zamadol Melt** (Meda Pharmaceuticals Ltd)
- **Zamadol Melt 50 mg** Zamadol Melt 50mg tablets sugar-free | 60 tablet [(Pd) £7.12 DT = £7.12 (C03)]

Combinations available: Tramadol with paracetamol, p. 474
Tramadol with dexketoprofen

The properties listed below are those particular to the combination only. For the properties of the components please consider, tramadol hydrochloride p. 471, dexketoprofen p. 1134.

- **INDICATIONS AND DOSE**
  - Moderate to severe acute pain
  - **BY MOUTH**
  - Adult: 75/25 mg every 8 hours as required for up to 5 days
  - Elderly: 75/25 mg every 8 hours as required for up to 5 days; Usual maximum 150/50 mg/24 hours

- **INTERACTIONS** → Appendix 1: NSAIDs - opioids

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Skudexa** (A. Menarini Farmaceutica Internazionale SRL) ▶
      - Dexketoprofen 25 mg, Tramadol hydrochloride 75 mg Skudexa 75mg/25mg tablets: 10 tablet (Pack £3.68 [CO] | 20 tablet (Pack £5.52 [DT] + £5.52 [CO])

Tramadol with paracetamol

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 444, tramadol hydrochloride p. 471.

- **INDICATIONS AND DOSE**
  - Moderate to severe pain
  - **BY MOUTH**
  - Child 12-17 years: 75/650 mg every 6 hours as required
  - Adult: 75/650 mg every 6 hours as required

- **DOSE EQUIVALENCE AND CONVERSION**
  - The proportions are expressed in the form x/y, where x and y are the strengths in milligrams of tramadol and paracetamol respectively.

- **INTERACTIONS** → Appendix 1: opioids - paracetamol

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Effervescent tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 2, 13, 29, 30
    - **ELECTROLYTES:** May contain Sodium
    - **Tramadol** (Grunenthal Ltd)
      - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg Tramadol 37.5mg/325mg effervescent tablets sugar-free | 60 tablet (Pack £9.68 DT + £9.68 [CO])
  - **Tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 2, 25, 29, 30
    - **Tramadol with paracetamol (Non-proprietary)**
      - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg Tramadol 37.5mg / Paracetamol 325mg tablets | 60 tablet (Pack £2.75-£9.68 DT + £2.35 [CO])
      - Tramadol hydrochloride 75 mg, Paracetamol 650 mg Tramadol 75mg / Paracetamol 650mg tablets | 30 tablet (Pack £19.50 DT + £19.50 [CO])
    - **Tramacet** (Grunenthal Ltd)
      - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg Tramadol 37.5mg/325mg tablets | 60 tablet (Pack £9.68 DT + £2.35 [CO])
    - **Tramacet** (Grunenthal Ltd)
      - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg Tramadol 37.5mg/325mg tablets | 60 tablet (Pack £9.68 DT + £2.35 [CO])
    - **Tramacet** (Grunenthal Ltd)
      - Tramadol hydrochloride 37.5 mg, Paracetamol 325 mg Tramadol 37.5mg/325mg tablets | 60 tablet (Pack £9.68 DT + £2.35 [CO])

6.1 Headache

Other drugs used for Headache: Clonidine hydrochloride, p. 145; Sumatriptan, p. 481; Verapamil hydrochloride, p. 164

- **ANTIHIHISTAMINES** > SEDATING ANTIHISTAMINES

Pizotifen

- **INDICATIONS AND DOSE**
  - Prevention of vascular headache | Prevention of classical migraine | Prevention of common migraine | Prevention of cluster headache
  - **BY MOUTH**
  - Adult: Initially 500 micrograms once daily, then increased to 1.5 mg once daily, dose to be increased gradually and taken at night, alternatively increased to 1.5 mg daily in 3 divided doses, doses to be increased gradually; increased if necessary up to 4.5 mg daily (max. per dose 3 mg), this dose is rarely necessary

- **CAUTIONARY AND ADVISORY LABELS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Pizotifen (as Pizotifen hydrogen maleate)**
      - Pizotifen (as Pizotifen hydrogen maleate) 1.5 mg Pizotifen 1.5mg tablets | 28 tablet (Pack £8.50 DT + £1.35)

www.getintopharma.com
6.1a Migraine

Migraine

Treatment of acute migraine

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as aspirin p. 121, paracetamol p. 444 (preferably in a soluble or dispersible form) or a NSAID is often effective; concomitant antiemetic treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as a 5HT1-receptor agonist (‘tripitan’). Ergot alkaloids are rarely required now; oral preparations are associated with many side-effects and should be avoided in cerebrovascular or cardiovascular disease. Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT1-receptor agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

Analgesics

Most migraine headaches respond to analgesics such as aspirin or paracetamol but because peristalsis is often limited by difflumes such as naproxen can be considered. Sumatriptan or naratriptan are also licensed for use in migraine.

Sufiently well absorbed to be effective; dispersible or effervescent preparations are therefore preferred. Compound preparations containing analgesics and antiemetics are available.

The NSAID tolfenamic acid p. 476 is licensed specifically for the treatment of an acute attack of migraine; diclofenac potassium p. 1135, flurbiprofen p. 1140, and ibuprofen p. 1141 are also licensed for use in migraine.

5HT1-receptor agonists

A 5HT1-receptor agonist is of considerable value in the treatment of an acute migraine attack. The 5HT1D-receptor agonists (‘tripitans’) act on the 5HT(D) receptors and they are therefore sometimes referred to as 5HT1B/D-receptor agonists. A 5HT1D-receptor agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics. 5HT1-receptor agonists are not indicated for the treatment of hemiplegic, basilar, or ophthalmoplegic migraine.

The 5HT1-receptor agonists available for treating migraine are almotriptan p. 478, eletriptan p. 479, frovatriptan p. 479, naratriptan p. 480, rizatriptan p. 480, sumatriptan p. 481, and zolmitriptan p. 482. If a patient does not respond to one 5HT1-receptor agonist, an alternative 5HT1-receptor agonist should be tried. For patients who have prolonged attacks that frequently recur despite treatment with a 5HT1-receptor agonist, combination therapy with a NSAID such as naproxen can be considered. Sumatriptan or zolmitriptan are also used to treat cluster headache.

Ergot Alkaloids

The value of ergotamine tartrate p. 478 for migraine is limited by difficulties in absorption and by its side-effects, particularly nausea, vomiting, abdominal pain, and muscular cramps; it is best avoided. The recommended doses of ergotamine tartrate preparations should not be exceeded and treatment should not be repeated at intervals of less than 4 days.

To avoid habituation the frequency of administration of ergotamine tartrate should be limited to no more than twice a month. It should never be prescribed prophylactically but in the management of cluster headache a low dose is occasionally given for 1 to 2 weeks [unlicensed indication].

Antiemetics

Antiemetics, such as metoclopramide hydrochloride p. 432 or domperidone p. 431, or phenothiazine and antihistamine antiemetics, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem. Metoclopramide hydrochloride and domperidone have the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms. Oral analgesic preparations containing metoclopramide hydrochloride are a convenient alternative.

Prophylaxis of migraine

Where migraine attacks are frequent, possible provoking factors such as stress, irregular lifestyle (e.g. lack of sleep), or chemical triggers (e.g. alcohol and nitrates) should be sought; combined oral contraceptives may also provoke migraine.

Preventive treatment for migraine should be considered for patients who:

- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine attacks.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migrainous infarction.

The beta-blockers propranolol hydrochloride p. 150, atenolol p. 152, metoprolol tartrate p. 154, nadolol p. 149, and timolol maleate p. 151 are all effective. Propranolol hydrochloride is the most commonly used.

Tricyclic antidepressants [unlicensed indication], gabapentin p. 315 [unlicensed indication], topiramate p. 331, sodium valproate p. 327 [unlicensed indication], and valproic acid p. 354 [unlicensed indication] are also effective for preventing migraine. See Conception and contraception, and Pregnancy in the topiramate drug monograph for information on use in females of childbearing potential and pregnancy.

Valproic acid and sodium valproate are highly teratogenic. They must not be used in females of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and alternative treatments are ineffective or not tolerated, and must not be used during pregnancy for migraine prophylaxis. For further information see Important safety information, Conception and contraception, and Pregnancy in the valproic acid and sodium valproate drug monographs.

Pizotifen p. 474 is an antihistamine and a serotonin-receptor antagonist, structurally related to the tricyclic antidepressants. It is of limited value and may cause weight gain.

Botulinum toxin type A p. 407 is licensed for the prophylaxis of headaches in adults with chronic migraine.

Cluster headache and the trigeminal autonomic cephalalgias

Cluster headache rarely responds to standard analgesics. Sumatriptan given by subcutaneous injection is the drug of choice for the treatment of cluster headache. If an injection is unsuitable, sumatriptan nasal spray or zolmitriptan nasal spray [both unlicensed use] may be used. Alternatively, 100% oxygen at a rate of 10–15 litres/minute for 10–20 minutes is useful in aborting an attack.

Prophylaxis of cluster headache is considered if the attacks are frequent, last over 3 weeks, or if they cannot be treated effectively. Verapamil hydrochloride p. 164 or lithium [both unlicensed use] are used for prophylaxis.

Prednisolone p. 678 can be used for short-term prophylaxis of episodic cluster headache [unlicensed use] either as monotherapy, or in combination with verapamil hydrochloride during verapamil titration.
Ergotamine tartrate, used on an intermittent basis is an alternative for patients with short bouts, but it should not be used for prolonged periods.

The other trigeminal autonomic cephalalgias, paroxysmal hemiarrhia (sensitive to indometacin p. 1143), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, are seen rarely and are best managed by a specialist.

Other drugs used for Migraine
Amitriptyline hydrochloride, p. 372 • Candesartan cilexetil, p. 175 • Clonidine hydrochloride, p. 145 • Cyclozine, p. 430 • Trifluoperazine, p. 390

Paracetamol with isometheptene
The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 444.

- **INDICATIONS AND DOSE**
  - **Treatment of acute attacks of migraine**
    - **BY MOUTH**
      - Adult: 2 capsules, to be taken at onset of attack, followed by 1 capsule every 1 hour if required, maximum of 5 capsules in 12 hours

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 1058

- **INTERACTIONS**
  - Appendix 1: paracetamol • sympathomimetics, vasoconstrictor

- **PATIENT AND CARER ADVICE**
  - Patient counselling is advised (dosage).

- **LESS SUITABLE FOR PRESCRIBING**
  - Isometheptene with paracetamol is less suitable for prescribing (more effective treatments available).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**
    - CAUTIONARY AND ADVISORY LABELS 30
      - *Midor (ChP Healthcare Ltd)*
      - Isometheptene mucate 65 mg, Paracetamol 325 mg
      - *Midor*
      - 325mg/65mg capsules | 30 capsule [P] £7.50

Paracetamol with metoclopramide
The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 444, metoclopramide hydrochloride p. 432.

- **INDICATIONS AND DOSE**
  - **Acute migraine**
    - **BY MOUTH**
      - Adult: 1 sachet, sachet to be mixed in water, and dose to be taken at the start of the attack, then 1 sachet after 2 hours if required; maximum 3 sachets per day

  - **INTERACTIONS**
    - Appendix 1: metoclopramide • paracetamol

  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.

  - **Capsule**
    - CAUTIONARY AND ADVISORY LABELS 30
      - *Paramax*
      - Metoclopramide hydrochloride 5 mg, Paracetamol 500 mg
      - *Paramax*
      - 500 mg Paramax tablets | 42 tablet [P] £9.64 DT + £9.64

**IMPORTANT SAFETY INFORMATION**
Metoclopramide can cause severe extrapyramidal effects, particularly in children and young adults.

- **CAUTIONS**
  - Treatment should not exceed 3 months due to risk of tardive dyskinesia

- **INTERACTIONS**
  - Appendix 1: metoclopramide • paracetamol

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 13, 30
      - *Paramax* (Sanofi)
      - Metoclopramide hydrochloride 5 mg, Paracetamol 500 mg
      - *Paramax* (Sanofi)
      - 500 mg Paramax tablets | 42 tablet [P] £12.52 DT + £12.52

Aspirin with metoclopramide
The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 121, metoclopramide hydrochloride p. 432.

- **INDICATIONS AND DOSE**
  - **Acute migraine**
    - **BY MOUTH**
      - Adult: 1 sachet, sachet to be mixed in water, and dose to be taken at the start of the attack, then 1 sachet after 2 hours if required; maximum 3 sachets per day

  - **INTERACTIONS**
    - Appendix 1: aspirin • metoclopramide

  - **PRESCRIBING AND DISPENSING INFORMATION**
    - Flavours of oral powder formulations may include lemon.

  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder**
    - CAUTIONARY AND ADVISORY LABELS 13, 17, 30
      - **EXCIPIENTS:** May contain Aspartame
      - *Migramax (Zentiva)*
      - Metoclopramide hydrochloride 10 mg, Aspirin DL-Lysine 900 mg
      - *Migramax*
      - Oral powder sachets sugar-free | 6 sachet [P] £6.61 DT + £6.61

Tolfenamic acid

- **INDICATIONS AND DOSE**
  - **Treatment of acute migraine**
    - **BY MOUTH**
      - Adult: 200 mg, dose to be taken at onset, then 200 mg after 1–2 hours if required

  - **CONTRA-INDICATIONS**
    - Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal haemorrhage (two or more distinct episodes) • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure

  - **CAUTIONS**
    - Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease.
coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · elderly (risk of serious side-effects and fatalities) · heart failure · ischaemic heart disease · peripheral arterial disease · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated) · uncontrolled hypertension

- **INTERACTIONS** → Appendix 1: NSAIDs
- **SIDE-EFFECTS** Agranulocytosis · angioedema · aplastic anaemia · asthma · confusion · constipation · Crohn’s disease aggravated · depression · diarrhoea · dizziness · drowsiness · dyspnoea · dysuria (most common in men) · euphoretic mood · fatigue · fertility decreased female · gastrointestinal discomfort · gastrointestinal disorders · haemolytic anaemia · haemorrhage · hallucination · headache · heart failure · hepatic disorders · hypersensitivity · hypertension · increased risk of arterial thromboembolism · malaise · meningeitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · nausea · nephritis tubulointerstitial · nephropathy · neutropenia · oedema · optic neuritis · oral ulceration · pancreatitis · paraesthesia · photosensitivity reaction · renal failure (more common in patients with pre-existing renal impairment) · respiratory disorders · severe cutaneous adverse reactions (SCARs) · skin reactions · thrombocytopenia · tinnitus · tremor · vertigo · visual impairment · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Amount too small to be harmful. Use with caution during breast-feeding.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. Dose adjustments The lowest effective dose should be used for the shortest possible duration. Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Paracetamol with buclizine hydrochloride and codeine phosphate**

**INDICATIONS AND DOSE**

**MIGRALEV®**

**Acute migraine**

- **BY MOUTH**
  - Child 12-14 years: Initially 1 tablet, (pink tablet) to be taken at onset of attack, or if it is imminent, followed by 1 tablet every 4 hours if required, (yellow tablet) to be taken following initial dose; maximum 1 pink and 3 yellow tablets in 24 hours
  - Child 15–17 years: Initially 2 tablets, (pink tablets) to be taken at onset of attack or if it is imminent, followed by 2 tablets every 4 hours if required, (yellow tablets) to be taken following initial dose; maximum 2 pink and 6 yellow tablets in 24 hours
  - Adult: Initially 2 tablets, (pink tablets) to be taken at onset of attack or if it is imminent, followed by 2 tablets every 4 hours if required, (yellow tablets) to be taken following initial dose; maximum 2 pink and 6 yellow tablets in 24 hours

**INTERACTIONS** → Appendix 1: antihistamines, sedating opioids, paracetamol

**PRESCRIBING AND DISPENSING INFORMATION** See co-codamol p. 453 for Migraleve Yellow preparations.

**LESS SUITABLE FOR PRESCRIBING** Migraleve® is less suitable for prescribing.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 2, 17, 30

- Migraleve Pink (McNeil Products Ltd)
  - Buclizine hydrochloride 6.25 mg, Codeine phosphate 8 mg,
  - Paracetamol 500 mg Migraleve Pink tablets | 12 tablet | £3.79 (C5) | 24 tablet | £6.08 (C5) | 48 tablet | £9.07 (C5)
- Migraleve Yellow (McNeil Products Ltd)
  - Codeine phosphate 8 mg, Paracetamol 500 mg Migraleve Yellow tablets | 16 tablet | £6.07 (C5)

**CALTITONIN GENE-RELATED PEPTIDE INHIBITORS**

**Erenumab**

14-May-2019

**DRUG ACTION** Erenumab is a human monoclonal antibody that binds to the calcitonin-gene related peptide (CGRP) receptor, inhibiting the function of CGRP, and thereby preventing migraine attacks.

**INDICATIONS AND DOSE**

Prophylaxis of migraine (in patients who have at least 4 migraine days per month) (initiated by a specialist)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 70 mg every 4 weeks; increased if necessary to 140 mg every 4 weeks, consider discontinuing if no response after 3 months of treatment

**SIDE-EFFECTS**

- Common or very common Constipation · muscle spasms · skin reactions
- Frequency not known Oedema · swelling

www.getintopharma.com
PREGNANCY  Manufacturer advises avoid—limited information available.

BREAST FEEDING  Manufacturer advises avoid during first few days after birth—possible risk from transfer of antibodies to infant. After this time, use during breast-feeding only if clinically needed.

DIRECTIONS FOR ADMINISTRATION  Manufacturer advises injection into the abdomen, thigh, or upper arm (if not self-administered). Patients may self-administer Aimovig® after appropriate training in subcutaneous injection technique.

HANDLING AND STORAGE  Manufacturer advises store in a refrigerator (2–8°C) and protect from light—consult product literature for further information regarding storage outside refrigerator.

PATIENT AND CARER ADVICE
Self-administration  Manufacturer advises that patients and their carers should be given training in subcutaneous injection technique if appropriate.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
SMC No. SMC2134
The Scottish Medicines Consortium has advised (April 2019) that erenumab (Aimovig®) is accepted for restricted use within NHS Scotland for the prophylaxis of migraine in adults who have at least four migraine days per month and in whom at least three prior prophylactic treatments have failed. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Aimovig (Novartis Pharmaceuticals UK Ltd) Erenumab 70 mg per 1 ml Aimovig 70mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection 188.50 (Hospital only)

ERGOT ALKALOIDS

Ergotamine tartrate

INDICATIONS AND DOSE
Management of cluster headache
BY MOUTH USING TABLETS
Adult: 1 mg once daily for 5 nights in 7; occasionally given for 1–2 weeks, dose to be taken at night

UNLICENSED USE  Not licensed for the management of cluster headache.

CONTRA-INDICATIONS  Acute porphyrias p. 1058 - coronary heart disease - hyperthyroidism - inadequately controlled hypertension - obliterative vascular disease - peripheral vascular disease - Raynaud’s syndrome - sepsis - severe hypertension - temporal arthritis

CAUTIONS  Anaemia - cardiac disease - dependence - elderly - risk of peripheral vasospasm

INTERACTIONS  Appendix 1: ergotamine

SIDE-EFFECTS

Common or very common  Abdominal pain - dizziness - nausea - vomiting

Uncommon  Cyanosis - diarrhoea - muscle weakness - pain in extremity - sensibility abnormal - vasoconstriction

Rare or very rare  Arrhythmias - cardiac valve fibrosis - dyspnoea - ergot poisoning (including absence of pulse and numbness in extremities) - gangrene - intestinal ischaemia - myalgia - myocardial infarction - myocarcial ischaemia - skin reactions

Frequency not known  Anxiety - arthralgia - blood disorder - cerebral ischaemia - confusion - constipation - depression -

Ergotamine tartrate with caffeine hydrate and cyclizine hydrochloride

INDICATIONS AND DOSE
Treatment of acute migraine

BY MOUTH
Adult: 1 tablet, to be taken at onset, followed by 0.5–1 tablet after 30 minutes, then 0.5–1 tablet every 30 minutes if required, max. 3 tablets in 24 hours, max. 4 tablets per attack, max. 6 tablets in one week

INTERACTIONS  Appendix 1: antihistamines, sedating - ergotamine

PATIENT AND CARER ADVICE  Patient counselling is advised for cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate tablets (dosage).

LESS SUITABLE FOR PRESCRIBING  Cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate (Migril®) is less suitable for prescribing.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS  2, 18

Migril (Wockhardt UK Ltd)
Ergotamine tartrate 2 mg, Cyclizine hydrochloride 50 mg, Caffeine hydrate 100 mg Migril tablets | 100 tablet 51.00

TRIPTANS

Almotriptan

INDICATIONS AND DOSE
Treatment of acute migraine

BY MOUTH
Adult: 12.5 mg, dose to be taken as soon as possible after onset, followed by 12.5 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 25 mg per day

UNLICENSED USE  Not licensed for use in elderly.

CONTRA-INDICATIONS  Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension

www.getintopharma.com
Migraine 479

**CAUTIONS** Conditions which predispose to coronary artery disease - elderly

**INTERACTIONS** → Appendix 1: almotriptan

**SIDE-EFFECTS**

- **Common or very common** Asthenia - dizziness - drowsiness - nausea - vomiting
- **Uncommon** Bone pain - chest pain - diarrhoea - dry mouth - dyspepsia - headache - myalgia - palpitations - paraesthesia - throat tightness - tinnitus
- **Rare or very rare** Coronary vasospasm - myocardial infarction - tachycardia
- **Frequency not known** Intestinal ischaemia - seizure - vision disorders

**SIDE-EFFECTS, FURTHER INFORMATION** Discontinue if symptoms of heat, heaviness, pressure or tightness (including throat and chest) occur.

**ALLERGY AND CROSS-SENSITIVITY** Caution in patients with sensitivity to sulfonamides.

**PREGNANCY** There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

**BREAST FEEDING** Present in milk in animal studies— withhold breast-feeding for 24 hours.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**

Dose adjustments Max. 12.5 mg in 24 hours if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 3

- Almotriptan (Non-proprietary)
  
  Almotriptan (as Almotriptan hydrochloride maleate) 12.5 mg Almotriptan 12.5 mg tablets | 3 tablet (PO) £6.65–£9.07 | 6 tablet (PO) £18.14 DT + £16.01 | 9 tablet (PO) £22.73–£27.20

- Almogran (Almirall Ltd)
  
  Almotriptan (as Almotriptan hydrochloride maleate) 12.5 mg Almogran 12.5 mg tablets | 3 tablet (PO) £9.07 | 6 tablet (PO) £18.14 DT + £16.01

**Eletriptan**

15-Mar-2017

**INDICATIONS AND DOSE**

Treatment of acute migraine

- **BY MOUTH**
  
  Adult: 40 mg, followed by 40 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); increased if necessary to 80 mg, dose to be taken for subsequent attacks if 40 mg dose inadequate; maximum 80 mg per day

**UNLICENSED USE** Not licensed for use in elderly.

**CONTRA-INDICATIONS** Arrhythmias - coronary vasospasm - heart failure - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension

**CAUTIONS** Conditions which predispose to coronary artery disease - elderly

**INTERACTIONS** → Appendix 1: eletriptan

**SIDE-EFFECTS**

- **Common or very common** Asthenia - chest discomfort - chills - dizziness - drowsiness - dry mouth - feeling hot - flushing - gastrointestinal discomfort - headache - hyperhidrosis - increased risk of infection - muscle complaints - muscle tone increased - muscle weakness - nausea - pain - palpitations - sensation abnormal - throat tightness - vertigo
- **Rare or very rare** Asthma - breast pain - burning - conjunctivitis - constipation - gastrointestinal disorders - hyperbilirubinaemia - lymphadenopathy - menstruation - myopathy - shock - voice alteration

**SIDE-EFFECTS, FURTHER INFORMATION** Discontinue if symptoms of heat, heaviness, pressure or tightness (including throat and chest) occur.

**PREGNANCY** There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

**BREAST FEEDING** Present in milk—avoid breast-feeding for 24 hours.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments Reduce initial dose to 20 mg; maximum 40 mg in 24 hours.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 3

- Relpax (Pfizer Ltd)
  
  Eletriptan (as Eletriptan hydrobromide) 20 mg Relpax tablets | 6 tablet (PO) £22.50 DT + £22.50

  Eletriptan (as Eletriptan hydrobromide) 40 mg Relpax tablets | 6 tablet (PO) £22.50 DT + £22.50

**Frovatriptan**

14-Jul-2018

**INDICATIONS AND DOSE**

Treatment of acute migraine

- **BY MOUTH**
  
  Adult: 2.5 mg, dose to be taken as soon as possible after onset, followed by 2.5 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

**UNLICENSED USE** Not licensed for use in elderly.

**CONTRA-INDICATIONS** Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular attack - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension

**CAUTIONS** Conditions which predispose to coronary artery disease - elderly

**INTERACTIONS** → Appendix 1: frovatriptan

**SIDE-EFFECTS**

- **Common or very common** Asthenia - chest discomfort - dizziness - drowsiness - dry mouth - flushing - gastrointestinal discomfort - headache - hyperhidrosis -
nausea • sensation abnormal • throat complaints • vision disorders

▶ Uncommon Anxiety • arrhythmias • arthralgia • concentration impaired • confusion • depression • diarrhoea • dysphagia • ear discomfort • eye discomfort • gastrointestinal disorders • hypertension • increased risk of infection • malaise • musculoskeletal stiffness • neuromuscular dysfunction • pain • palpitations • peripheral coldness • psychiatric disorders • skin reactions • sleep disorders • taste altered • temperature sensation altered • thirst • tinnitus • tremor • urinary disorders • vertigo

▶ Rare or very rare Breast tenderness • burping • constipation • ear disorder • epistaxis • fever • hiccup • hyperacusia • hypoglycaemia • irritable bowel syndrome • lymphadenopathy • memory loss • movement disorder • oesophageal spasm • oral disorders • piloerection • reflexes decreased • renal pain • respiratory disorders • self mutilation

▶ Frequency not known Angioedema • coronary vasospasm • hypersensitivity • myocardial infarction

SIDE-EFFECTS, FURTHER INFORMATION
Discontinue if symptoms of heat, heaviness, pressure or tightness (including throat and chest) occur.

▶ PREGNANCY There is limited experience of using 5HT1 receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

▶ BREAST FEEDING Present in milk in animal studies— withhold breast-feeding for 24 hours.

▶ HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment—no information available.

▶ MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3

▶ Naratriptan (Non-proprietary)

Naratriptan (as Naratriptan hydrochloride) 2.5 mg Naratriptan 2.5 mg tablets | 6 tablet P(†) £4.40–£16.67 DT = £4.56

Miscarini Farmaceutica Internazionale SRL

Manufacturer advises caution in use with other 5HT1 receptor agonists, including ergotamine, if required.

Frovatriptan (as Frovatriptan succinate monohydrate)

Tablet

2.5 mg Frovatriptan 2.5 mg tablets | 6 tablet P(†) £4.40–£16.67 DT = £4.56

Migard (A. Menarini Farmaceutica Internazionale SRL)

Frovatriptan (as Frovatriptan succinate monohydrate)

Tablet

2.5 mg Migard 2.5 mg tablets | 6 tablet P(†) £4.40–£16.67 DT = £4.56

Mylatap (Mylan)

Frovatriptan (as Frovatriptan succinate monohydrate)

Tablet

2.5 mg Mylatap 2.5 mg tablets | 6 tablet P(†) £16.50 DT = £4.56

Rizatriptan

INDICATIONS AND DOSE

Treatment of acute migraine

▶ BY MOUTH

Adult: 2.5 mg, followed by 2.5 mg after at least 4 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

UNLICENSED USE Not licensed for use in elderly.

CONTRA-INDICATIONS Coronary vasospasm • ischaemic heart disease • peripheral vascular disease • previous cerebrovascular accident • previous myocardial infarction • previous transient ischaemic attack • Prinzmetal’s angina • severe hypertension • uncontrolled hypertension

CAUTIONS Conditions which predispose to coronary artery disease • elderly

INTERACTIONS ▶ Appendix 1: rizatriptan

SIDE-EFFECTS

▶ Common or very common Dizziness • drowsiness • fatigue • feeling hot • malaise • nausea • paraesthesia • vomiting

▶ Uncommon Arrhythmias • feeling abnormal • pain • palpitations • visual impairment

▶ Rare or very rare Angina pectoris • colitis ischaemic • coronary vasospasm • face oedema • myocardial infarction • peripheral vascular disease • skin reactions

UNLICENSED USE Not licensed for use in elderly.

CONTRA-INDICATIONS Coronary vasospasm • ischaemic heart disease • peripheral vascular disease • previous cerebrovascular accident • previous myocardial infarction • previous transient ischaemic attack • Prinzmetal’s angina • severe hypertension • uncontrolled hypertension

CAUTIONS Conditions which predispose to coronary artery disease • elderly

INTERACTIONS ▶ Appendix 1: rizatriptan

SIDE-EFFECTS

▶ Common or very common Alertness decreased • asthenia • diarrhoea • dizziness • drowsiness • dry mouth • dyspepsia • feeling abnormal • headache • insomnia • musculoskeletal stiffness • nausea • pain • palpitations • sensation abnormal • throat complaints • vasodilation • vomiting

▶ Uncommon Angioedema • arthralgias • ataxia • dizziness • disorientation • dysphoria • face oedema • hyperhidrosis •
hypertension • muscle weakness • myalgia • nervousness • skin reactions • syncope • taste altered • thirst • tongue swelling • tremor • vertigo • vision blurred

- Rare or very rare Hypersensitivity • stroke • wheezing

- Frequency not known Colitis ischaemic • myocardial infarction • myocardial ischaemia • peripheral vascular disease • seizure • serotonin syndrome • toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION Discontinue if symptoms of heat, heaviness, pressure or tightness (including throat and chest) occur.

- PREGNANCY There is limited experience of using SHT • receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

- BREAST FEEDING Present in milk in animal studies— withhold breast-feeding for 24 hours.

- HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

Dose adjustments Manufacturer advises dose reduction to 5 mg in mild to moderate impairment.

- RENAL IMPAIRMENT Avoid in severe impairment.

Dose adjustments Reduce dose to 5 mg in mild to moderate impairment.

DIRECTIONS FOR ADMINISTRATION Rizatriptan orodispersible tablets should be placed on the tongue, allowed to disperse and swallowed. Rizatriptan oral lyophilisates should be placed on the tongue and allowed to dissolve.

PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer rizatriptan orodispersible tablets and oral lyophilisates.

Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving).

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Orodispersible tablet

CAUTIONARY AND ADVISORY LABELS 3

EXCIPIENTS: May contain Aspartame

Rizatriptan (Non-proprietary) Rizatriptan benzoate 5 mg Rizatriptan 5 mg orodispersible tablets sugar free sugar-free | 3 tablet [POD] 26,74 DT = 26,74
Rizatriptan (as Rizatriptan benzoate) 10 mg Rizatriptan 10 mg orodispersible tablets sugar free sugar-free | 3 tablet [POD] 31,33 DT = 31,33
Rizatriptan (as Rizatriptan benzoate) 10 mg Rizatriptan 10 mg tablets | 3 tablet [POD] 44,17 | 6 tablet [POD] 89,34 – 26,74

Maxalt (Merck Sharp & Dohme Ltd) Rizatriptan (as Rizatriptan benzoate) 5 mg Maxalt 5 mg tablets | 6 tablet [POD] 26,74 DT = 26,74
Rizatriptan (as Rizatriptan benzoate) 10 mg Maxalt 10 mg tablets | 3 tablet [POD] 44,17 | 6 tablet [POD] 89,34 – 26,74

Maxalt Melt (Merck Sharp & Dohme Ltd) Rizatriptan (as Rizatriptan benzoate) 10 mg Maxalt Melt 10 mg oral lyophilisates sugar-free | 3 tablet [POD] 13,37 DT = 13,37 sugar-free | 6 tablet [POD] 26,74 DT = 26,74 sugar-free | 12 tablet [POD] 53,48

Oral lyophilisate

CAUTIONARY AND ADVISORY LABELS 3

EXCIPIENTS: May contain Aspartame

Maxalt Melt (Merck Sharp & Dohme Ltd) Rizatriptan (as Rizatriptan benzoate) 10 mg Maxalt Melt 10 mg oral lyophilisates sugar-free | 3 tablet [POD] 13,37 DT = 13,37 sugar-free | 6 tablet [POD] 26,74 DT = 26,74 sugar-free | 12 tablet [POD] 53,48

Sumatriptan

- INDICATIONS AND DOSE Treatment of acute migraine

- BY MOUTH
  • Adult: Initially 50–100 mg for 1 dose, followed by 50–100 mg after at least 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 300 mg per day

- BY SUBCUTANEOUS INJECTION
  • Adult: Initially 6 mg for 1 dose, followed by 6 mg after at least 1 hour if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack), dose to be administered using an auto-injector; not for intravenous injection which may cause coronary vasospasm and angina; maximum 12 mg per day

- BY INTRANASAL ADMINISTRATION
  • Adult 18–65 years: Initially 10–20 mg, to be administered into one nostril, followed by 10–20 mg after at least 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 40 mg per day

Treatment of acute cluster headache

- BY SUBCUTANEOUS INJECTION
  • Adult: Initially 6 mg for 1 dose, followed by 6 mg after at least 1 hour if required, to be taken only if headache recurs (patient not responding to initial dose should not take second dose for same attack), dose to be administered using an auto-injector; not for intravenous injection which may cause coronary vasospasm and angina; maximum 12 mg per day

- BY INTRANASAL ADMINISTRATION
  • Adult 18–65 years: Initially 10–20 mg, dose to be administered into one nostril, followed by 10–20 mg after at least 2 hours if required, to be taken only if headache recurs (patient not responding to initial dose should not take second dose for same attack); maximum 40 mg per day

- UNLICENSED USE Not licensed for use in elderly.

- CONTRA-INDICATIONS Coronary vasospasm • ischaemic heart disease • mild uncontrolled hypertension • moderate and severe hypertension • peripheral vascular disease • previous cerebrovascular accident • previous myocardial infarction • previous transient ischaemic attack • Prinzmetal’s angina

- CAUTIONS Conditions which predispose to coronary artery disease • elderly • history of seizures • mild, controlled hypertension • pre-existing cardiac disease • risk factors for seizures

- INTERACTIONS → Appendix 1: sumatriptan

- SIDE-EFFECTS

  GENERAL SIDE-EFFECTS

- Common or very common Asthenia • dizziness • drowsiness • dyspnoea • feeling abnormal • flushing • myalgia • nausea • pain • sensation abnormal • skin reactions • temperature sensation altered • vomiting

- Rare or very rare Hypersensitivity

- Frequency not known Angina pectoris • anxiety • arrhythmias • arthralgia • colitis ischaemic • coronary vasospasm • diarrhoea • dystonia • hyperhidrosis • hypotension • myocardial infarction • nystagmus • palpitations • Raynaud’s phenomenon • seizure • tremor • vision disorders

  SPECIFIC SIDE-EFFECTS

- Common or very common
  • With intranasal use Epistaxis • nasal irritation • taste altered • throat irritation
Zolmitriptan

- **INDICATIONS AND DOSE**

  **Treatment of acute migraine**
  - **BY MOUTH**
    - Adult: 2.5 mg, followed by 2.5 mg after at least 2 hours if required, dose to be taken only if migraine recurs, then increased if necessary to 5 mg, dose to be taken only for subsequent attacks in patients not achieving satisfactory relief with 2.5 mg dose; maximum 10 mg per day
  - **BY INTRanasal administration**
    - Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day

  **Treatment of acute cluster headache**
  - **BY INTRanasal administration**
    - Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day

  **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises max. dose 5 mg in 24 hours with concurrent use of moderate and potent inhibitors of CYP2C19, cimetidine and moclobemide.

  **DOSE EQUIVALENT AND CONVERSION**
  - 1 spray of Zomig nasal spray = 5 mg zolmitriptan.

- **UNLICENSED USE** Not licensed for use in elderly. Not licensed for treatment of cluster headaches.

- **CONTRA-INDICATIONS** Arrhythmias associated with accessory cardiac conduction pathways - coronary vasospasm - ischaemic heart disease - moderate to severe hypertension - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - Prinzmetal’s angina - transient ischaemic attack - uncontrolled hypertension. Wolff-Parkinson-White syndrome.

- **CAUTIONS** Conditions which predispose to coronary artery disease - elderly. should not be taken within 24 hours of any other 5HT₁ receptor agonist.

- **INTERACTIONS** → Appendix 1: zolmitriptan

- **SIDE-EFFECTS**

  **GENERAL SIDE-EFFECTS**
  - Common or very common Abdominal pain - asthenia - chest discomfort - dizziness - drowsiness - dry mouth - dysphagia - feeling hot - headache - limb discomfort - muscle weakness - nausea - pain - palpitations - sensation abnormal - vomiting
  - Uncommon Tachycardia - urinary disorders
  - Rare or very rare Angina pectoris - angioedema - coronary vasospasm - gastrointestinal disorders - gastrointestinal infection - hypersensitivity - myocardial infarction - splenic infection - urticaria

  **SPECIFIC SIDE-EFFECTS**
  - Common or very common
    - With intranasal use Feeling abnormal - haemorrhage - myalgia - nasal discomfort - taste altered - throat pain
    - With oral use Muscle complaints - sensation of pressure - throat complaints
  - Rare or very rare
    - With oral use Diarrhoea

  **SIDE-EFFECTS, FURTHER INFORMATION** Discontinue if symptoms of heat, heaviness, pressure or tightness (including throat and chest) occur.

- **PREGNANCY** There is limited experience of using 5HT₁ receptor agonists during pregnancy; manufacturers advise
Neuropathic pain 483

Neuropathic pain

Overview and management

Neuropathic pain, which occurs as a result of damage to neural tissue, includes phantom limb pain, compression neuropathies, peripheral neuropathies (e.g. due to Diabetic complications p. 688, chronic excessive alcohol intake, HIV infection p. 640, chemotherapy, idiopathic neuropathy), trauma, central pain (e.g. pain following stroke, spinal cord injury, and syringomyelia), and postherpetic neuralgia (peripheral nerve damage following acute herpes zoster infection (shingles)). The pain may occur in an area of sensory deficit and is sometimes accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Trigeminal neuralgia is also caused by dysfunction of neural tissue, but its management is distinct from other forms of neuropathic pain.

Neuropathic pain is generally managed with a tricyclic antidepressant or with certain antiepileptic drugs. Amitriptyline hydrochloride p. 372 [unlicensed indication] and pregabalin p. 324 are effective treatments for neuropathic pain. Amitriptyline hydrochloride and pregabalin can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose.

Nortriptyline p. 378 [unlicensed indication] may be better tolerated than amitriptyline hydrochloride. Gabapentin p. 315 is also effective for the treatment of neuropathic pain.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for tramadol hydrochloride p. 471, morphine p. 463, and oxycodone hydrochloride p. 466; however, treatment with morphine or oxycodone hydrochloride should be initiated only under specialist supervision. Tramadol hydrochloride can be prescribed when other treatments have been unsuccessful, while the patient is waiting for assessment by a specialist.

Patients with localised pain who are unable to take oral medicines may benefit from topical local anaesthetic preparations, such as lidocaine hydrochloride medicated plasters p. 1352, while awaiting specialist review.

Capsaicin below is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia. A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients. It should be used under specialist supervision.

A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain. Neuroumodulation by spinal cord stimulation may be of benefit in some patients. Many patients with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support.

Trigeminal neuralgia

Surgery may be the treatment of choice in many patients; a neurological assessment will identify those who stand to benefit. Carbamazepine p. 311 taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. It is very effective for the severe pain associated with trigeminal neuralgia and (less commonly) glossopharyngeal neuralgia. Blood counts and electrolytes should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness. Some cases respond to phenytoin p. 323; the drug may be given by intravenous infusion (possibly as fosphenytoin sodium p. 314) in a crisis (specialist use only).

Chronic facial pain

Chronic oral and facial pain including persistent idiopathic facial pain (also termed ‘atypical facial pain’) and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs.

Tricyclic antidepressants may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners’ List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Patients on long-term therapy need to be monitored both for progress and for side-effects.

Other drugs used for Neuropathic pain Amantadine hydrochloride, p. 418

CAPSAICIN

Capsaicin

- INDICATIONS AND DOSE

AIXSAIN ®

Post-herpetic neuralgia

- TO THE SKIN

Adult: Apply 3–4 times a day, dose to be applied sparingly; important; after lesions have healed, not more often than every 4 hours

continued →
7 Sleep disorders

7.1 Insomnia

Hypnotics and anxiolytics

Overview
Most anxiolytics (‘sedatives’) will induce sleep when given at night and most hypnotics will sedate when given during the day. Prescribing of these drugs is widespread but dependence (both physical and psychological) and tolerance occur. This may lead to difficulty in withdrawing the drug after the patient has been taking it regularly for more than a few weeks. Hypnotics and anxiolytics should therefore be reserved for short courses to alleviate acute conditions after causal factors have been established.

Benzodiazepines are the most commonly used anxiolytics and hypnotics; they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors. Older drugs such as meprobamate p. 346 and barbiturates are not recommended—they have more side-effects and interactions than benzodiazepines and are much more dangerous in overdose.

Benzodiazepine indications

- Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness. The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate.
- Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress.

Dependence and withdrawal
Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines.

Benzodiazepine withdrawal should be flexible and carried out at a reduction rate that is tolerable for the patient. The rate should depend on the initial dose of benzodiazepine, duration of use, and the patient’s clinical response. Short-term users of benzodiazepines (2–4 weeks only) can usually
taper off within 2–4 weeks. However, long-term users should be withdrawn over a much longer period of several months or more.

A suggested protocol for withdrawal for prescribed long-term benzodiazepine patients is as follows:

- Transfer patient stepwise, one dose at a time over about a week, to an equivalent daily dose of diazepam preferably taken at night.
- Reduce diazepam dose, usually by 1–2 mg every 2–4 weeks (in patients taking high doses of benzodiazepines, initially it may be appropriate to reduce the dose by up to one-tenth every 1–2 weeks). If uncomfortable withdrawal symptoms occur, maintain this dose until symptoms lessen.
- Reduce diazepam dose further, if necessary in smaller steps; steps of 500 micrograms may be appropriate towards the end of withdrawal. Then stop completely.
- For long-term patients, the period needed for complete withdrawal may vary from several months to a year or more.

Approximate equivalent doses, diazepam 5 mg

- Alprazolam 250 micrograms
- Clobazam 10 mg
- Clonazepam 250 micrograms
- Flurazepam 7.5–15 mg
- Chloridiazepoxide 12.5 mg
- Lorazepam 0.5–1 mg
- Lorazepam 500 micrograms
- Lorazepam 5 mg
- Oxazepam 10 mg
- Temazepam 10 mg

Withdrawal symptoms for long-term users usually resolve within 6–18 months of the last dose. Some patients will recover more quickly, others may take longer. The addition of beta-blockers, antidepressants and antipsychotics should be avoided where possible.

Counselling can be of considerable help both during and after the taper.

**Hypnotics**

Before a hypnotic is prescribed the cause of the insomnia should be established and, where possible, underlying factors should be treated. However, it should be noted that some patients have unrealistic sleep expectations, and others understate their alcohol consumption which is often the cause of the insomnia. Short-acting hypnotics are preferable in patients with sleep onset insomnia, when sedation the following day is undesirable, or when prescribing for elderly patients. Long-acting hypnotics are indicated in patients with poor sleep maintenance (e.g. early morning waking) that causes daytime effects, when an anxiolytic effect is needed during the day, or when sedation the following day is acceptable.

*Transient insomnia* may occur in those who normally sleep well and may be due to extraneous factors such as noise, shift work, and jet lag. If a hypnotic is indicated one that is rapidly eliminated should be chosen, and only one or two doses should be given.

*Short-term insomnia* is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.

*Chronic insomnia* is rarely benefited by hypnotics and is sometimes due to mild dependence caused by injudicious prescribing of hypnotics. Psychiatric disorders such as anxiety, depression, and abuse of drugs and alcohol are common causes. Sleep disturbance is very common in depressive illness and early wakening is often a useful pointer. The underlying psychiatric complaint should be treated, adapting the drug regimen to alleviate insomnia. For example, clomipramine hydrochloride p. 373 or mirtazapine p. 372 prescribed for depression will also help to promote sleep if taken at night. Other causes of insomnia include daytime cat-napping and physical causes such as pain, pruritus, and dyspnoea.

Hypnotics should not be prescribed indiscriminately and routine prescribing is undesirable. They should be reserved for short courses in the acutely distressed. Tolerance to their effects develops within 3 to 14 days of continuous use and long-term efficacy cannot be assured. A major drawback of long-term use is that withdrawal can cause rebound insomnia and a withdrawal syndrome.

Where prolonged administration is unavoidable hypnotics should be discontinued as soon as feasible and the patient warned that sleep may be disturbed for a few days before normal rhythm is re-established; broken sleep with vivid dreams may persist for several weeks.

**Elderly**

Benzodiazepines and the Z-drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.

**Dental patients**

Some anxious patients may benefit from the use of hypnotics during dental procedures such as temazepam p. 488 or diazepam p. 343. Temazepam is preferred when it is important to minimise any residual effect the following day.

**Benzodiazepines**

Benzodiazepines used as hypnotics include nitrazepam p. 487 and flurazepam p. 486 which have a prolonged action and may give rise to residual effects on the following day; repeated doses tend to be cumulative. Lorazepam p. 487, lormetazepam p. 487, and temazepam act for a shorter time and they have little or no hangover effect. Withdrawal phenomena are more common with the short-acting benzodiazepines. If insomnia is associated with daytime anxiety then the use of a long-acting benzodiazepine anxiolytic such as diazepam given as a single dose at night may effectively treat both symptoms.

**Zolpidem, and zopiclone**

Zolpidem tartrate p. 490 and zopiclone p. 490 are non-benzodiazepine hypnotics (sometimes referred to as Z-drugs), but they act at the benzodiazepine receptor. They are not licensed for long-term use; dependence has been reported in a small number of patients. Both zolpidem tartrate and zopiclone have a short duration of action.

**Chloral and derivatives**

There is no convincing evidence that they are particularly useful in the elderly and their role as hypnotics is now very limited.

**Clomethiazole**

Clomethiazole p. 489 may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs.

**Antihistamines**

Some antihistamines such as promethazine hydrochloride p. 286 are on sale to the public for occasional insomnia; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

**Alcohol**

Alcohol is a poor hypnotic because the diuretic action interferes with sleep during the latter part of the night. Alcohol also disturbs sleep patterns, and so can worsen sleep disorders.
Melatonin
Melatonin p. 489 is a pineal hormone; it is licensed for the short-term treatment of insomnia in adults over 55 years.

Anxiolytics
Benzodiazepine anxiolytics can be effective in alleviating anxiety states. Although these drugs are sometimes prescribed for stress-related symptoms, unhappiness, or minor physical disease, their use in such conditions is inappropriate. Benzodiazepine anxiolytics should not be used as sole treatment for chronic anxiety, and they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines.

Anxiolytic benzodiazepine treatment should be limited to the lowest possible dose for the shortest possible time. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.

Some antidepressant drugs are licensed for use in anxiety and related disorders. Some antipsychotic drugs, in low doses, are also sometimes used in severe anxiety for their sedative action, but long-term use should be avoided because of the risk of adverse effects. The use of antihistamines (e.g. hydroxyzine hydrochloride p. 285) for their sedative effect in anxiety is not appropriate.

Beta-adrenoceptor blocking drugs do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but they do reduce autonomic symptoms, such as palpitation and tremor; they do not reduce non-autonomic symptoms, such as muscle tension. Beta-blockers are therefore indicated for patients with predominantly somatic symptoms; this, in turn, may prevent the onset of worry and fear.

Benzodiazepines
Benzodiazepines are indicated for the short-term relief of severe anxiety; long-term use should be avoided. Diazepam, alprazolam p. 342, clorazepoxide hydrochloride p. 343, and clobazam p. 336 have a sustained action. Shorter-acting compounds such as lorazepam p. 339 and oxazepam p. 345 may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

In panic disorders (with or without agoraphobia) resistant to antidepressant therapy, a benzodiazepine may be used; alternatively, a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam or lorazepam are very occasionally administered intravenously for the control of panic attacks. This route is the most rapid but the procedure is not without risk and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

Buspirone
Buspirone hydrochloride p. 342 is thought to act at specific serotonin (5HT1A) receptors. Response to treatment may take up to 2 weeks. It does not alleviate the symptoms of benzodiazepine withdrawal. Therefore a patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone hydrochloride. The dependence and abuse potential of buspirone hydrochloride is low; it is, however, licensed for short-term use only (but specialists occasionally use it for several months).

Meprobamate
Meprobamate p. 346 is less effective than the benzodiazepines, more hazardous in overdosage, and can also induce dependence. It is not recommended.

Barbiturates
The intermediate-acting barbiturates have a place only in the treatment of severe intractable insomnia in patients already taking barbiturates; they should be avoided in the elderly. Intermediate-acting barbiturate preparations containing amobarbital sodium, butobarbital, and secobarbital sodium are available on a named patient basis.

The long-acting barbiturate phenobarbital is still sometimes of value in epilepsy but its use as a sedative is unjustified.

The very short-acting barbiturate thiopental sodium p. 338 is used in anaesthesia.

Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

HYPNOTICS, SEDATIVES AND ANXIOLYRICS  BENZODIAZEPINES

Flurazepam

- INDICATIONS AND DOSE
  - Insomnia (short-term use)
    - BY MOUTH
      - Adult: 15–30 mg once daily, dose to be taken at bedtime, for debilitated patients, use elderly dose
      - Elderly: 15 mg once daily, dose to be taken at bedtime

- CONTRA-INDICATIONS
  - Not for use alone to treat chronic psychosis, not for use alone to treat depression (or anxiety associated with depression), respiratory depression

- CAUTIONS
  - Acute porphyrias p. 1058 - hypoalbuminaemia - muscle weakness

  **CAUTIONS, FURTHER INFORMATION**

- Paradoxical effects
  - A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

- INTERACTIONS
  - Appendix 1: flurazepam

- SIDE-EFFECTS
  - Common or very common
    - Taste altered
  - Rare or very rare
    - Abdominal discomfort - skin eruption
  - Frequency not known
    - Agranulocytosis - extrapyramidal symptoms - leucopenia - pancytopenia - suicide attempt - thrombocytopenia

- BREAST FEEDING
  - Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

- HEPATIC IMPAIRMENT
  - Dose adjustments
  - Manufacturer advises dose of 15 mg in mild to moderate impairment.

- RENAL IMPAIRMENT
  - Dose adjustments
  - Start with small doses in severe impairment.

- NATIONAL FUNDING/ACCESS DECISIONS
  - NHS restrictions
  - Flurazepam capsules are not prescribable in NHS primary care.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - CAUTIONARY AND ADVISORY LABELS
  - Dalmane (Meda Pharmaceuticals Ltd)
    - Flurazepam (as Flurazepam hydrochloride) 15 mg Dalmane 15mg capsules | 30 capsule (PO) £6.73 (C07A)
    - Flurazepam (as Flurazepam hydrochloride) 30 mg Dalmane 30mg capsules | 30 capsule (PO) £8.63 (C07A)
**BNF 78**

**Loprazolam**

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**
- **BY MOUTH**
  - Adult: 1 mg once daily, then increased to 1.5–2 mg once daily if required, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 0.5–1 mg once daily, dose to be taken at bedtime

**CONTRA-INDICATIONS** Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

**CAUTIONS** Acute porphyrias p. 1058 - hypoalbuminaemia - muscle weakness

**CAUTIONS, FURTHER INFORMATION**
- Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**INTERACTIONS** → Appendix 1: loprazolam

**SIDE-EFFECTS** Adjustment disorder - cognitive disorder - muscle tone decreased - speech disorder

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**RENAI IMPAIRMENT**
- **Dose adjustments** Start with small doses in severe impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 19
  - Lormetazepam (Non-proprietary)
  - Lormetazepam 500 microgram tablets | 30 tablet
  - Lormetazepam 1 mg tablets | 30 tablet
  - Lormetazepam 500 microgram | 30 tablet

**Nitrazepam**

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**
- **BY MOUTH**
  - Adult: 5–10 mg daily, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 2.5–5 mg daily, dose to be taken at bedtime

**CONTRA-INDICATIONS** Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

**CAUTIONS** Acute porphyrias p. 1058 - hypoalbuminaemia - muscle weakness

**CAUTIONS, FURTHER INFORMATION**
- Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**INTERACTIONS** → Appendix 1: nitrazepam

**SIDE-EFFECTS**
- Common or very common Movement disorders
- Uncommon Concentration impaired
- Rare or very rare Abdominal distress - muscle cramps - psychiatric disorder - skin reactions - Stevens-Johnson syndrome

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**RENAI IMPAIRMENT**
- **Dose adjustments** Start with small doses in severe impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Oral suspension**
- **CAUTIONARY AND ADVISORY LABELS** 19
  - Nitrazepam (Non-proprietary)
  - Nitrazepam 500 microgram per 1 ml Nitrazepam 2.5mg/5ml oral suspension | 70 ml
  - Nitrazepam 500 microgram | 30 tablet

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS** 19
  - Nitrazepam (Non-proprietary)
  - Nitrazepam 5 mg Nitrazepam 5mg tablets | 28 tablet

www.getintopharma.com
Sleep disorders

**Mogadon** (Meda Pharmaceuticals Ltd)
Nitrazepam 5 mg Mogadon 5mg tablets | 30 tablet
£5.76 [G43]

### Temazepam

#### INDICATIONS AND DOSE

**Insomnia (short-term use)**
- **BY MOUTH**
  - Adult: 10–20 mg once daily, alternatively 30–40 mg once daily, higher dose range only to be administered in exceptional circumstances, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 10 mg once daily, alternatively 20 mg once daily, higher dose only to be administered in exceptional circumstances, dose to be taken at bedtime

**Conscious sedation for dental procedures**
- **BY MOUTH**
  - Adult: 15–30 mg, to be administered 30–60 minutes before procedure

**Premedication before surgery or investigatory procedures**
- **BY MOUTH**
  - Adult: 10–20 mg, to be taken 1–2 hours before procedure, alternatively 30 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances
  - Elderly: 10 mg, to be taken 1–2 hours before procedure, alternatively 20 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances

#### UNLICENSED USE

Temazepam doses in BNF may differ from those in product literature.
Not licensed for conscious sedation for dental procedures.

#### CONTRA-INDICATIONS

CNS depression - compromised airway - hyperkinesis - not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - obsessional state - phobic states - respiratory depression

#### CAUTIONS

Hypoaalbuminaemia - muscle weakness - organic brain changes

#### CAUTIONS, FURTHER INFORMATION

Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

#### INTERACTIONS

Appendix 1: temazepam

#### SIDE-EFFECTS

Drug abuse - dry mouth - hypersalivation - speech slurred

#### BREAST FEEDING

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

#### HEPATIC IMPAIRMENT

**Dose adjustments** When used for Insomnia Manufacturer advises initiate at 5 mg once daily, increase to 10 mg or 20 mg once daily in extreme cases. Dose to be taken at bedtime.

#### RENAL IMPAIRMENT

**Dose adjustments** Start with small doses in severe impairment.

#### PATIENT AND CARER ADVICE

**Driving and skilled tasks** Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of undertaking skilled tasks (e.g. driving) afterwards. Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

#### PROFESSION SPECIFIC INFORMATION

**Dental practitioners’ formulary**
Temazepam Tablets and Oral Solution may be prescribed.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 19**

**Temazepam (Non-proprietary)**

- Temazepam 2 mg per 1 ml
  - Oral solution sugar free sugar-free | 300 ml [P8] £183.26 DT + £183.25 [C3]

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 19**

**Temazepam (Non-proprietary)**

- Temazepam 10 mg

- Temazepam 20 mg
  - Tablet | 20mg tablets | 25 tablet [P8] £13.93–£307.94 [C3]

### Chloral hydrate

#### INDICATIONS AND DOSE

**Insomnia (short-term use), using chloral hydrate 143.3 mg/5 mL oral solution**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 430–860 mg once daily (max. per dose 2 g), dose to be taken with water or milk at bedtime

**Insomnia (short-term use), using chloral betaine 707 mg (≈ 414 mg chloral hydrate) tablets**
- **BY MOUTH USING TABLETS**
  - Adult: 1–2 tablets, alternatively 414–828 mg once daily, dose to be taken with water or milk at bedtime; maximum 4 tablets per day; maximum 2 g per day

#### CONTRA-INDICATIONS

Acute porphyrias p. 1058 - gastritis - severe cardiac disease

#### CAUTIONS

Avoid contact with mucous membranes - avoid contact with skin - avoid prolonged use (and abrupt withdrawal thereafter) - reduce dose in debilitated - reduce dose in frail elderly

#### INTERACTIONS

Appendix 1: chloral hydrate

#### SIDE-EFFECTS

Agitation - allergic dermatitis - ataxia - confusion - delirium (more common on abrupt discontinuation) - drug use disorders - gastrointestinal discomfort - gastrointestinal disorders - headache - injury - ketonuria - kidney injury

#### PREGNANCY

Avoid.

#### BREAST FEEDING

Risk of sedation in infant—avoid.

#### HEPATIC IMPAIRMENT

Manufacturer advises avoid in marked impairment.

#### DIRECTIONS FOR ADMINISTRATION

For administration by mouth dilute liquid with plenty of water or juice to mask unpleasant taste.

#### PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include black currant.

#### PATIENT AND CARER ADVICE

**Driving and skilled tasks** Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.
LESS SUITABLE FOR PRESCRIBING Chloral hydrate is less suitable for prescribing in insomnia.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

Chloral hydrate (Non-proprietary)
- Chloral betaine 707 mg tablet 30 (£138.59 DT + £138.59)

Oral solution

CAUTIONARY AND ADVISORY LABELS 19, 27
- Chloral hydrate (Non-proprietary)
- Chloral hydrate 28.66 mg per 1 ml oral solution BP 150 ml (£244.25 DT + £244.25)

Clomethiazole (Chlormethiazole)

INDICATIONS AND DOSE

Severe insomnia (short-term use)
- BY MOUTH USING CAPSULES
  - Elderly: 192 – 384 mg once daily, dose to be taken at bedtime
  - BY MOUTH USING ORAL SOLUTION
  - Elderly: 5 – 10 mg once daily, dose to be taken at bedtime

Restlessness and agitation
- BY MOUTH USING CAPSULES
  - Elderly: 192 mg 3 times a day
  - BY MOUTH USING ORAL SOLUTION
  - Elderly: 5 ml 3 times a day

Alcohol withdrawal
- BY MOUTH USING CAPSULES
  - Adult: Initially 2 – 4 capsules, to be repeated if necessary after some hours. 9 – 12 capsules daily in 3 – 4 divided doses on day 1 (first 24 hours), then 6 – 8 capsules daily in 3 – 4 divided doses on day 2, then 4 – 6 capsules daily in 3 – 4 divided doses on day 3, dose then to be gradually reduced over days 4 – 6, total duration of treatment for no more than 9 days
  - BY MOUTH USING ORAL SOLUTION
  - Adult: Initially 10 – 20 mL, to be repeated if necessary after some hours, then 45 – 60 mL daily in 3 – 4 divided doses on day 1 (first 24 hours), then 30 – 40 mL daily in 3 – 4 divided doses on day 2, then 20 – 30 mL daily in 3 – 4 divided doses on day 3, dose then to be gradually reduced over days 4 – 6, total duration of treatment for no more than 9 days

CONTRA-INDICATIONS Acute pulmonary insufficiency • alcohol-dependent patients who continue to drink

CAUTIONS Avoid prolonged use (and abrupt withdrawal thereafter) • cardiac disease (confusional state may indicate hypoxia) • chronic pulmonary insufficiency • elderly • excessive sedation may occur (particularly with higher doses) • history of drug abuse • marked personality disorder • respiratory disease (confusional state may indicate hypoxia) • sleep apnoea syndrome

INTERACTIONS → Appendix 1: clomethiazole

SIDE-EFFECTS Agitation • bronchial secretion increased • confusion • conjunctival irritation • drug dependence • excessive sedation • gastrointestinal disorder • hangover • nasal complaints • skin reactions • upper airway secretion increased

PREGNANCY Avoid if possible—especially during the first and third trimesters.

BREAST FEEDING Use only if benefit outweighs risk—present in breast milk but effects unknown.

HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).

Dose adjustments Manufacturer advises consider dose reduction in moderate hepatic disorders associated with alcoholism.

RENAL IMPAIRMENT Increased cerebral sensitivity.

Dose adjustments Start with small doses in severe impairment.

PATIENT AND CARER ADVICE

Driving and skilled tasks Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral solution

CAUTIONARY AND ADVISORY LABELS 19, 27
- Clomethiazole (Non-proprietary)
  - Clomethiazole (as Clomethiazole edisilate) 50 mg per 1 ml Clomethiazole 31.5mg/ml oral solution sugar free sugar-free 300 ml (£60.00)

Capsule

CAUTIONARY AND ADVISORY LABELS 19
- Clomethiazole (Non-proprietary)
  - Clomethiazole 192 mg Clomethiazole 192mg capsules 60 capsule (£32.80 DT + £32.80)

Melatonin

INDICATIONS AND DOSE

Insomnia (short-term use)
- BY MOUTH USING MODIFIED-RELEASE TABLETS
  - Adult 55 years and over: 2 mg once daily for up to 13 weeks, dose to be taken 1 – 2 hours before bedtime

CAUTIONS Autoimmune disease (manufacturer advises avoid—no information available)

INTERACTIONS → Appendix 1: melatonin

SIDE-EFFECTS

Common or very common Arthralgia • headaches • increased risk of infection • pain

Uncommon Anxiety • asthenia • chest pain • dizziness • drowsiness • dry mouth • gastrointestinal discomfort • hyperbilirubinemia • hypertension • leucopenia • meningitis • mood altered • movement disorders • nausea • night sweats • oral disorders • skin reactions • sleep disorders • urinary abnormalities • weight increased

Rare or very rare Aggression • angina pectoris • arthrosis • concentration impaired • crying • depression • disorientation • electrolyte imbalance • excessive tearing • gastrointestinal disorders • haematuria • hot flush • hypertiglyceridaemia • leucopenia • memory loss • muscle complaints • nail disorder • palpitations • paraesthesia • partial complex seizure • prostatitis • sexual dysfunction • syncope • thirst • thrombocytopenia • urinary disorders • vertigo • vision disorders • vomiting

Frequency not known Angioedema • galactorrhea

PREGNANCY No information available—avoid.

BREAST FEEDING Present in milk—avoid.

HEPATIC IMPAIRMENT Manufacturer advises avoid (risk of decreased clearance; limited information available).

RENAL IMPAIRMENT No information available—use with caution.
Zolpidem tartrate
02-Feb-2019

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

**BY MOUTH**
- Adult: 10 mg daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 5 mg daily for up to 4 weeks, dose to be taken at bedtime
- Elderly: 5 mg daily for up to 4 weeks, dose to be taken at bedtime

**CONTRA-INDICATIONS**
Acute respiratory depression • marked neuromuscular respiratory weakness • obstructive sleep apnoea • psychotic illness • severe respiratory depression • unstable myasthenia gravis

**CAUTIONS**
Avoid prolonged use (and abrupt withdrawal thereafter) • depression • elderly • history of alcohol abuse • history of drug abuse • muscle weakness • myasthenia gravis

**INTERACTIONS** → Appendix 1: zolpidem

**SIDE-EFFECTS**
- Common or very common Abdominal pain • anterograde amnesia • anxiety • back pain • diarrhoea • dizziness • fatigue • hallucination • headache • increased risk of infection • nausea • sleep disorders • vomiting
- Uncommon Confusion • diplopia • irritability
- Frequency not known Angioedema • behaviour abnormal • concentration impaired • delusions • depression • drug dependence • fall • gait abnormal • hepatic disorders • hyperhidrosis • level of consciousness decreased • libido disorder • muscle weakness • psychosis • respiratory depression • skin reactions • speech disorder • withdrawal syndrome

**PREGNANCY**
Avoid regular use (risk of neonatal withdrawal symptoms); high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

**BREAST FEEDING**
Small amounts present in milk—avoid.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in mild to moderate impairment (risk of decreased clearance); avoid in severe impairment.

**Dose adjustments**
Manufacturer advises initial dose reduction to 5 mg daily in mild to moderate impairment.

**RENAL IMPAIRMENT**
Use with caution.

**PATIENT AND CARER ADVICE**

**Driving and skilled tasks**
Drowsiness may persist the next day—leave at least 8 hours between taking zolpidem and performing skilled tasks (e.g. driving, or operating machinery); effects of alcohol and other CNS depressants enhanced.

**INTERACTIONS** → Appendix 1: zolpidem

**SIDE-EFFECTS**
- Common or very common Dry mouth • taste bitter
- Uncommon Anxiety • dizziness • fatigue • headache • nausea • sleep disorders • vomiting
- Rare or very rare Behaviour abnormal • confusion • dysphoria • fall • hallucination • irritability • libido disorder • memory impairment • skin reactions
- Frequency not known Cognitive disorder • concentration impaired • delusions • depressed mood • diplopia • drug dependence • dyspepsia • movement disorders • muscle weakness • paraesthesia • respiratory depression • speech disorder • withdrawal syndrome

**PREGNANCY**
Not recommended (risk of neonatal withdrawal symptoms). Use during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

**BREAST FEEDING**
Present in milk—avoid.

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Zopiclone
02-Feb-2019

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

**BY MOUTH**
- Adult: 7.5 mg once daily for up to 4 weeks, dose to be taken at bedtime
- Elderly: Initially 3.75 mg once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily

**Insomnia (short-term use) in patients with chronic pulmonary insufficiency**

**BY MOUTH**
- Adult: Initially 3.75 mg once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily

**CONTRA-INDICATIONS**
Marked neuromuscular respiratory weakness • respiratory failure • severe sleep apnoea syndrome • unstable myasthenia gravis

**CAUTIONS**
Avoid prolonged use (risk of tolerance and withdrawal symptoms) • chronic pulmonary insufficiency (increased risk of respiratory depression) • elderly • history of drug abuse • muscle weakness • myasthenia gravis (avoid if unstable) • psychiatric illness

**INTERACTIONS** → Appendix 1: zopiclone

**SIDE-EFFECTS**
- Common or very common Dry mouth • taste bitter
- Uncommon Anxiety • dizziness • fatigue • headache • nausea • sleep disorders • vomiting
- Rare or very rare Behaviour abnormal • confusion • dysphoria • fall • hallucination • irritability • libido disorder • memory impairment • skin reactions
- Frequency not known Cognitive disorder • concentration impaired • delusions • depressed mood • diplopia • drug dependence • dyspepsia • movement disorders • muscle weakness • paraesthesia • respiratory depression • speech disorder • withdrawal syndrome

**PREGNANCY**
Not recommended (risk of neonatal withdrawal symptoms). Use during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

**BREAST FEEDING**
Present in milk—avoid.
7.2 Narcolepsy

Other drugs used for Narcolepsy Dexamfetamine sulfate, p. 350 · Methylphenidate hydrochloride, p. 348

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Sodium oxybate

- **DRUG ACTION** A central nervous system depressant.

- **INDICATIONS AND DOSE**

  Narcolepsy with cataplexy (under expert supervision)

  - **BY MOUTH**
    - Adult: Initially 2.25 g daily, dose to be taken on retiring and 2.25 g after 2.5–4 hours, then increased in steps of 1.5 g daily in 2 divided doses; dose adjusted according to response at intervals of 1–2 weeks; dose titration should be repeated if restarting after interval of more than 14 days, maximum 9 g daily in 2 divided doses

  **DOSAGE ADJUSTMENTS DUE TO INTERACTIONS**

  - Manufacturer advises reduce dose by 20% with concurrent use of sodium valproate or valproic acid.

- **CONTRA-INDICATIONS**

  Major depression · sleep apnoea · sedation · lethargy · weight gain · nausea · vomiting · taste alteration · dizziness · respiratory depression · loss of consciousness · sleep disorders · sleep paralysis · mood disorders · insomnia · anxiety · delusions · hallucinations · depression · delirium · agitation · psychoses · suicidal tendencies

- **CAUTIONS**

  - Body mass index of 40 kg/m² or greater (higher risk of sleep apnoea) · elderly · epilepsy · heart failure (high sodium content) · history of depression · history of drug abuse · hypertension (high sodium content) · respiratory disorders · risk of discontinuation effects including rebound cataplexy and withdrawal symptoms

- **INTERACTIONS** → Appendix 1: sodium oxybate

- **SIDE-EFFECTS**

  - Common or very common Abdominal pain upper · anxiety · appetite abnormal · arthralgia · asthenia · back pain · concentration impaired · confusion · depression · diarrhoea · dizziness · dysphoria · fall · feeling drunk · headache · hyperhidrosis · hypertension · increased risk of infection · movement disorders · muscle spasms · nasal congestion · nausea · palpitations · peripheral oedema · sedation · sensation abnormal · skin reactions · sleep disorders · sleep paralysis · snoring · taste altered · tremor · urinary disorders · vertigo · vision blurred · vomiting · weight decreased

  - Uncommon Behaviour abnormal · faecal incontinence · hallucination · memory loss · psychosis · suicidal tendencies · thinking abnormal

  - Frequency not known Angioedema · dehydrogenase · delusions · dry mouth · homicidal ideation · loss of consciousness · mood altered · respiratory depression · seizure · sleep apnoea

  - **PREGNANCY** Avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure).

  **DOSAGE ADJUSTMENTS** Manufacturer advises initial dose reduction of 50%.

- **RENA L IMPAIRMENT** Caution—contains 3.96 mmol Na⁺ per mL

- **DIRECTIONS FOR ADMINISTRATION** Dilute each dose with 50 mL water; prepare both doses before retiring. Observe the same time interval (2–3 hours) each night between the last meal and the first dose.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer sodium oxybate oral solution.

  - **Driving and skilled tasks** Leave at least 6 hours between taking sodium oxybate and performing skilled tasks (e.g. driving or operating machinery); effects of alcohol and other CNS depressants enhanced.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

  **Tablet**

  **CAUTIONARY AND ADVISORY LABELS** 19, 25

  - **Zopiclone (Non-proprietary)**
    - Zopiclone 3.75 mg Zopiclone 3.75 mg tablets | 28 tablet | £1.50 DT £0.87 (CD-1)
    - Zopiclone 7.5 mg Zopiclone 7.5 mg tablets | 28 tablet | £3.75 DT £0.87 (CD-3)
    - Zimovane (Sanofi)
      - Zopiclone 3.75 mg Zimovane LS 3.75mg tablets | 28 tablet | £2.24 DT £0.88 (CD-1)
      - Zopiclone 7.5 mg Zimovane 7.5mg tablets | 28 tablet | £3.26 DT £0.97 (CD-3)

### CNS STIMULANTS

Pitolisant

- **DRUG ACTION** Pitolisant is a histamine H₂-receptor antagonist which enhances the activity of brain histaminergic neurons.

- **INDICATIONS AND DOSE**

  Narcolepsy with or without cataplexy (initiated by a specialist)

  - **BY MOUTH**
    - Adult: Initially 9 mg once daily for 1 week, then increased if necessary to 18 mg once daily for 1 week, then increased if necessary to 36 mg once daily, dose to be taken in the morning with breakfast, dose can be decreased (down to 4.5 mg per day) or increased (up to 36 mg per day) according to response and tolerance

  **CAUTIONS**

  - Acid-related gastric disorders · epilepsy · history of psychiatric disorders · severe anorexia · severe obesity
ventricular hypertrophy • moderate uncontrolled hypertension • severe uncontrolled hypertension

**CAUTIONS**  
History of alcohol abuse • history of depression • history of drug abuse • history of mania • history of psychosis • possibility of dependence

**INTERACTIONS**  
Appendix 1: pitolisant

**SIDE-EFFECTS**

- Common or very common  
  Anxiety • asthenia • depression • dizziness • gastrointestinal discomfort • headaches • mood altered • nausea • sleep disorders • tremor • vertigo • vomiting

- Uncommon  
  Appetite abnormal • arrhythmias • arthralgia • blepharospasm • chest pain • concentration impaired • constipation • diarrhea • drowsiness • dry mouth • epilepsy • feeling abnormal • fluid retention • gastrointestinal disorders • hallucinations • hot flush • hypertension • hypotension • malaise • metrorrhagia • movement disorders • muscle complaints • muscle weakness • oedema • on and off phenomenon • oral intolernce • pain • paraesthesia • QT interval prolongation • sexual dysfunction • skin reactions • sweat changes • tinnitus • urinary frequency increased • visual acuity decreased • weight decreased • weight increased

- Rare or very rare  
  Blepharospasm • vomiting • dizziness • hallucinations • muscle complaints • muscle tone increased • muscle weakness • oedema • on and off phenomenon • oral intolernce • pain • paraesthesia • QT interval prolongation • sexual dysfunction • skin reactions • sweat changes • tinnitus • urinary frequency increased • visual acuity decreased • weight decreased • review treatment if significant • weight increased • review treatment if significant • yawning

**SIDE-EFFECTS, FURTHER INFORMATION**

- Common or very common  
  Anxiety • appetite abnormal • arrhythmias • asthenia • chest pain • confusion • constipation • depression • diarrhea • dizziness • drowsiness • dry mouth • gastrointestinal discomfort • headaches • mood altered • nausea • palpitations • sensation abnormal • sleep disorders • thinking abnormal • vasodilation • vision disorders

- Uncommon  
  Allergic rhiinitis • arthralgia • asthma • behaviour abnormal • central nervous system stimulation • cough aggravated • diabetes mellitus • dry eye • dysphagia • dyspnoea • eosinophilia • epistaxis • gastrointestinal disorders • hypercholesterolaemia • hyperglycaemia • hyperhidrosis • hypertension • hypotension • increased risk of infection • leucopenia • libido decreased • memory loss • menstrual disorder • movement disorders • muscle complaints • muscle tone increased • muscle weakness • oral disorders • pain • peripheral oedema • psychiatric disorders • skin reactions • speech disorder • suicidal ideation • taste altered • thirst • tremor • urinary frequency increased • urine abnormal • vertigo • vomiting • weight changes

**SIDE-EFFECTS**

- Common or very common  
  Anxiety • appetite abnormal • arrhythmias • arthralgia • chest pain • confusion • constipation • depression • diarrhea • dizziness • drowsiness • dry mouth • gastrointestinal discomfort • headaches • mood altered • nausea • palpitations • sensation abnormal • sleep disorders • thinking abnormal • vasodilation • vision disorders

**CONCEPATION AND CONTRACEPTION**  
Manufacturer advises effective contraception in women of childbearing potential for at least 21 days after treatment discontinuation—pitolisant may reduce the effectiveness of hormonal contraceptives.

**PREGNANCY**  
Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

**BREAST FEEDING**  
Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**  
Manufacturer advises caution in moderate impairment; avoid in severe impairment.

**Dose adjustments**  
Manufacturer advises consider dose increase after two weeks after initiation in moderate impairment; maximum daily dose of 18 mg.

**RENAL IMPAIRMENT**

**Dose adjustments**  
Manufacturer advises use with caution; maximum daily dose should not exceed 18 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Wakix (Lincoln Medical Ltd) ▼  
  Pitolisant (as Pitolisant hydrochloride) 4.5 mg  
  Wakix 4.5 mg tablets | 30 tablet [PoM] £310.00 DT = £310.00
  Pitolisant (as Pitolisant hydrochloride) 18 mg  
  Wakix 18 mg tablets | 30 tablet [PoM] £310.00 DT = £310.00

**CNS STIMULANTS**  
**CENTRALLY ACTING SYMPATHOMIMETICS**

**Modafinil**

**INDICATIONS AND DOSE**

Excessive sleepiness associated with narcolepsy with or without cataplexy

- **BY MOUTH**
  Adult: Initially 200 mg daily in 2 divided doses, dose to be taken in the morning and at noon, alternatively initially 200 mg once daily, dose to be taken in the morning, adjusted according to response to 200–400 mg daily in 2 divided doses, alternatively adjusted according to response to 200–400 mg once daily
  Elderly: Initially 100 mg daily

**CONTRA-INDICATIONS**  
Arrhythmia • history of clinically significant signs of CNS stimulant-induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias) • history of cor pulmonale • history of left
8 Substance dependence

Substance dependence

Guidance on treatment of drug misuse


Alcohol dependence

See Alcohol dependence p. 494.

Nicotine dependence

See Smoking cessation p. 497.

Opioid dependence

The management of opioid dependence requires medical, social, and psychological treatment; access to a multidisciplinary team is recommended. Treatment for opioid dependence should be initiated under the supervision of an appropriately qualified prescriber. Untreated heroin dependence shows early withdrawal symptoms within 8 hours, with peak symptoms at 36–72 hours; symptoms subside substantially after 5 days. Methadone hydrochloride or buprenorphine should be prescribed for patients when there is a risk of dose diversion for parenteral medications; there is also a lower risk of overdose.

Opioid substitution therapy

Methadone hydrochloride and buprenorphine are used as substitution therapy in opioid dependence. Substitute medication should be commenced with a short period of stabilisation, followed by either a withdrawal regimen or by maintenance treatment. Maintenance treatment enables patients to achieve stability, reduces drug use and crime, and improves health; it should be regularly reviewed to ensure the patient continues to derive benefit. The prescriber should monitor for signs of toxicity, and the patient should be told to be aware of warning signs of toxicity on initiation and during titration. A withdrawal regimen after stabilisation with methadone hydrochloride or buprenorphine should be attempted only after careful consideration. Enforced withdrawal is ineffective for sustained abstinence, and it increases the risk of patients relapsing and subsequently overdosing because of loss of tolerance. Complete withdrawal from opioids usually takes up to 4 weeks in an inpatient or residential setting, and up to 12 weeks in a community setting. If abstinence is not achieved, illicit drug use is resumed, or the patient cannot tolerate withdrawal, the withdrawal regimen should be stopped and maintenance therapy should be resumed at the optimal dose. Following successful withdrawal treatment, further support and monitoring to maintain abstinence should be provided for a period of at least 6 months.

Missed doses

Patients who miss 3 days or more of their regular prescribed dose of opioid maintenance therapy are at risk of overdose because of loss of tolerance. Consider reducing the dose in these patients. If the patient misses 5 or more days of treatment, an assessment of illicit drug use is also recommended before restarting substitution therapy; this is particularly important for patients taking buprenorphine because of the risk of precipitated withdrawal.

Buprenorphine

Buprenorphine is preferred by some patients because it is less sedating than methadone hydrochloride; for this reason it may be more suitable for employed patients or those undertaking other skilled tasks such as driving.

Buprenorphine is safer than methadone hydrochloride when used in conjunction with other sedating drugs, and has fewer drug interactions. Dose reductions may be easier than with methadone hydrochloride because the withdrawal symptoms are milder, and patients generally require fewer adjunctive medications; there is also a lower risk of overdose.

Buprenorphine can be given on alternate days in higher doses and it requires a shorter drug-free period than methadone hydrochloride before induction with naltrexone hydrochloride p. 497 for prevention of relapse.

Patients dependent on high doses of opioids may be at increased risk of precipitated withdrawal. Precipitated withdrawal can occur in any patient if buprenorphine is administered when other opioid agonist drugs are in circulation. Precipitated opioid withdrawal, if it occurs, starts within 1–3 hours of the first buprenorphine dose and peaks at around 6 hours. Non-opioid adjunctive therapy, such as lofexidine hydrochloride p. 504, may be required if symptoms are severe.

To reduce the risk of precipitated withdrawal, the first dose of buprenorphine should be given when the patient is exhibiting signs of withdrawal, or 6–12 hours after the last use of heroin (or other short-acting opioid), or 24–48 hours after the last dose of methadone hydrochloride. It is possible to titrate the dose of buprenorphine within one week—more rapidly than with methadone hydrochloride therapy—but care is still needed to avoid toxicity or precipitated withdrawal; dividing the dose on the first day may be useful.

A combination preparation containing buprenorphine with naloxone p. 503 (Suboxone®) can be prescribed for patients when there is a risk of dose diversion for parenteral administration; the naloxone hydrochloride p. 1369 component precipitates withdrawal if the preparation is injected, but it has little effect when the preparation is taken sublingually.

Methadone

Methadone hydrochloride, a long-acting opioid agonist, is usually administered in a single daily dose as methadone hydrochloride oral solution 1 mg/mL. Patients with a long history of opioid misuse, those who typically abuse a variety of sedative drugs and alcohol, and those who experience increased anxiety during withdrawal of opioids may prefer methadone hydrochloride to buprenorphine because it has a more pronounced sedative effect.

Methadone hydrochloride is initiated at least 8 hours after the last heroin dose, provided that there is objective evidence of withdrawal symptoms. A supplementary dose on the first day may be considered if there is evidence of persistent opioid withdrawal symptoms. Because of the long half-life, plasma concentrations progressively rise during initial treatment even if the patient remains on the same daily dose (it takes 3–10 days for plasma concentrations to reach steady-state in patients on a stable dose); a dose tolerated on the first day of treatment may become a toxic dose on the third day as cumulative toxicity develops. Thus, titration to the optimal dose in methadone hydrochloride maintenance treatment may take several weeks.

Opioid substitution during pregnancy

Acute withdrawal of opioids should be avoided in pregnancy because it can cause fetal death. Opioid substitution therapy is recommended during pregnancy because it carries a lower risk to the fetus than continued use of illicit drugs. If a woman who is stabilised on methadone hydrochloride or buprenorphine for treatment of opioid dependence becomes pregnant, therapy should be continued (buprenorphine is not licensed for use in pregnancy). Many pregnant patients choose a withdrawal regimen, but withdrawal during the first trimester should be avoided because it is associated with an increased risk of spontaneous miscarriage. Withdrawal of methadone hydrochloride or buprenorphine should be undertaken gradually during the second trimester, with dose

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reductions made every 3–5 days. If illicit drug use occurs, the patient should be re-stabilised at the optimal maintenance dose and consideration should be given to stopping the withdrawal regimen.

Further withdrawal of methadone hydrochloride or buprenorphine in the third trimester is not recommended because maternal withdrawal, even if mild, is associated with fetal distress, stillbirth, and the risk of neonatal mortality. Drug metabolism can be increased in the third trimester; it may be necessary to either increase the dose of methadone hydrochloride p. 502 or change to twice-daily consumption (or a combination of both strategies) to prevent withdrawal symptoms from developing.

The neonate should be monitored for respiratory depression and signs of withdrawal if the mother is prescribed high doses of opioid substitute.

Signs of neonatal withdrawal from opioids usually develop 24–72 hours after delivery but symptoms may be delayed for up to 14 days, so monitoring may be required for several weeks. Symptoms include a high-pitched cry, rapid breathing, hungry but ineffective suckling, and excessive wakefulness; severe, but rare symptoms include hypertonicity and convulsions.

Opioid substitution during breastfeeding
Dosage of methadone and buprenorphine should be kept as low as possible in breast-feeding mothers. Increased sleepiness, breathing difficulties, or limpopness in breast-fed babies of mothers taking opioid substitutes should be reported urgently to a healthcare professional.

Adjunctive therapy and symptomatic treatment
Adjunctive therapy may be required for the management of opioid withdrawal symptoms. Loperamide hydrochloride p. 66 may be used for the control of diarrhoea; beverine hydrochloride p. 56 for controlling stomach cramps; paracetamol p. 444 and non-steroidal anti-inflammatory drugs for muscular pains and headaches; metoclopromide hydrochloride p. 432 or prochlorperazine p. 389 may be useful for nausea or vomiting. Topical rubefacients can be helpful for relieving muscle pain associated with methadone hydrochloride withdrawal. If a patient is suffering from insomnia, short-acting benzodiazepines or zopiclone p. 490 may be prescribed, but because of the potential for abuse, prescriptions should be limited to a short course of a few days only. If anxiety or agitation is severe, specialist advice should be sought.

Lofexidine
Lofexidine hydrochloride p. 504 may alleviate some of the physical symptoms of opioid withdrawal by attenuating the increase in adrenergic neurotransmission that occurs during opioid withdrawal. Lofexidine hydrochloride can be prescribed as an adjuvant to opioid substitution therapy, initiated either at the same time as the opioid substitute or during withdrawal of the opioid substitute. Alternatively, lofexidine hydrochloride may be prescribed instead of an opioid substitute in patients who have mild or uncertain dependence (including young people), and those with a short history of illicit drug use.

Opioid-receptor antagonists
Patients dependant on opioids can be given a supply of naloxone hydrochloride p. 1369 to be used in case of accidental overdose. Naltrexone hydrochloride p. 497 precipitates withdrawal symptoms in opioid-dependent subjects. Because the effects of opioid-receptor agonists are blocked by naltrexone hydrochloride, it is prescribed as an aid to prevent relapse in formerly opioid-dependent patients.

Opioid dependence in children
In younger patients (under 18 years), the harmful effects of drug misuse are more often related to acute intoxication than to dependence, so substitution therapy is usually inappropriate. Maintenance treatment with opioid substitution therapy is therefore controversial in young people; however, it may be useful for the older adolescent who has a history of opioid use to undergo a period of stabilisation with buprenorphine p. 447 or methadone hydrochloride before starting a withdrawal regimen.

8.1 Alcohol dependence

Alcohol dependence

Description of condition
Alcohol dependence is a cluster of behavioural, cognitive and physiological factors that typically include a strong desire to drink alcohol, tolerance to its effects, and difficulties controlling its use. Someone who is alcohol-dependent may persist in drinking, despite harmful consequences, such as physical or mental health problems.

In severely dependent patients who have been drinking excessively for a prolonged period of time, an abrupt reduction in alcohol intake may result in the development of an alcohol withdrawal syndrome, which, in the absence of medical management, can lead to seizures, delirium tremens, and death.

Assisted alcohol withdrawal

Patients with mild alcohol dependence usually do not need assisted alcohol withdrawal. Patients with moderate dependence can generally be treated in a community setting unless they are at high risk of developing alcohol withdrawal seizures or delirium tremens; individuals with severe dependence should undergo withdrawal in an inpatient setting. Patients with uncomplicated liver disease should be treated under specialist supervision.

A long-acting benzodiazepine, such as chloridiazepoxide hydrochloride p. 343 or diazepam p. 343, is recommended to attenuate alcohol withdrawal symptoms; local clinical protocols should be followed.

In primary care, fixed-dose reducing regimens are used. This involves using a standard, initial dose (determined by the severity of alcohol dependence or level of alcohol consumption), followed by dose reduction to zero, usually over 7–10 days. In inpatient or residential settings, a fixed-dose regimen or a symptom-triggered regimen can be used. A symptom-triggered approach involves involving the drug regimen according to the severity of withdrawal and any complications in an individual patient; adequate monitoring facilities should be available. The patient should be monitored on a regular basis and treatment only continued as long as there are withdrawal symptoms.

Carbamazepine p. 311 [unlicensed indication] can be used as an alternative treatment in acute alcohol withdrawal. Clomethiazole p. 489 may be considered as an alternative to a benzodiazepine or carbamazepine p. 311. It should only be used in an inpatient setting and should not be prescribed if the patient is liable to continue drinking alcohol. Note: Alcohol combined with clomethiazole p. 489, particularly in patients with cirrhosis, can lead to fatal respiratory depression even with short-term use.

When managing withdrawal from co-existing benzodiazepine and alcohol dependence, the dose of benzodiazepine used for withdrawal should be increased. The initial daily dose is calculated, based on the requirements for alcohol withdrawal plus the equivalent regularly used daily dose of benzodiazepine. A single benzodiazepine (chloridiazepoxide hydrochloride p. 343 or diazepam p. 343) should be used rather than multiple benzodiazepines. Inpatient withdrawal regimens should last for 2–3 weeks or longer, depending on the severity of benzodiazepine dependence. When withdrawal is managed...
in the community, or where there is a high level of benzodiazepine dependence, or both, the regimen should last for a minimum of 3 weeks (according to the patient’s symptoms).

If alcohol withdrawal seizures occur, a fast-acting benzodiazepine (such as lorazepam p. 339 [unlicensed indication]) should be prescribed to reduce the likelihood of further seizures. If alcohol withdrawal seizures develop in a person during treatment for acute alcohol withdrawal, review their withdrawal drug regimen. ▶ Delirium tremens

Delirium tremens is a medical emergency that requires specialist inpatient care. In patients with delirium tremens (characterised by agitation, confusion, paraesthesia, and visual and auditory hallucinations), oral lorazepam p. 339 should be used as first-line treatment. If symptoms persist or oral medication is declined, parenteral lorazepam p. 339 [unlicensed], or haloperidol p. 386 [unlicensed] can be given as adjunctive therapy. If delirium tremens develops during treatment for acute alcohol withdrawal, the withdrawal drug regimen should also be reviewed. ▶

**Alcohol dependence**

In harmful drinkers or patients with mild alcohol dependence, a psychological intervention (such as cognitive behavioural therapy) should be offered. In those who have not responded to psychological interventions alone or who have specifically requested a pharmacological treatment, acamprosate calcium p. 496 or oral naltrexone hydrochloride p. 497 can be used in combination with a psychological intervention.

Acamprosate calcium p. 496 or oral naltrexone hydrochloride p. 497 in combination with a psychological intervention are recommended for relapse prevention in patients with moderate and severe alcohol dependence, to start after successful assisted withdrawal. Disulfiram below is an alternative for patients in whom acamprosate calcium p. 496 and oral naltrexone hydrochloride p. 497 are not suitable, or if the patient prefers disulfiram below and understands the risks of taking the drug.

Nalmefene p. 496 is recommended for the reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms, and who do not require immediate detoxification (see National funding/access decisions for nalmefene p. 496). Patients with severe alcohol-related hepatitis with a discriminant function of 32 or more can be given corticosteroids but only after any active infection or gastrointestinal bleeding is treated, any renal impairment is controlled, and following discussion of the potential benefits and risks of treatment. Corticosteroid treatment has been shown to improve survival in the short term (1 month) but not over a longer term (3 months to 1 year). It has also been shown to increase the risk of serious infections within the first 3 months of starting treatment.

Patients with chronic alcohol-related pancreatitis should be offered nutritional support; those who have symptoms of steatorrhoea or who have poor nutritional status due to Exocrine pancreatic insufficiency p. 95 should be prescribed pancreatic enzyme supplements; supplements are not indicated when pain is the only symptom.

**Wernicke’s encephalopathy**

Patients with alcohol dependence are at risk of developing Wernicke’s encephalopathy; patients at high risk are those who are malnourished, at risk of malnourishment, or have decompensated liver disease. Parenteral thiamine p. 1080, followed by oral thiamine p. 1080, should be given to patients with suspected Wernicke’s encephalopathy, those who are malnourished or at risk of malnourishment, those who have decompensated liver disease or who are attending hospital for acute treatment. Prophylactic oral thiamine p. 1080 should also be given to harmful or dependent drinkers if they are in acute withdrawal, or before and during assisted alcohol withdrawal. ▶ Parenteral thiamine is available as part of a vitamin B substances with ascorbic acid p. 1081 preparation.

**Useful Resources**


**ALDEHYDE DEHYDROGENASE INHIBITORS**

**Disulfiram**

- **INDICATIONS AND DOSE**

  Adjunct in the treatment of alcohol dependence (under expert supervision)

- **BY MOUTH**

  - Adult: 200 mg daily, increased if necessary up to 500 mg daily

- **UNLICENSED USE** Disulfiram doses in BNF may differ from those in product literature.

- **CONTRA-INDICATIONS** Cardiac failure - coronary artery disease - history of cerebrovascular accident - hypertension - psychosis - severe personality disorder - suicide risk

- **CAUTIONS** Alcohol challenge not recommended on routine basis (if considered essential—specialist units only with resuscitation facilities). Avoid in Acute porphyrias p. 1058. Diabetes mellitus - epilepsy - respiratory disease

- **INTERACTIONS** ▶ Appendix 1: disulfiram

- **SIDE-EFFECTS** Allergic dermatitis - breath odour - depression - drowsiness - encephalopathy - fatigue - hepatocellular injury - libido decreased - mania - nausea - nerve disorders - paraesthesia - psychosis - vomiting

- **PREGNANCY** High concentrations of acetaldehyde which occur in presence of alcohol may be teratogenic; avoid in first trimester.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution.

- **RENAL IMPAIRMENT** Use with caution.

- **PRE-TREATMENT SCREENING** Before initiating disulfiram, prescribers should evaluate the patient’s suitability for treatment, because some patient factors, for example memory impairment or social circumstances, make compliance to treatment or abstinence from alcohol difficult.

- **MONITORING REQUIREMENTS** During treatment with disulfiram, patients should be monitored at least every 2 weeks for the first 2 months, then each month for the following 4 months, and at least every 6 months thereafter.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and their carers should be counselled on the disulfiram-alcohol reaction—reactions may occur following exposure to small amounts of alcohol found in perfume, aerosol sprays, or low alcohol and “non-alcohol” beers and wines; symptoms may be severe and life-threatening and can include nausea, flushing, palpitations, arrhythmias, hypotension, respiratory depression, and coma. ▶ Patients and their carers should be counselled on the signs of hepatotoxicity—patients should
### 496 Substance dependence

**discontinue treatment and seek immediate medical attention if they feel unwell or symptoms such as fever or jaundice develop.**

- **MEDICINAL FORMS** There can be a variation in the licensing of different medicines containing the same drug.

**Table**

**CAUTIONARY AND ADVISORY LABELS**

- **Disulfiram (Non-proprietary)**
  - Disulfiram 200 mg | 50 tablet
  - 91.73–£120.00 DT = £105.86

### GAMMA-AMINOBUTYRIC ACID ANALOGUES AND DERIVATIVES

**Acamprosate calcium**

10-Sep-2018

- **INDICATIONS AND DOSE**
  - **Maintenance of abstinence in alcohol-dependent patients**
    - **BY MOUTH**
      - Adult 18–65 years (body-weight up to 60 kg): 666 mg once daily at breakfast and 333 mg twice daily at midday and at night
      - Adult 18–65 years (body-weight 60 kg and above): 666 mg 3 times a day

- **CAUTIONS** Continued alcohol abuse (risk of treatment failure)

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · diarrhoea · flatulence · nausea · sexual dysfunction · skin reactions · vomiting

- **PREGNANCY**

- **BREAST FEEDING** Avoid

- **HEPATIC IMPAIRMENT**

- **RENAL IMPAIRMENT**

- **PRE-TREATMENT SCREENING**

- **RENEAL IMPAIRMENT**

- **INTERACTIONS**

- **CONTRA-INDICATIONS**

- **CAUTIONS**

- **INTERACTIONS**
  - **SIDE-EFFECTS**
    - **Common or very common** Appetite decreased · asthenia · concentration impaired · confusion · diarrhoea · dizziness · drowsiness · dry mouth · feeling abnormal · headache · hyperhidrosis · libido decreased · malaise · muscle spasms · nausea · palpitations · restlessness · sensation abnormal · sleep disorders · tachycardia · tremor · vomiting · weight decreased

- **Frequency not known** Dissociation · hallucinations

- **PREGNANCY**

- **RENAL IMPAIRMENT**

**NICE decisions**

- **Nalmefene for reducing alcohol consumption in people with alcohol dependence (November 2014) NICE TA325**

  Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for patients with alcohol dependence:
  - who have a high drinking risk level (defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization’s drinking risk levels) without physical withdrawal symptoms, and
  - who do not require immediate detoxification.

  The marketing authorisation states that nalmefene should:
  - only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption, and
  - be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

  www.nice.org.uk/TA325

- **MEDICINAL FORMS**

- **Indications and dose**

- **Reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms, and who do not require immediate detoxification**

- **BY MOUTH**

- **Adult**
  - 18 mg daily if required, taken on each day there is a risk of drinking alcohol, preferably taken 1–2 hours before the anticipated time of drinking, if a dose has not been taken before drinking alcohol, 1 dose should be taken as soon as possible; maximum 18 mg per day

- **Contra-indications** Recent history of acute alcohol withdrawal syndrome · recent or current opioid use

- **Caution** Continued treatment for more than 1 year · history of seizure disorders (including alcohol withdrawal seizures) · psychiatric illness

- **Interactions**

- **Side-effects**
  - **Common or very common** Appetite decreased · asthenia · concentration impaired · confusion · diarrhoea · dizziness · drowsiness · dry mouth · feeling abnormal · headache · hyperhidrosis · libido decreased · malaise · muscle spasms · nausea · palpitations · restlessness · sensation abnormal · sleep disorders · tachycardia · tremor · vomiting · weight decreased

- **Frequency not known** Dissociation · hallucinations

- **Pregnancy**

- **Breast feeding** Avoid

- **Hepatic impairment**

- **Renal impairment** Use with caution—avoid in severe impairment.

- **Pre-treatment screening** Before initiating treatment, prescribers should evaluate the patient’s clinical status, alcohol dependence, and level of alcohol consumption.

- **Nalmefene for reducing alcohol consumption in people with alcohol dependence (November 2014) NICE TA325**

- **Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for patients with alcohol dependence:**

- **Who have a high drinking risk level (defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization’s drinking risk levels) without physical withdrawal symptoms, and**

- **Who do not require immediate detoxification.**

  The marketing authorisation states that nalmefene should:

  - **only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption, and**

  - **be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment.**

  www.nice.org.uk/TA325

- **Medicinal forms**

  - **There can be variation in the licensing of different medicines containing the same drug.**

**Gastro-resistant tablet**

**Cautionary and Advisory Labels**

- **Acamprosate calcium (Non-proprietary)**
  - Acamprosate calcium 333 mg | 168 tablet
  - £28.80 DT = £33.75
  - Campral EC (Merck Serono Ltd)
  - Acamprosate calcium 333 mg | 168 tablet
  - £28.80 DT = £33.75

**OPIOID RECEPTOR ANTAGONISTS**

**Nalmefene**

- **Indications and dose**

  - **Reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms, and who do not require immediate detoxification**

- **By mouth**

- **Adult**
  - 18 mg daily if required, taken on each day there is a risk of drinking alcohol, preferably taken 1–2 hours before the anticipated time of drinking, if a dose has not been taken before drinking alcohol, 1 dose should be taken as soon as possible; maximum 18 mg per day
Naltrexone hydrochloride

**Drug Action**
Naltrexone is an opioid-receptor antagonist.

**Indications and Dose**

Adjunct to prevent relapse in formerly opioid-dependent patients (who have remained opioid-free for at least 7-10 days) (initiated under specialist supervision)

- **By mouth**
  - Adult: Initially 25 mg daily, then increased to 50 mg daily, total weekly dose may be divided and given on 3 days of the week for improved compliance (e.g. 100 mg on Monday and Wednesday, and 150 mg on Friday); maximum 350 mg per week

Adjunct to prevent relapse in formerly alcohol-dependent patients (initiated under specialist supervision)

- **By mouth**
  - Adult: 25 mg once daily on the first day, then increased if tolerated to 50 mg daily

**Unlicensed Use**
25 mg dose for adjunct to prevent relapse in formerly alcohol-dependent patients is an unlicensed dose.

**Contra-Indications**
Patients currently dependent on opioids

**Cautions**
Concomitant use of opioids

**Caution, Further Information**
Concomitant use of opioids

**Side-Effects**
Common or very common
- Abdominal pain
- Anxiety
- Appetite abnormality
- Arthralgia
- Asthenia
- Chest pain
- Chills
- Constipation
- Diarrhoea
- Dizziness
- Eye disorders
- Headache
- Hyperhidrosis
- Mood altered
- Myalgia
- Nausea
- Palpitations
- Sexual dysfunction
- Skin reactions
- Sleep disorders
- Tachycardia
- Thirst
- Vomiting

Uncommon
- Alopecia
- Confusion
- Cough
- Depression
- Drowsiness
- Dry mouth
- Dysphoria
- Dysphonia
- Ear discomfort
- Eye discomfort
- Eye swelling
- Feeling hot
- Fever
- Flatulence
- Flushing
- Hallucination
- Hepatic disorders
- Lymphadenopathy
- Nasal complaints
- Oropharyngeal pain
- Pain
- Paranoia
- Perioral coldness
- Seborrhoea
- Sinus disorder
- Sputum increased
- Tinnitus
- Tremor
- Ulcer
- Urinary disorders
- Vertigo
- Vision disorders
- Weight changes
- Yawning

Rare or very rare
- Immune thrombocytopenic purpura
- Rhabdomyolysis
- Suicidal tendencies

Frequency not known
Withdrawal syndrome

**Pregnancy**
Use only if benefit outweighs risk.

**Breast Feeding**
Avoid—potential toxicity.

**Hepatic Impairment**
Manufacturer advises caution in mild to moderate impairment; avoid in severe or acute impairment, acute hepatitis, or hepatic failure.

**Dose Adjustments**
Manufacturer advises consider dose adjustment in mild to moderate impairment.

**Renal Impairment**
Avoid in severe impairment.

**Pre-Treatment Screening**
Test for opioid dependence with naloxone before treatment.

**Monitoring Requirements**
Liver function tests needed before and during treatment.

**Patient and Carer Advice**
Patients should be warned that an attempt to overcome the blockade of opioid receptors by overdosing could result in acute opioid intoxication.

**National Funding/Access Decisions**
**NICE Decisions**
- Naltrexone for the management of opioid dependence (January 2007) NICE TA115

Naltrexone is recommended for the prevention of relapse in formerly opioid-dependent patients who are motivated to remain in a supportive care abstinence programme. Naltrexone should be administered under supervision and its effectiveness in preventing opioid misuse reviewed regularly. www.nice.org.uk/TA115

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

**Tablet**
- Naltrexone hydrochloride (Non-proprietary)
  - Naltrexone hydrochloride 50 mg
  - 28 tablet £23.00-£51.21 DT + £47.46
  - Adepend (AOP Orphan Pharmaceuticals AG)
  - Naltrexone hydrochloride 50 mg
  - 28 tablet £47.43 DT + £47.46

**8.2 Nicotine dependence**

**Smoking Cessation**

**Overview**
Smoking tobacco is the main cause of preventable illness and premature death in the UK. It is linked to a number of diseases such as cancer (primarily lung cancer), chronic obstructive pulmonary disease, and cardiovascular disease, and can lead to complications during pregnancy. Smoking cessation reduces the risk of developing or worsening of smoking-related illnesses, and the benefits begin as soon as a person stops smoking.

Smoking cessation may be associated with temporary withdrawal symptoms caused by nicotine dependence, making it difficult for people to stop. These symptoms include nicotine cravings, irritability, depression, restlessness, poor concentration, light-headedness, sleep disturbances, and increased appetite. Weight gain is a concern for many people who stop smoking, however it is less likely to occur when drug treatment is used to aid smoking cessation.

**Non-drug treatment**

All smokers, including those who smoke e-cigarettes, should be advised to stop smoking and be offered support to facilitate smoking cessation. They should also be advised that stopping in one step (‘abrupt quitting’) offers the best chance of lasting success, and that a combination of drug treatment and behavioural support is likely to be the most effective approach.

‘Abrupt quitting’ is when a smoker makes a commitment to stop smoking or before a particular date (the quit date), rather than by gradually reducing their smoking.

Smokers who wish to stop smoking should be referred to their local NHS Stop Smoking Services, where they will be provided with advice, drug treatment, and behavioural support options such as individual counselling or group meetings. Smokers who decline to attend their local NHS Stop Smoking Services should be referred to a suitable healthcare professional who can also offer drug treatment and practical advice.

**Drug treatment**
Nicotine replacement therapy (NRT), varenicline p. 501, and bupropion hydrochloride p. 498, are effective drug treatments to aid smoking cessation.
Nervous system

Stop smoking in the long-term. Smokers should be advised that NRT will make it easier to temporarily abstinence with or without the use of NRT. These approaches can reduce how much they smoke and improve their chance of quitting. Using NRT to prevent relapse, and smoking reduction or complete abstinence not achieved at 7 weeks, is much lower and less addictive than in smoking tobacco.

E-cigarettes

E-cigarettes deliver nicotine without the toxins found in tobacco smoke. Evidence suggests that e-cigarettes are substantially less harmful to health than tobacco smoking, but long-term effects are still largely unknown. Some smokers have found e-cigarettes useful for smoking cessation, however they cannot be prescribed or supplied by smoking cessation services. People who wish to use e-cigarettes should be advised that although these products are not licensed drugs, they are regulated by the Tobacco and Health Act 2009. 

Pregnancy

Pregnant females should be advised to stop smoking completely, and be informed about the risks to the unborn child of smoking during pregnancy, and the harmful effects of exposure to second-hand smoke for both mother and baby. All pregnant females who smoke or have stopped smoking in the last 2 weeks should be referred to their local NHS Stop Smoking Services, and ongoing support should be offered during and following pregnancy. Smoking cessation should also be encouraged for all members of the household. Pregnant females who smoke should be advised to contact the NHS Pregnancy Smoking Helpline for further information (Tel: 0800 169 9169). NRT should be used in pregnant females in non-drug treatment options have failed. Clinical judgement should be used when deciding whether to prescribe NRT following a discussion about its risks and benefits. Subsequent prescriptions should only be given to pregnant females who have demonstrated they are still not smoking.

Concomitant drugs

Polycyclic aromatic hydrocarbons found in tobacco smoke increase the metabolism of some drugs by inducing hepatic enzymes, often requiring an increase in dose. Information about drugs interacting with tobacco smoke can be found under Interactions of the relevant drug monograph.

Useful Resources


Antidepressants > Serotonin and Noradrenaline Re-uptake Inhibitors

Bupropion hydrochloride

(Amfebutamone hydrochloride)

- INDICATIONS AND DOSE

To aid smoking cessation in combination with motivational support in nicotine-dependent patients

- BY MOUTH

Adult: Initially 150 mg daily for 6 days, then 150 mg twice daily (max. per dose 150 mg), minimum 8 hours between doses; period of treatment 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks, consider maximum 150 mg daily in patients with risk factors for seizures; maximum 300 mg per day

Elderly: 150 mg daily for 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks, maximum 150 mg per day

- CONTRA-INDICATIONS

Acute alcohol withdrawal - acute benzodiazepine withdrawal - bipolar disorder - CNS tumour - eating disorders - history of seizures - severe hepatic cirrhosis

- CAUTIONS

Alcohol abuse - diabetes - elderly - history of head trauma - predisposition to seizures (prescribe only if benefit clearly outweighs risk)

- INTERACTIONS

Appendix 1: bupropion

- SIDE-EFFECTS

Common or very common Abdominal pain - anxiety - concentration impaired - constipation - dizziness - dry mouth - fever - gastrointestinal disorder - headache - hyponatraemia - hypersensitivity - insomnia (reduced by avoiding dose at bedtime) - nausea - skin reactions - taste altered - tremor - vomiting

Uncommon Appetite decreased - asthenia - chest pain - confusion - tachycardia - tinnitus - vasodilation - visual impairment

Rare or very rare Angioedema - arthralgia - behaviour abnormal - bronchoospasm - delusions - depersonalisation - dysphoria - hallucination - hepatic disorders - irritability - memory loss - movement disorders - muscle complaints - palpitations - paraesthesia - parkinsonism - postural hypotension - seizure - sleep disorders - Stevens-Johnson syndrome - syncope - urinary disorders

Frequency not known Anaemia - hyponatraemia - leukocytopenia - myelosuppression - suicidal tendencies - thrombocytopenia

PREGNANCY

Avoid—no information available.

BREAST FEEDING

Present in milk—avoid.

HEPATIC IMPAIRMENT

Manufacturer advises use with caution—monitor closely for adverse effects; avoid in severe cirrhosis.

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NICOTINIC RECEPTOR AGONISTS

Dose adjustments  Manufacturer advises reduce dose to 150 mg daily in mild to moderate impairment

Renal impairment

Dose adjustments  Reduce dose to 150 mg daily.

Monitoring requirements  Manufacturer advises monitor blood pressure before and during treatment.

Patient and carer advice  Manufacturer advises patients and carers should be instructed to report any clinical worsening of depression, suicidal behaviour or thoughts and unusual changes in behaviour.

Driving and skilled tasks  Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and light-headedness.

Medicinal forms  There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet  Cautionary and advisory labels

- Zyban (GlaxoSmithKline UK Ltd)
- Bupropion hydrochloride 150 mg Zyban 150mg modified-release tablets 60 [PDR] £41.76 DT + £41.76

Nicotine replacement therapy in individuals who smoke fewer than 20 cigarettes each day

By mouth using chewing gum

Adult: 2 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose

By sublingual administration using sublingual tablets

Adult: 1 tablet every 1 hour, increased to 2 tablets every 1 hour if required, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose; maximum 40 tablets per day

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day or who require more than 15 pieces of 2-mg strength gum each day

By mouth using chewing gum

Adult: 4 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, individuals should not exceed 15 pieces of 4-mg strength gum daily, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day

By sublingual administration using sublingual tablets

Adult: 2 tablets every 1 hour, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose; maximum 40 tablets per day

Nicotine replacement therapy by inhalation

Adult: As required, the cartridges can be used when the urge to smoke occurs or to prevent cravings, individuals should not exceed 12 cartridges of the 10-mg strength daily, or 6 cartridges of the 15-mg strength daily

By mouth using lozenges

Adult: 1 lozenge every 1–2 hours as required, one lozenge should be used when the urge to smoke occurs, individuals who smoke less than 20 cigarettes each day should usually use the lower-strength lozenges; individuals who smoke more than 20 cigarettes each day and those who fail to stop smoking with the lower-strength lozenges should use the higher-strength lozenges; if attempting smoking cessation, treatment should continue for 6–12 weeks before attempting a reduction in dose; maximum 15 lozenges per day

By mouth using oromucosal spray

Adult: 1–2 sprays as required, individuals can spray in the mouth when the urge to smoke occurs or to prevent cravings, individuals should not exceed 2 sprays per episode (up to 4 sprays every hour); maximum 64 sprays per day

By intranasal administration using nasal spray

Adult: 1 spray as required, individuals can spray into each nostril when the urge to smoke occurs, up to twice every hour for 16 hours daily, if attempting smoking cessation, treatment should continue for 8 weeks before reducing the dose; maximum 64 sprays per day

By transdermal application using patches

Adult: Individuals who smoke more than 10 cigarettes daily should apply a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks; individuals who smoke fewer than 10 cigarettes daily can usually start with the medium-strength patch for 6–8 weeks, followed by the low-strength patch for 2–4 weeks; a slower titration schedule can be used in individuals who are not ready to quit but want to reduce cigarette consumption before a quit attempt; if abstinence is not achieved, or if withdrawal symptoms are experienced, the strength of the patch used should be maintained or increased until the patient is stabilised; individuals using the high-strength patch who experience excessive side-effects, that do not resolve within a few days, should change to a medium-strength patch for the remainder of the initial period and then use the low-strength patch for 2–4 weeks

Nicotine dependence 499
SPECIFIC SIDE-EFFECTS

- Common or very common
  - When used by inhalation: Asthenia, cough, dry mouth, flatulence, gastrointestinal discomfort, hiccup, hypersensitivity, nasal complaints, oral disorders, taste altered, throat complaints
  - When used by intranasal use: Chest discomfort, cough, dypnoea, epistaxis, nasal complaints, paraesthesia, throat irritation
  - With oral use: Anxiety, appetite abnormal, burping, diarrhoea, dypesia (may be caused by swallowed nicotine), gastrointestinal disorders, hiccup, increased risk of infection, mood altered, oral disorders, sleep disorders
  - With sublingual use: Asthenia, cough, dry mouth, flatulence, gastrointestinal discomfort, hiccup, hypersensitivity, oral disorders, rhinitis, taste altered, throat complaints

- Uncommon
  - When used by inhalation: Abnormal dreams, arrhythmias, bronchospasm, burping, chest discomfort, dysphonia, dypnoea, hypertension, malaise
  - With intranasal use: Abnormal dreams, asthenia, hypertension, malaise
  - With oral use: Anger, asthma exacerbated, cough, dypesia aggravated, dysphagia, haemorrhage, laryngospasm, nasal complaints, nocturia, numbness, overdose, pain, palpatations exacerbated, peripheral oedema, tachycardia, taste altered, throat complaints, vascular disorders
  - With sublingual use: Abnormal dreams, arrhythmias, bronchospasm, burping, chest discomfort, dysphonia, dypnoea, hypertension, malaise, nasal complaints
  - With transdermal use: Arrhythmias, asthenia, chest discomfort, dypnoea, hypertension, malaise, myalgia, paraesthesia

- Rare or very rare
  - When used by inhalation: Dysphagia
  - With intranasal use: Arrhythmias
  - With oral use: Coagulation disorder, platelet disorder
  - With sublingual use: Dysphagia
  - With transdermal use: Abdominal discomfort, angioedema, pain in extremity

- Frequency not known
  - When used by inhalation: Angioedema, excessive tearing, vision blurred
  - With intranasal use: Abdominal discomfort, angioedema, excessive tearing, oropharyngeal complaints
  - With sublingual use: Excessive tearing, muscle tightness, vision blurred

SIDE-EFFECTS, FURTHER INFORMATION

Some systemic effects occur on initiation of therapy, particularly if the patient is using high-strength preparations; however, the patient may confuse side-effects of the nicotine-replacement preparation with nicotine withdrawal symptoms. Common symptoms of nicotine withdrawal include malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, aphthous ulcers, decreased heart rate, and impaired concentration.

- PREGNANCY
  - The use of nicotine replacement therapy in pregnancy is preferable to the continuation of smoking, but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferable to patches but avoid liqueurice-flavoured nicotine products. Patches are useful, however, if the patient is experiencing pregnancy-related nausea and vomiting. If patches are used, they should be removed before delivery.

- BREAST FEEDING
  - Nicotine is present in milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.

- HEPATIC IMPAIRMENT
  - Manufacturer advises caution in moderate to severe impairment (risk of decreased clearance).

- RENAL IMPAIRMENT
  - Use with caution in severe renal impairment.

- DIRECTIONS FOR ADMINISTRATION
  - Acidic beverages, such as coffee or fruit juice, may decrease the absorption of nicotine through the buccal mucosa and should be avoided for 15 minutes before the use of oral nicotine replacement therapy.
  - Administration by transdermal patch: Patches should be applied on waking to dry, non-hairy skin on the hip, trunk, or upper arm and held in position for 10–20 seconds to ensure adhesion; place next patch on a different area and avoid using the same site for several days.
  - Administration by nasal spray: Initially 1 spray should be used in both nostrils but when withdrawing from therapy, the dose can be gradually reduced to 1 spray in 1 nostril.
  - Administration by oral spray: The oral spray should be released into the mouth, holding the spray as close to the mouth as possible and avoiding the lips. The patient should not inhale while spraying and avoid swallowing for a few seconds after use. If using the oral spray for the first time, or if unit not used for 2 or more days, prime the unit before administration.
  - Administration by sublingual tablet: Each tablet should be placed under the tongue and allowed to dissolve. Administration by lozenge: Slowly allow each lozenge to dissolve in the mouth; periodically move the lozenge from one side of the mouth to the other. Lozenges last for 10–30 minutes, depending on their size.
  - Administration by inhalation: Insert the cartridge into the device and draw in air through the mouthpiece; each session can last for approximately 5 minutes. The amount of nicotine from 1 puff of the cartridge is less than that from a cigarette, therefore if it is necessary to inhale more often than when smoking a cigarette. A single 10 mg cartridge lasts for approximately 20 minutes of intense use; a single 15 mg cartridge lasts for approximately 40 minutes of intense use.
  - Administration by medicated chewing gum: Chew the gum until the taste becomes strong, then rest it between the cheek and gum; when the taste starts to fade, repeat this process. One piece of gum lasts for approximately 30 minutes.

- PRESCRIBING AND DISPENSING INFORMATION
  - Flavours of chewing gum and lozenges may include mint, freshfruit, freshmint, icy white, or cherry.

- PATIENT AND CARER ADVICE
  - Patient or carers should be given advice on how to administer nicotine chewing gum, inhalators, lozenges, sublingual tablets, oral spray, nasal spray and patches.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Spray
EXCIPIENTS: May contain Ethanol
- Nicorette (McNeil Products Ltd)
  - Nicorette (Nicotine 500 microgram per 1 actuation)
    - Nicorette 500mcg/dose/dose nasal spray | 10 ml (GSL) £16.18 DT + £16.18
    - Nicorette 1mg/dose mouthspray freshmint sugar-free | 13.2 ml (GSL) £13.03 DT + £13.03 sugar-free | 26.4 ml (GSL) £20.58
    - Nicorette QuickMist (McNeil Products Ltd)
      - Nicorette 1mg per 1 actuation
        - Nicorette QuickMist 1mg/dose mouthspray freshmint sugar-free | 13.2 ml (GSL) £13.03 DT + £13.03 sugar-free | 26.4 ml (GSL) £20.58
  - Sublingual tablet
    - Cautionary and Advisory Labels 26
      - Nicorette Microtab (McNeil Products Ltd)
        - Nicorette Microtab 2mg sublingual tablets sugar-free | 100 tablet (GSL) £15.23 DT + £15.23

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Transdermal patch

- **Nicotinell (Omega Pharma Ltd)**
  - Nicotine 5 mg per 24 hour Nicotinell 5mg patches [7 patch (GSL) £9.97 DT = £9.40]
  - Nicotine 7.5 mg per 24 hour Nicotinell 7.5 mg patches [7 patch (GSL) £11.90 DT = £11.37]
  - Nicotine 15 mg per 24 hour 15 mg patches [7 patch (GSL) £17.97 DT = £17.40]

- **NiQuitin (Omega Pharma Ltd)**
  - Nicotine 2 mg per 24 hour Lozenge 2 mg [72 piece (GSL) £1.64]
  - Nicotine 3 mg per 24 hour Lozenge 3 mg [72 piece (GSL) £2.64]

Medicated chewing-gum

- **Nicorette (McNeil Products Ltd)**
  - Nicotine 1 mg per 16 hour Nicorette 1 mg [7 patch (GSL) £11.00 DT = £10.47]
  - Nicotine 2 mg per 16 hour Nicorette 2 mg [7 patch (GSL) £11.10 DT = £10.57]
  - Nicotine 3 mg per 16 hour Nicorette 3 mg [7 patch (GSL) £11.20 DT = £10.67]
  - Nicotine 4 mg per 16 hour Nicorette 4 mg [7 patch (GSL) £11.30 DT = £10.77]

- **NiQuitin (Omega Pharma Ltd)**
  - Nicotine 1 mg per 16 hour NiQuitin 1 mg [105 piece (GSL) £16.97 DT = £16.45]
  - Nicotine 2 mg per 16 hour NiQuitin 2 mg [105 piece (GSL) £17.87 DT = £17.34]

- **Nicotinell (GlaxoSmithKline Consumer Healthcare)**
  - Nicotine 4 mg per 24 hour Nicotinell TTS 4 mg [7 patch (GSL) £1.92 DT = £1.39]
  - Nicotine 10 mg per 24 hour Nicotinell TTS 10 mg [7 patch (GSL) £3.79 DT = £3.26]

- **NiQuitin Clear (Omega Pharma Ltd)**
  - Nicotine 1 mg per 24 hour Lozenge 1 mg [72 piece (GSL) £1.97 DT = £1.44]
  - Nicotine 4 mg per 24 hour Lozenge 4 mg [72 piece (GSL) £5.97 DT = £5.44]

- **Nicotine dependence**  

  **Varenicline**

  **DRUG ACTION** Varenicline is a selective nicotine-receptor partial agonist.

  **INDICATIONS AND DOSE** To aid smoking cessation

  **BY MOUTH**

  - Adult: Initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks; reduced if not tolerated to 500 micrograms twice daily, usually to be started 1–2 weeks before target stop date but can be started up to a maximum of 5 weeks before target stop date, 12-week course can be repeated in abstinent individuals to reduce risk of relapse

  **SIDE-EFFECTS**

  - Common or very common Appetite abnormal - asthenia - chest discomfort - constipation - diarrhoea - dizziness

  **IMPORTANT SAFETY INFORMATION**

  **MHRA/CHM ADVICE: SUICIDAL BEHAVIOUR AND VARENICLINE**

  Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood, or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline.

  **CAUTIONS** Conditions that may lower seizure threshold - history of cardiovascular disease - history of psychiatric illness (may exacerbate underlying illness including depression) - predisposition to seizures

  www.getintopharma.com
502 Substance dependence

Nervous system

Opioid dependence

MEDICINAL FORMS

Tablet

Varenicline for smoking cessation (July 2011)

=form=""alignment=""top"">① NATIONALLY FUNDING/ACCESS DECISIONS

TREATMENT CESSATION

Driving and skilled tasks

FREQUENCY NOT KNOWN

Pregnancy

Breast feeding

RENAL IMPAIRMENT

Dose adjustments

Severe pain

BY MOUTH, OR BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

Adult: 5–10 mg every 6–8 hours, adjusted according to response, on prolonged use not to be given more frequently than every 12 hours

Adjuvant in treatment of opioid dependence

Adjunct in treatment of opioid dependence if tolerance low or not known

BY MOUTH USING ORAL SOLUTION

Adult: Initially 10–30 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily

Adjunct in treatment of opioid dependence if tolerance high (under expert supervision)

BY MOUTH USING ORAL SOLUTION

Adult: Initially up to 40 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily

Cough in palliative care

INITIALLY BY MOUTH USING LINCTUS

Adult: 1–2 mg every 4–6 hours, (by mouth) reduced to 1–2 mg twice daily, use twice daily frequency if prolonged use

DOSE EQUIVALENCES AND CONVERSION

See buprenorphine p. 447 for dose adjustments in opioid substitution therapy, for patients taking methadone who want to switch to buprenorphine.

UNLICENSED USE

Methadone hydrochloride doses for opioid dependence in the BNF may differ from those in the product literature.

IMPORTANT SAFETY INFORMATION

Methadone oral solution 1 mg/mL is 2½ times the strength of Methadone Linctus (2 mg/5mL). Many preparations of Methadone oral solution are licensed for opioid drug addiction only but some are also licensed for analgesia in severe pain.

CONTRA-INDICATIONS

Phaeochromocytoma

CAUTIONS

Family history of sudden death (ECG monitoring recommended) - history of cardiac conduction abnormalities

CAUTIONS, FURTHER INFORMATION

QT-interval prolongation Patients with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored.

INTERACTIONS

Other drugs used for Opioid dependence

Buprenorphine, p. 447 • Naltrexone hydrochloride, p. 497

www.getintopharma.com
SIDE-EFFECTS

GENERAL SIDE-EFFECTS
Asthma exacerbated, dry eye, dysuria, hyperprolactinaemia, hyperthermia, menstrual cycle irregularities, mood altered, nasal dryness, QT interval prolongation

SPECIFIC SIDE-EFFECTS
- With oral use: Galactorrhoea, intracranial pressure increased
- With parenteral use: Biliary spasm, muscle rigidity, oedema, restlessness, sexual dysfunction, sleep disorder, ureteral spasm, withdrawal syndrome neonatal

SIDE-EFFECTS, FURTHER INFORMATION
Methadone is a long-acting opioid therefore effects may be cumulative.

Methadone, even in low doses is a special hazard for children; non-dependent adults are also at risk of toxicity; dependent adults are at risk if tolerance is incorrectly assessed during induction.

Overdose
Methadone has a very long duration of action; patients may need to be monitored for long periods following large overdoses.

BREAST FEEDING
Withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate).

HEPATIC IMPAIRMENT
Manufacturer advises caution; consider avoiding in severe impairment (risk of increased exposure).

Dose adjustments
Manufacturer advises consider dose reduction.

RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

TREATMENT CESSATION
Avoid abrupt withdrawal.

DIRECTIONS FOR ADMINISTRATION
Syrup preserved with hydroxybenzoate (paraben) esters may be incompatible with methadone hydrochloride.

PRESCRIBING AND DISPENSING INFORMATION
- Flavours of oral liquid formulations may include tolu.
- Palliative care: For further information on the use of methadone in palliative care, see www.medicinescomplete.com/#/content/palliative/methadone

METHADOSE
- The final strength of the methadone mixture to be dispensed to the patient must be specified on the prescription.

Important:—care is required in prescribing and dispensing the correct strength since any confusion could lead to an overdose; this preparation should be dispensed only after dilution as appropriate with Methadose.

Diluent (life of diluted solution 3 months) and is for drug dependent persons.

NATIONAL FUNDING/ACCESS DECISIONS
NICE decisions
- Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TA14

- Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

www.nice.org.uk/TA14

LESS SUITABLE FOR PRESCRIBING
Methadone linctus is less suitable for prescribing for cough in terminal disease (has a tendency to accumulate).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, solution for injection

Table:
- CAUTIONARY AND ADVISORY LABELS
  - Phystepone (Martindale Pharmaceuticals Ltd)
    - Methadone hydrochloride 5 mg
      - 50 tablet
      - £2.84 DT = £2.84
  - Solution for injection
    - Methadone hydrochloride (Non-proprietary)
      - Methadone hydrochloride 50 mg per 1 ml
        - 10 ampoule
        - £16.33
    - Phystepone (Martindale Pharmaceuticals Ltd)
      - Methadone hydrochloride 10 mg per 1 ml
        - 10 ampoule
        - £11.72

Phystepone 20mg/2ml solution for injection ampoules
- 10 ampoule
  - £7.63
  - £17.72

- Methadone hydrochloride 50 mg per 1 ml
  - 10 ampoule
  - £17.72

Methadone hydrochloride 50 mg per 1 ml
- 10 ampoule
  - £17.72

Methadone hydrochloride 5 mg per 1 ml
- 10 ampoule
  - £16.33

Phystepone 20mg/2ml solution for injection ampoules
- 10 ampoule
  - £7.63
  - £17.72

Phystepone 50mg/5ml solution for injection ampoules
- 10 ampoule
  - £16.33

Phystepone 20mg/2ml solution for injection ampoules
- 10 ampoule
  - £7.63
  - £17.72

Phystepone 50mg/5ml solution for injection ampoules
- 10 ampoule
  - £17.72

Oral solution
- CAUTIONARY AND ADVISORY LABELS
  - Methadone hydrochloride (Non-proprietary)
    - Methadone hydrochloride l mg per 1 ml
      - Methadone 1mg/ml oral solution | 100 ml
      - £1.00
      - £1.20
      - £0.90
      - 500 ml
    - Methadone hydrochloride 1 mg per 1 ml
      - Methadone 1mg/ml oral solution | 100 ml
      - £4.15–£6.10
      - £4.50
      - 2500 ml
      - £22.50–£32.10
    - Methadone 1mg/ml oral solution sugar-free sugar-free | 50 ml
      - £1.00
      - £0.89
      - 500 ml
      - £4.10–£5.18
      - £4.45
    - 2500 ml
      - £73.05

- Methadose (Rosemont Pharmaceuticals Ltd)
  - Methadone hydrochloride 10 mg per 1 ml
    - Methadose 10mg/ml oral solution concentrate sugar-free | 150 ml
    - £2.01
    - £1.20
    - £0.75
  - Methadone hydrochloride 20 mg per 1 ml
    - Methadose 20mg/ml oral solution concentrate sugar-free | 150 ml
    - £2.04
    - £2.02

- Metharose (Rosemont Pharmaceuticals Ltd)
  - Methadone hydrochloride 1 mg per 1 ml
    - Metharose 1mg/ml oral solution sugar-free sugar-free | 500 ml
    - £6.82
    - £4.43
  - Methadone hydrochloride 1 mg per 1 ml
    - Metharose 1mg/ml oral solution sugar-free sugar-free | 500 ml
    - £1.27
    - £0.89
    - 500 ml
    - £6.42
    - £4.45
  - 2500 ml
    - £32.10

- Physeptone 1mg/ml mixture | 100 ml
  - £1.27
  - £0.90
  - 500 ml
  - £6.42
  - £4.45
  - 2500 ml
  - £32.10

OPIOID RECEPTOR ANTAGONISTS

Buprenorphine with naloxone

The properties listed below are those particular to the combination only. For the properties of the components please consider, buprenorphine p. 447, naloxone hydrochloride p. 1369.

INDICATIONS AND DOSE
- Adjunct in the treatment of opioid dependence (dose expressed as buprenorphine)
  - BY SUBLINGUAL ADMINISTRATION
    - Adult: Initially 2–4 mg once daily, an additional dose of 2–4 mg may be administered on day 1 depending on the individual patient’s requirement, increased in steps of 2–8 mg, adjusted according to response, total weekly dose may be divided and given on alternate days or 3 times weekly; maximum 24 mg per day

INTERACTIONS
- Appendix 1: opioids
Lofexidine hydrochloride

**INDICATIONS AND DOSE**

**Management of symptoms of opioid withdrawal**

- **BY MOUTH**
  - Adult: Initially 800 micrograms daily in divided doses, increased in steps of 400–800 micrograms daily (max. per dose 800 micrograms) as required recommended duration of treatment 7–10 days if no opioid use (but longer may be required); maximum 2.4 mg per day

**CAUTIONS**
- Bradycardia - cerebrovascular disease - depression - history of QT prolongation - hypotension (monitor pulse rate and blood pressure) - metabolic disturbances - recent myocardial infarction - severe coronary insufficiency

**INTERACTIONS**

- Appendix 1: Lofexidine

**SIDE-EFFECTS**
- Common or very common: Bradycardia - dizziness - drowsiness - hypotension - mucosal dryness

**FREQUENCY NOT KNOWN**
- QT interval prolongation

**PREGNANCY**
- Use only if benefit outweighs risk—no information available.

**BREAST FEEDING**
- Use only if benefit outweighs risk—no information available.

**RENAL IMPAIRMENT**
- Caution in chronic impairment.

**MONITORING REQUIREMENTS**
- Monitoring of blood pressure and pulse rate is recommended on initiation, for at least 72 hours or until a stable dose is achieved, and on discontinuation.

---

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 355/07

The Scottish Medicines Consortium has advised (March 2007) that buprenorphine/naloxone (Suboxone®) is accepted for restricted use within NHS Scotland for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment in whom methadone is not suitable.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Sublingual tablet**

- **Buprenorphine with naloxone (Non-proprietary)**
- Naloxone (as Naloxone hydrochloride dihydrate) 500 microgram,
- Buprenorphine (as Buprenorphine hydrochloride) 2 mg
- Buprenorphine 2mg / Naloxone 500 microgram sublingual tablets sugar-free (28 tablets)

- **Buprenorphine (as Buprenorphine hydrochloride)**
- Buprenorphine 8 mg / Naloxone 2 mg sublingual tablets sugar-free (28 tablets)

- **Suboxone (Indivior UK Ltd)**
- Naloxone (as Naloxone hydrochloride dihydrate) 500 microgram,
- Buprenorphine (as Buprenorphine hydrochloride) 2 mg
- Buprenorphine 2 mg / Naloxone 500 microgram sublingual tablets sugar-free (28 tablets)

- **Suboxone 2mg/500microgram sublingual tablets**
- Buprenorphine 8 mg / Naloxone 2 mg sublingual tablets sugar-free (28 tablets)

- **Suboxone 2mg/500microgram sublingual tablets**
- Buprenorphine 8 mg / Naloxone 2 mg sublingual tablets sugar-free (28 tablets)

**DISTRIBUTION**

Available from specialist importing companies.

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**SYMPATHOMIMETICS**

- **ALPHA2-ADRENOCEPTOR AGONISTS**

- **Lofexidine hydrochloride**

- **DRUG ACTION** Lofexidine is an alpha2-adrenergic agonist.

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Chapter 5
Infection

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1 Amoebic infection

Other drugs used for Amoebic infection Metronidazole, p. 542 - Tinidazole, p. 544

**ANTIPROTOZOALS**

**Mepacrine hydrochloride**

- **INDICATIONS AND DOSE**
  - **Giardiasis**
    - **BY MOUTH**
    - Adult: 100 mg every 8 hours for 5–7 days

- **UNLICENSED USE** Not licensed for use in giardiasis.

- **CAUTIONS** Avoid in psoriasis - elderly - history of psychosis

- **INTERACTIONS** → Appendix 1: mepacrine

- **SIDE-EFFECTS** Aplastic anaemia (long term use) - central nervous system stimulation (with high doses) - corneal deposits - dermatosis (long term use) - dizziness - exfoliative dermatitis (severe; long term use) - gastrointestinal disorder - headache - hepatitis (long term use) - nail discouloration - nausea (with high doses) - oral discouloration - skin discouloration (long term use) - toxic psychosis (transient; with high doses) - urine discouloration (long term use) - visual impairment - vomiting (with high doses)

- **HEPATIC IMPAIRMENT** Use with caution.

- **MEDICINAL FORMS** Forms available from special-order manufacturers include: tablet

2 Bacterial infection

**Antibacterials, principles of therapy**

07-Mar-2017

**Antibacterial drug choice**

Before selecting an antibacterial the clinician must first consider three factors—the patient, the known or likely causative organism, and the risk of bacterial resistance with repeated courses.

Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, risk of complications, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the factors above, will provide one or more antibacterial option.

In patients receiving antibacterial prophylaxis, an antibacterial from a different class should be used.

An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a patient complaining of nausea and symptoms of a urinary-tract infection in early pregnancy. The organism is reported as being resistant to ampicillin p. 550 but sensitive to nitrofurantoin p. 590 (can cause nausea), gentamicin p. 519 (can be given only by injection and best avoided in pregnancy), tetracycline p. 567 (causes dental discoloration) and trimethoprim p. 574 (folic acid antagonist therefore theoretical teratogenic risk), and cefalexin p. 524. The safest antibiotics in pregnancy are the penicillins and cephalosporins; therefore, cefalexin would be indicated for this patient.

Some patients may be at higher risk of treatment failure. They include those who have had repeated antibacterial courses, a previous or current culture with resistant bacteria, or those at higher risk of developing complications.
Antibacterial policies

Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Antibacterials, considerations before starting therapy

The following precepts should be considered before starting:

- **Viral infections should not be treated with antibacterials.** However, antibacterials may be used to treat secondary bacterial infection (e.g. bacterial pneumonia secondary to influenza);
- **Samples should be taken for culture and sensitivity testing;** an antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- **Knowledge of prevalent organisms** and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication (e.g. life-threatening sepsis);
- **The dose** of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. The describing of the so-called ‘standard’ dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- **The route** of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;
- **Duration** of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections. The prescription for an antibacterial should specify the duration of treatment or the date when treatment is to be reviewed.

Advice to be given to patients

If an antibacterial is given, advise patients about:

- **Possible adverse effects** e.g. diarrhoea;
- **Seeking medical help** if symptoms worsen rapidly or significantly at any time, symptoms do not start to improve within an agreed time, or if the patient becomes systemically very unwell.

If an antibacterial is **not** given, advise patients about:

- **Seeking medical help** if symptoms worsen rapidly or significantly at any time, if symptoms do not start to improve within an agreed time, or if the patient becomes systemically very unwell.

Antibacterials, considerations during therapy

**Review choice of antibacterial if susceptibility results indicate bacterial resistance and symptoms are not improving**—consult local microbiologist as needed. If no bacterium is cultured, the antibacterial can be continued or stopped on clinical grounds.

**Review intravenous antibacterials within 48 hours and consider stepping down to oral antibacterials where possible.**

Superinfection

In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. **fungal infections or antibiotic-associated colitis** (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Notifiable diseases

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) or local health protection unit when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Notifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Yes</td>
</tr>
<tr>
<td>Botulism</td>
<td>Yes</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Cholera</td>
<td>Yes</td>
</tr>
<tr>
<td>Diarrhoea (infectious bloody)</td>
<td>Yes</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Yes</td>
</tr>
<tr>
<td>Encephalitis, acute</td>
<td>Yes</td>
</tr>
<tr>
<td>Food poisonings</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemorrhagic fever (viral)</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis, viral</td>
<td>Yes</td>
</tr>
<tr>
<td>Legionnaires’ disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Yes</td>
</tr>
<tr>
<td>Malaria</td>
<td>Yes</td>
</tr>
<tr>
<td>Measles</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningococcal septicaemia</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Note** It is good practice for doctors to also inform the consultant in communicable disease control of instances of other infections (e.g. psittacosis) where there could be a public health risk.

Sepsis, early management

**Patients identified as being at high risk of severe illness or death due to suspected sepsis should be given a broad-spectrum antibacterial at the maximum recommended dose without delay (ideally within one hour).** Microbiological samples and blood cultures must be taken prior to administration of antibiotics; the prescription should be adjusted subsequently according to susceptibility results. A thorough clinical examination should be carried out to identify sources of infection. If the source of infection is identified, treatment in line with local antibacterial guidance or susceptibility results.

Patients who require empirical intravenous treatment for a suspected infection, but who have no confirmed diagnosis, should be treated with an intravenous antibiotic from the local formulary and in line with national guidelines.

The need for intravenous fluids, inotropes, vasopressors and oxygen should also be assessed without delay, taking into consideration the patient’s lactate concentration, systolic blood pressure, and their risk of severe illness or
death. Patients at high risk should be monitored continuously if possible, and no less than every 30 minutes. Patients with suspected sepsis who are not immediately deemed to be at high risk of severe illness or death, should be re-assessed regularly for the need for empirical treatment, taking into consideration all risk factors including lactate concentration and evidence of acute kidney injury.

### Antibacterials, use for prophylaxis

**Rheumatic fever: prevention of recurrence**
- Phenoxymethylpenicillin p. 548 or sulfadiazine p. 563.

**Invasive group A streptococcal infection: prevention of secondary cases**
- Phenoxymethylpenicillin.

**Meningococcal meningitis: prevention of secondary cases**
- Ciprofloxacin p. 558 or rifampicin p. 582 or i/m ceftriaxone p. 528 [unlicensed indication].

**Haemophilus influenzae type b disease: prevention of secondary cases**
- Rifampicin or (if rifampicin cannot be used) i/m or i/v ceftriaxone [unlicensed indication].

**Diphtheria in non-immune patients: prevention of secondary cases**
- Erythromycin (or another macrolide e.g. azithromycin or clarithromycin p. 538).

### Bacterial infection 507

**Pertussis, antibacterial prophylaxis**
- Clarithromycin (or azithromycin or erythromycin).

Within 3 weeks of onset of cough in the index case, give antibacterial prophylaxis to all close contacts if amongst them there is at least one unimmunised or partially immunised child under 1 year of age, or if there is at least one individual who has not received a pertussis-containing vaccine more than 1 week and less than 5 years ago (so long as that individual lives or works with children under 4 months of age, is pregnant at over 32 weeks gestation, or is a healthcare worker who works with children under 1 year of age or with pregnant women).

**Pneumococcal infection in asplenia or in patients with sickle-cell disease, antibacterial prophylaxis**
- Phenoxymethylpenicillin.

If penicillin-allergic, erythromycin.

Antibacterial prophylaxis is not fully reliable. Antibacterial prophylaxis may be discontinued in children over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection.

**Tuberculosis antibacterial prophylaxis in susceptible close contacts or those who have become tuberculin positive**
- See Close contacts and Chemoprophylaxis for latent tuberculosis under Tuberculosis p. 578.

**Animal and human bites, antibacterial prophylaxis**
- Co-amoxiclav p. 551 alone (or doxycycline p. 564 + metronidazole p. 542 if penicillin-allergic).

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1292 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection).

Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

**Early-onset neonatal infection, antibacterial prophylaxis**
- i/v benzylpenicillin sodium p. 547 (or i/v clindamycin p. 535 if history of allergy to penicillins).

Give intrapartum prophylaxis to women with group B streptococcal colonisation, bacteriuria, or infection in the current pregnancy, or to women who had a previous baby with an invasive group B streptococcal infection. Consider prophylaxis for women in preterm labour if there is prelabour rupture of membranes or if intrapartum rupture of membranes lasting more than 18 hours is suspected.
Infection

Gastro-intestinal procedures, antibacterial prophylaxis

Operations on stomach or oesophagus
- Single dose of i/v gentamicin p. 519 or i/v cefuroxime p. 526 or i/v co-amoxiclav (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v teicoplanin p. 532 (or vancomycin p. 534) if high risk of meticillin-resistant Staphylococcus aureus.

Open biliary surgery
- Single dose of i/v cefuroxime + i/v metronidazole or i/v gentamicin + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant Staphylococcus aureus.

Resections of colon and rectum for carcinoma, and resections in inflammatory bowel disease, and appendicectomy
- Single dose of i/v gentamicin + i/v metronidazole or i/v cefuroxime + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant Staphylococcus aureus.

Endoscopic retrograde cholangiopancreatography
- Single dose of i/v gentamicin p. 519 or oral or i/v ciprofloxacin p. 558.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Prophylaxis recommended if pancreatic pseudocyst, immunocompromised, history of liver transplantation, or risk of incomplete biliary drainage. For biliary complications following liver transplantation, add i/v amoxicillin p. 546 or i/v teicoplanin p. 532 (or vancomycin p. 534).

Percutaneous endoscopic gastrostomy or jejunostomy
- Single dose of i/v co-amoxiclav p. 551 or i/v cefuroxime p. 526.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v teicoplanin (or vancomycin) if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant Staphylococcus aureus.

Orthopaedic surgery, antibacterial prophylaxis

Joint replacement including hip and knee
- Single dose of i/v cefuroxime alone or i/v flucloxacillin p. 554 + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant Staphylococcus aureus, use single dose of i/v teicoplanin (or vancomycin) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Closed fractures
- Single dose of i/v cefuroxime or i/v flucloxacillin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant Staphylococcus aureus, use single dose of i/v teicoplanin (or vancomycin) (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Open fractures
- Use i/v co-amoxiclav alone or i/v cefuroxime + i/v metronidazole p. 542 (or i/v clindamycin p. 535 alone if history of allergy to penicillins or to cephalosporins).

Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant Staphylococcus aureus. Start prophylaxis within 3 hours of injury and continue until soft tissue closure (max. 72 hours).

At first debridement also use a single dose of i/v cefuroxime + i/v metronidazole + i/v gentamicin or i/v co-amoxiclav + i/v gentamicin (or i/v clindamycin + i/v gentamicin if history of allergy to penicillins or to cephalosporins).

At time of skeletal stabilisation and definitive soft tissue closure use a single dose of i/v gentamicin + i/v teicoplanin (or vancomycin) (intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure).

High lower-limb amputation
- Use i/v co-amoxiclav alone or i/v cefuroxime + i/v metronidazole.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Continue antibacterial prophylaxis for at least 2 doses after procedure (max. duration of prophylaxis 5 days). If history of allergy to penicillin or to cephalosporins, or if high risk of meticillin-resistant Staphylococcus aureus, use i/v teicoplanin (or vancomycin) + i/v gentamicin + i/v metronidazole.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Urological procedures, antibacterial prophylaxis

Transrectal prostate biopsy
- Single dose of oral ciprofloxacin + oral metronidazole or i/v gentamicin + i/v metronidazole (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin + i/v metronidazole if high risk of meticillin-resistant Staphylococcus aureus (additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss).

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Transurethral resection of prostate
- Single dose of oral ciprofloxacin or i/v gentamicin or i/v cefuroxime (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).
Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

- Use single dose of i/v gentamicin if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Obstetric and gynaecological surgery, antibacterial prophylaxis**

**Caesarean section**
- Single dose of i/v cefuroxime (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

- Substitute i/v clindamycin if history of allergy to penicillins or cephalosporins. Add i/v teicoplanin (or vancomycin) if high risk of meticillin-resistant *Staphylococcus aureus*.

**Hysterectomy**
- Single dose of i/v cefuroxime + i/v metronidazole or i/v gentamicin + i/v metronidazole or i/v co-amoxiclav alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

- Use single dose of i/v gentamicin + i/v metronidazole or add i/v teicoplanin (or vancomycin) to other regimens if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss). Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

**Termination of pregnancy**
- Single dose of oral metronidazole (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

If genital chlamydial infection cannot be ruled out, give doxycycline p. 564 postoperatively.

**Cardiology procedures, antibacterial prophylaxis**

**Cardiac pacemaker insertion**
- Single dose of i/v cefuroxime alone or i/v flucloxacillin + i/v gentamicin or i/v teicoplanin (or vancomycin) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

- Use single dose of i/v teicoplanin (or vancomycin) + i/v cefuroxime or i/v teicoplanin (or vancomycin) + i/v gentamicin if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Vascular surgery, antibacterial prophylaxis**

**Reconstructive arterial surgery of abdomen, pelvis or legs**
- Single dose of i/v cefuroxime alone or i/v flucloxacillin + i/v gentamicin p. 519 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v metronidazole p. 542 for patients at risk from anaerobic infections including those with diabetes, gangrene, or undergoing amputation. Use single dose of i/v

**Bacterial infection**

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The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

**Immunosuppression and indwelling intraperitoneal catheters**
Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

**Blood infections, antibacterial therapy**

**Septicaemia (community-acquired)**
- A broad-spectrum antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 545, ticarcillin with clavulanic acid p. 546) or a broad-spectrum cephalosporin (e.g. cefuroxime p. 526).
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin p. 534 (or teicoplanin p. 532).
- If anaerobic infection suspected, add metronidazole p. 542 to broad-spectrum cephalosporin.
- If other resistant micro-organisms suspected, use a more broad-spectrum beta-lactam antibacterial (e.g. meropenem p. 523).

**Septicaemia (hospital-acquired)**
- A broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam, ticarcillin with clavulanic acid, ceftazidime p. 528, imipenem with cilastatin p. 522, or meropenem).
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin (or teicoplanin).
- If anaerobic infection suspected, add metronidazole to broad-spectrum cephalosporin.

**Septicaemia related to vascular catheter**
- Vancomycin (or teicoplanin).
- If Gram-negative sepsis suspected, especially in the immunocompromised, add a broad-spectrum antipseudomonal beta-lactam.
- Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus*, pseudomonas, or *Candida* species.

**Meningococcal septicaemia**
If meningococcal disease suspected, a single dose of benzylpenicillin sodium p. 547 should be given before urgent transfer to hospital, so long as this does not delay the transfer; cefotaxime p. 527 may be an alternative in penicillin allergy; chloramphenicol p. 568 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- Benzylpenicillin sodium or cefotaxime (or ceftriaxone p. 528)
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol

To eliminate nasopharyngeal carriage, ciprofloxacin p. 558, or rifampicin p. 582, or ceftriaxone may be used.

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**Cardiovascular system infections, antibacterial therapy**

**Endocarditis: initial ‘blind’ therapy**
- Native valve endocarditis, amoxicillin p. 548 (or ampicillin p. 550)
- Consider adding low-dose gentamicin p. 519
- If penicillin-allergic, or if meticillin-resistant *Staphylococcus aureus* suspected, or if severe sepsis, use vancomycin p. 534 + low-dose gentamicin
- If severe sepsis with risk factors for Gram-negative infection, use vancomycin + meropenem p. 523
- If prosthetic valve endocarditis, vancomycin + rifampicin p. 582 + low-dose gentamicin

**Endocarditis (native valve) caused by staphylococci**
- Flucloxacillin p. 554
- Suggested duration of treatment 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)
- If penicillin-allergic or if meticillin-resistant *Staphylococcus aureus*, vancomycin + rifampicin
- Suggested duration of treatment 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)

**Endocarditis (prosthetic valve) caused by staphylococci**
- Flucloxacillin + rifampicin + low-dose gentamicin
- Suggested duration of treatment 4–6 weeks (at least 6 weeks if prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- If penicillin-allergic or if meticillin-resistant *Staphylococcus aureus*, vancomycin + rifampicin + low-dose gentamicin
- Suggested duration of treatment at least 6 weeks; review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks

**Endocarditis caused by fully-sensitive streptococci**
- Benzylpenicillin sodium p. 547
- Suggested duration of treatment 4–6 weeks (6 weeks for prosthetic valve endocarditis)
- If penicillin-allergic, vancomycin (or teicoplanin p. 532) + low-dose gentamicin
- Suggested duration of treatment 4–6 weeks (stop gentamicin after 2 weeks)

**Endocarditis caused by less-sensitive streptococci**
- Benzylpenicillin sodium + low-dose gentamicin
- Suggested duration of treatment 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin
- If penicillin-allergic or highly penicillin-resistant, vancomycin (or teicoplanin) + low-dose gentamicin
- Suggested duration of treatment 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin

**Endocarditis caused by enterococci**
- Amoxicillin (or ampicillin) + low dose gentamicin or benzylpenicillin sodium + low-dose gentamicin
- Suggested duration of treatment 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue
### Bacterial infection

**Benzylpenicillin sodium**

- Meningitis caused by meningococci
  - Consider adding vancomycin if prolonged or multiple use
  - **Suggested duration of treatment** 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue benzylpenicillin at 2 weeks—seek specialist advice if benzylpenicillin considered necessary beyond 2 weeks
  - If penicillin-allergic or penicillin-resistant, vancomycin (or teicoplanin) + low-dose gentamicin
  - **Suggested duration of treatment** 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue benzylpenicillin at 2 weeks—seek specialist advice if benzylpenicillin considered necessary beyond 2 weeks
  - If penicillin resistant, amoxicillin (or ampicillin)
  - Add streptomycin p. 520 (if susceptible) for 2 weeks
  - **Suggested duration of treatment** at least 6 weeks

**Endocarditis caused by Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella species (‘HACEK’ micro-organisms)**

- Amoxicillin (or ampicillin) + low-dose gentamicin
- **Suggested duration of treatment** 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks
- If amoxicillin-resistant, ceftriaxone p. 528 (or cefotaxime p. 527) + low-dose gentamicin
- **Suggested duration of treatment** 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

### Central nervous system infections, antibacterial therapy

**Meningitis: initial empirical therapy**

- Transfer patient to hospital urgently.
- If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) suspected, benzylpenicillin sodium p. 547 should be given before transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, benzylpenicillin sodium should be given before the transfer. Cefotaxime p. 527 may be an alternative in penicillin allergy; chloramphenicol p. 568 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- In hospital, consider adjunctive treatment with dexamethasone p. 675 (particularly if pneumococcal meningitis suspected in adults), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery. In hospital, if aetiology unknown:
  - **Adult and child 3 months**–50 years, cefotaxime (or ceftriaxone p. 528)
  - Consider adding vancomycin p. 534 if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
  - **Suggested duration of treatment** at least 10 days
  - **Adult over 50 years** cefotaxime (or ceftriaxone) + amoxicillin p. 548 (or ampicillin p. 550)
  - Consider adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
  - **Suggested duration of treatment** at least 10 days

**Meningitis caused by meningococci**

- Benzylpenicillin sodium or cefotaxime (or ceftriaxone)
  - **Suggested duration of treatment** 7 days.
  - If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol
  - **Suggested duration of treatment** 7 days.

**Meningitis caused by pneumococci**

- Cefotaxime (or ceftriaxone)
- Consider adjunctive treatment with dexamethasone, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
- **Suggested duration of treatment** 10 days.
- For H. influenzae type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts
  - If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if micro-organism resistant to cefotaxime, chloramphenicol
  - Consider adjunctive treatment with dexamethasone, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
  - **Suggested duration of treatment** 10 days.
  - For H. influenzae type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts

**Meningitis caused by Listeria**

- Amoxicillin (or ampicillin) + gentamicin p. 519
  - **Suggested duration of treatment** 21 days.
  - Consider stopping gentamicin after 7 days.
  - If history of immediate hypersensitivity reaction to penicillin, co-trimoxazole p. 562
  - **Suggested duration of treatment** 21 days.

### Ear infections, antibacterial therapy

**Otitis externa**

- Otitis externa can be triggered by a bacterial infection caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Consider systemic antibacterial if spreading cellulitis or patient systemically unwell.

**Choice of antibacterial therapy**

**No penicillin allergy**

- Flucoxacinil p. 554

**Penicillin allergy or intolerance**

- Clarithromycin p. 538 (or azithromycin p. 536 or erythromycin p. 539)

If *pseudomonas* suspected

- Ciprofloxacin p. 558 (or an aminoglycoside)
  - For topical treatments, see *Otitis externa*, under Ear p. 1194.
512  Bacterial infection

Otitis media
- Acute otitis media is an inflammation in the middle ear associated with effusion and accompanied by an ear infection. Acute otitis media is commonly seen in children and is generally caused by viruses (respiratory syncytial virus and rhinovirus) or bacteria (Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, and Moraxella catarrhalis); both virus and bacteria often co-exist. For further information see Acute otitis media in Ear p. 1194.

Alternative if micro-organism sensitive
Cipro

Shigellosis
- Treat invasive or severe infection. Do not treat less severe infection, unless there is a risk of developing invasive infection (e.g. immunocompromised patients, those with haemoglobinopathy, or children under 6 months of age).
- Ciprofloxacin or cefotaxime p. 527

Genital system infections, antibacterial therapy

Bacterial vaginosis
- Oral metronidazole p. 542
- Suggested duration of treatment 5–7 days (or high-dose metronidazole as a single dose)
- Alternatively, topical metronidazole for 5 days or topical clindamycin p. 828 for 7 days

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Uncomplicated genital chlamydial infection, non-gonococcal urethritis, and non-specific genital infection

- Contact tracing recommended.
- Azithromycin p. 536 or doxycycline p. 564
  - Suggested duration of treatment azithromycin as a single dose or doxycycline for 7 days
- Alternatively, erythromycin p. 539.
- Suggested duration of treatment 14 days

Gonorrhea: uncomplicated

- Contact tracing recommended. Consider chlamydia co-infection. Choice of alternative antibacterial regimen depends on locality where infection acquired.
- Azithromycin + i/m ceftriaxone p. 528
  - Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, when parenteral administration is not possible, cefixime p. 527 + azithromycin
  - Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, if micro-organism is sensitive to a quinolone, ciprofloxacin p. 558 + azithromycin
  - Suggested duration of treatment is a single-dose of each antibacterial
- Pharyngeal infection, azithromycin + i/m ceftriaxone
  - Suggested duration of treatment is a single-dose of each antibacterial

Pelvic inflammatory disease

- Contact tracing recommended.
- Doxycycline + metronidazole + single-dose of i/m ceftriaxone or ofloxacin p. 561 + metronidazole
  - Suggested duration of treatment 14 days (except i/m ceftriaxone).
  - In severely ill patients initial treatment with doxycycline + i/v ceftriaxone + i/v metronidazole, then switch to oral treatment with doxycycline + metronidazole to complete 14 days’ treatment

Early syphilis (infection of less than 2 years)

- Contact tracing recommended.
- Benzathine benzylpenicillin [unlicensed]
  - Suggested duration of treatment single-dose (repeat dose after 7 days for women in the third trimester of pregnancy)
- Alternatively, doxycycline or erythromycin
  - Suggested duration of treatment 14 days

Late latent syphilis (asymptomatic infection of more than 2 years)

- Contact tracing recommended.
- Benzathine benzylpenicillin [unlicensed]
  - Suggested duration of treatment once weekly for 2 weeks
- Alternatively, doxycycline
  - Suggested duration of treatment 28 days

Asymptomatic contacts of patients with infectious syphilis

- Doxycycline
  - Suggested duration of treatment 14 days

Musculoskeletal system infections, antibacterial therapy

Osteomyelitis

- Seek specialist advice if chronic infection or prostheses present.
- Ceftriaxone p. 554
  - Consider adding fusidic acid p. 571 or rifampicin p. 582 for initial 2 weeks.
  - Suggested duration of treatment 6 weeks for acute infection
- If penicillin-allergic, clindamycin p. 535
  - Consider adding fusidic acid or rifampicin for initial 2 weeks.
  - Suggested duration of treatment 6 weeks for acute infection

Septic arthritis

- Seek specialist advice if prostheses present.
- Flucloxacillin
  - Suggested duration of treatment 4–6 weeks (longer if infection complicated).
- If penicillin-allergic, clindamycin
  - Suggested duration of treatment 4–6 weeks (longer if infection complicated).
- If meticillin-resistant Staphylococcus aureus suspected, vancomycin p. 534 (or teicoplanin p. 532)
  - Consider adding fusidic acid or rifampicin for initial 2 weeks.
  - Suggested duration of treatment 6 weeks for acute infection

Nose infections, antibacterial therapy

Sinusitis (acute)

Acute sinusitis is generally triggered by a viral infection, although occasionally it may become complicated by a bacterial infection caused by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, or Staphylococcus aureus. For further information see Sinusitis (acute) p. 1203.

Treatment

Antibacterial therapy should only be offered to patients with acute sinusitis who are systemically very unwell, have signs and symptoms of a more serious illness, those who are at high-risk of complications due to pre-existing comorbidities, or whenever bacterial sinusitis is suspected. Patients presenting with symptoms for around 10 days or more with no improvement may be prescribed a back-up antibiotic prescription, which can be used if symptoms do not improve within 7 days or if they worsen significantly at any time. ▶ For further information see, Sinusitis (acute) p. 1203.

Choice of antibacterial therapy

No penicillin allergy

- First line:
Oral bacterial infections

Antibacterial drugs
Antibacterial drugs should only be prescribed for the treatment of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The ‘blind’ prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. In severe oral infections, a sample should always be taken for bacteriology. Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be required if treatment has to be delayed, in immunocompromised patients, or in those with conditions such as diabetes or Paget’s disease. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig’s angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or a macrolide) with metronidazole p. 542 may sometimes be helpful for the treatment of severe oral infections or oral infections that have not responded to initial antibacterial treatment.

Penicillins
- Phenoxyemepenicillin p. 548 is effective for dentoalveolar abscess.

Broad-spectrum penicillins
Amoxicillin p. 548 is as effective as phenoxyemepenicillin but is better absorbed; however, it may encourage emergence of resistant organisms.

Like phenoxyemepenicillin, amoxicillin is ineffective against bacteria that produce beta-lactamases.

Amoxicillin may be useful for short course oral regimens.

Co-amoxiclav p. 551 is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

Cephalosporins
The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cephalosporins. This is of importance in the case of patients who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin p. 524 and cefradine p. 525 have been used in the treatment of oral infections.

Tetracyclines
In adults, tetracyclines can be effective against oral anaerobes but the development of resistance (especially by oral streptococci) has reduced their usefulness for the treatment of acute oral infections; they may still have a role in the treatment of destructive (refractory) forms of periodontal disease. Doxycycline p. 564 has a longer duration of action than tetracycline p. 567 or oxytetracycline p. 567 and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

Doxycycline may have a role in the treatment of recurrent aphthous ulceration, or as an adjunct to gingival scaling and root planing for periodontitis.

Macrolides
The macrolides are an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to macrolides or rapidly develop resistance; their use should therefore be limited to short courses.

Clindamycin
Clindamycin p. 535 should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin-resistant bacteria.

Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

Metronidazole and tinidazole
Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes. It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent’s infection) and pericoronitis; amoxicillin is a suitable alternative. For these purposes metronidazole for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole p. 544 is licensed for the treatment of acute ulcerative gingivitis.
Respiratory system infections, antibacterial therapy

Epiglottitis (Haemophilus influenzae)
- Cefotaxime p. 527 (or ceftixime p. 528)
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol p. 568

Bronchiectasis (non-cystic fibrosis), acute exacerbation
Bronchiectasis is a persistent or progressive condition, caused by chronic inflammatory damage to the airways and is characterised by thick-walled, dilated bronchi. Signs and symptoms may range from intermittent expectoration and infection, to chronic cough, persistent daily production of sputum, bacterial colonisation, and recurrent infections. An acute exacerbation is defined as sustained deterioration of the patient’s signs and symptoms from their baseline, and presents with worsening local symptoms, with or without increased wheeze, breathlessness or haemoptysis and may be accompanied by fever or pleurisy.

Treatment
- Obtain a sputum sample and send for culture and susceptibility testing. Antibacterial therapy should be given to all patients with an acute exacerbation.
  - For patients receiving prophylactic antibacterial therapy, switching from intravenous to oral antibacterials, and for advice to be given to patients, see Antibacterials, principles of therapy p. 505.
  - Refer patients to hospital if they have signs or symptoms suggestive of a more serious illness such as cardiorespiratory failure or sepsis.

Reassessment
- Reassess if symptoms worsen rapidly or significantly at any time and consider:
  - Other diagnoses such as pneumonia, or signs and symptoms of a more serious illness such as cardiorespiratory failure, or sepsis;
  - Previous antibacterial use that may have led to resistance.
  - Review choice of antibacterial if susceptibility results indicate bacterial resistance and symptoms are not improving—consult local microbiologist as needed.

Choice of antibacterial therapy
- The recommended total duration of treatment is 7–14 days.
  - Alternative therapy should be guided by the most recent sputum culture and susceptibility results when available.
  - Seek specialist advice for patients whose symptoms are not improving with repeated courses, or who are resistant to, or cannot take oral antibacterials.

  - Oral first line:
    - Amoxicillin p. 548, clarithromycin p. 538, or doxycycline p. 564.
    - Alternative if at high risk of treatment failure (repeated courses of antibacterials, previous culture with resistant or atypical bacteria, or high risk of complications): co-amoxiclav p. 551, or levofloxacin p. 559.
  - Intravenous first line (severely unwell or unable to take oral treatment):
    - Co-amoxiclav, piperacillin with tazobactam p. 545, or levofloxacin.
  - For patients with repeated acute exacerbations, a trial of antibacterial prophylaxis may be given on specialist advice only.

Chronic obstructive pulmonary disease, acute exacerbation
An acute exacerbation of chronic obstructive pulmonary disease (COPD) is a sustained worsening of symptoms from the patient’s usual stable state, that is beyond the usual day to day variations. Many exacerbations are not caused by bacterial infections, but instead can be triggered by other factors such as smoking or viral infections.

Treatment
- Consider antibacterial treatment taking into account:
  - The severity of symptoms, sputum colour changes and increases in volume and thickness;
  - The need for hospital admission;
  - Previous exacerbations and hospital admission history, and risk of developing complications.
  - For other considerations such as in patients receiving prophylactic antibacterial therapy, switching from intravenous to oral antibacterials, and for advice to be given to patients, see Antibacterials, principles of therapy p. 505. Refer patients to hospital if they have signs or symptoms suggestive of a more serious illness such as cardiorespiratory failure or sepsis.

Reassessment
- Reassess if symptoms worsen rapidly or significantly at any time and consider:
  - Other diagnoses such as pneumonia, or signs and symptoms of a more serious illness such as cardiorespiratory failure, or sepsis;
  - Previous antibacterial use that may have led to resistance;
  - Sending a sputum sample for testing if there is no improvement after antibacterial therapy and this has not already been done.

Choice of antibacterial therapy
- The recommended total duration of treatment is 5 days.
  - Treatment should be guided by the most recent sputum culture and susceptibility results when available.
  - Seek specialist advice for patients whose symptoms are not improving with repeated courses, or who are resistant to, or cannot take oral antibacterials.

  - Oral first line:
    - Amoxicillin, clarithromycin, or doxycycline.
    - Alternative if at high risk of treatment failure (repeated courses of antibacterials, previous culture with resistant or atypical bacteria, or high risk of complications): co-amoxiclav, or levofloxacin.

  - Intravenous second line (if no improvement after at least 2 to 3 days):
    - Use a first line antibacterial from a different class to the antibacterial used previously.
    - Alternative if at high risk of treatment failure: co-amoxiclav, levofloxacin, or co-trimoxazole p. 562 (only when sensitivities are available and there is good reason to use co-trimoxazole over single antibacterials).

  - Intravenous first line (severely unwell or unable to take oral treatment):
    - Amoxicillin, co-amoxiclav, clarithromycin, co-trimoxazole, or piperacillin with tazobactam.

  - Intravenous second line: Choice should be made in consultation with a local microbiologist.
  - For further information on COPD, see Chronic obstructive pulmonary disease p. 242.

Cough, acute
Acute cough is usually self-limiting and often resolves within 3–4 weeks without antibacterials. It is most commonly caused by a viral upper respiratory tract infection,
but can have other infective causes such as acute bronchitis or pneumonia, or non-infective causes such as interstitial lung disease or gastro-oesophageal reflux disease.

**Treatment**

Patients should be advised that an acute cough is usually self-limiting and to manage their symptoms using self-care treatments. These include honey and over-the-counter cough medicines containing expectorants or cough suppressants, however there is limited evidence to support the use of such products. For more information, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 296.

Patients with an acute cough who are systemically very unwell should be offered immediate antibiotic treatment. Do not routinely offer an antibacterial to treat an acute cough associated with an upper respiratory tract infection or acute bronchitis in patients who are not systemically very unwell or at higher risk of complications. 

Patients with a pre-existing co-morbidity, young children who were born prematurely, and patients aged over 70 years of age and the presence of certain criteria (hospitalisation in the previous year, type 1 or 2 diabetes, history of congestive heart failure, or currently taking oral corticosteroids) are considered to be at a higher risk of complications if they present with an acute cough. Immediate or back-up antibiotic treatment should be considered in these patients based on the face-to-face clinical examination. If back-up treatment is given, advise patients to start treatment if symptoms worsen rapidly or significantly at any time.

For general advice to give to patients, see Antibacterials, principles of therapy p. 505.

Seek specialist advice, or refer patients with an acute cough to hospital if they have signs or symptoms of a more serious illness or condition.

**Reassessmment**

Reassess if symptoms worsen rapidly or significantly taking into account alternative diagnoses, signs or symptoms suggestive of a more serious condition, and previous antibacterial use which may have led to resistant bacteria.

**Choice of antibacterial therapy**

The recommended duration of oral treatment is 5 days.

- **First line** Doxycycline p. 564.
- **Alternative first line choices**: amoxicillin p. 548, clarithromycin p. 538, or erythromycin p. 539.
- **Choice during pregnancy**:
  - Amoxicillin or erythromycin.

**Community-acquired pneumonia: low-severity**

- Amoxicillin (or ampicillin p. 550)
- Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
- If atypical pathogens suspected, add clarithromycin (or azithromycin p. 536 or erythromycin).
- If staphylococci suspected (e.g. in influenza or measles), add fluclaxacillin p. 554.
- Suggested duration of treatment 7 days (14–21 days for infections caused by staphylococci)

**Community-acquired pneumonia: moderate-severity**

- Amoxicillin (or ampicillin) + clarithromycin (or azithromycin or erythromycin) or doxycycline alone
- Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin p. 534 (or teicoplanin p. 532).
- Suggested duration of treatment 7 days (14–21 days for infections caused by staphylococci)

**Community-acquired pneumonia: high-severity**

- Benzylpenicillin sodium p. 547 + clarithromycin (or azithromycin or erythromycin) or benzylpenicillin sodium + doxycycline
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci suspected)
- If life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, co-amoxiclav p. 551 + clarithromycin (or azithromycin or erythromycin)
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

- Alternatives if life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, cefuroxime p. 526+ clarithromycin (or azithromycin or erythromycin) or cefotaxime p. 527 (or ceftriaxone p. 528) + clarithromycin (or azithromycin or erythromycin)
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin (or teicoplanin).
- Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

**Pneumonia possibly caused by atypical pathogens**

- Clarithromycin (or azithromycin or erythromycin)
- If high-severity Legionella infection, add rifampicin p. 582 for the first few days.
- Suggested duration of treatment 14 days (usually 7–10 days for Legionella)
- Alternative if Legionella infection suspected, a quinolone
- If high-severity Legionella infection, add clarithromycin (or azithromycin or erythromycin) or rifampicin for the first few days.
- Suggested duration of treatment usually 7–10 days
- Alternative for chlamydial or mycoplasmal infections, doxycycline
- Suggested duration of treatment 14 days

**Hospital-acquired pneumonia**

- Early-onset infection less than 5 days after admission to hospital, co-amoxiclav or cefuroxime
- If life-threatening infection, or if history of antibacterial treatment in the last 3 months, or if resistant micro-organisms suspected, treat as for late-onset hospital-acquired pneumonia.
- Suggested duration of treatment 7 days
- Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 545) or a broad-spectrum cephalosporin (e.g. ceftazidine p. 528) or another antipseudomonal beta-lactam or a quinolone (e.g. ciprofloxacin p. 558)
- If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin.
- For severe illness caused by *Pseudomonas aeruginosa*, consider adding an aminoglycoside.
Skin infections, antibacterial therapy

Impetigo: small areas of skin infected
- Seek local microbiology advice before using topical treatment in hospital.
- Topical fusidic acid p. 571
- Suggested duration of treatment 7 days is usually adequate (max. 10 days).
- Alternatively, if meticillin-resistant Staphylococcus aureus, topical mupirocin p. 1232
- Suggested duration of treatment 7 days is usually adequate (max. 10 days).

Impetigo: widespread infection
- Oral flucloxacillin p. 554
- If streptococci suspected in severe infection, add phenoxymethylpenicillin p. 548.
- Suggested duration of treatment 7 days.
- If penicillin-allergic, oral clarithromycin p. 538 (or azithromycin p. 536 or erythromycin p. 539)
- Suggested duration of treatment 7 days.

Erysipelas
- Phenoxymethylpenicillin or benzylpenicillin sodium p. 547
- If severe infection, replace phenoxymethylpenicillin or benzylpenicillin sodium with high-dose flucloxacillin
- Suggested duration of treatment at least 7 days.
- If penicillin-allergic, clindamycin p. 535 or clarithromycin (or azithromycin or erythromycin)
- Suggested duration of treatment at least 7 days.

Cellulitis
- Flucloxacillin (high-dose)
- If streptococcal infection confirmed, replace flucloxacillin with phenoxymethylpenicillin or benzylpenicillin sodium
- If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials.
- If penicillin-allergic, clindamycin or clarithromycin (or azithromycin or erythromycin) or vancomycin p. 534 (or teicoplanin p. 532)
- If Gram-negative bacteria suspected, use broad-spectrum antibacterials.

Animal and human bites
Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1292 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection). Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.
- Co-amoxiclav p. 551
- If penicillin-allergic, doxycycline p. 564 + metronidazole p. 542

Mastitis during breast-feeding
Treat if severe, if systemically unwell, if nipple fissure present, if symptoms do not improve after 12–24 hours of effective milk removal, or if culture indicates infection. Continue breast-feeding or expressing milk during treatment.
- Flucloxacillin

Suggested duration of treatment 7 days (longer if Pseudomonas aeruginosa confirmed)

ANTIBACTERIALS > AMINOGLYCOSIDES

Aminoglycosides

Overview
These include amikacin p. 518, gentamicin p. 519, neomycin sulfate p. 520, streptomycin p. 520, and tobramycin p. 520. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against Pseudomonas aeruginosa; streptomycin is active against Mycobacterium tuberculosis and is now almost entirely reserved for tuberculosis.

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the ‘blind’ therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole p. 542 (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis. Streptomycin may be used as an alternative in gentamicin-resistant enterococcal endocarditis.

Loading and maintenance doses of gentamicin may be calculated on the basis of the patient’s weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate, in the patient with cystic fibrosis, or in the immunocompromised patient. Whenever possible treatment should not exceed 7 days.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is slightly more active against Ps. aeruginosa but shows less activity against certain other Gram-negative bacteria. Tobramycin can be administered by nebuliser or by inhalation of powder on a cyclical basis (28 days of tobramycin followed by a 28-day tobramycin-free interval) for the treatment of chronic pulmonary Ps. aeruginosa infection in cystic fibrosis; however, resistance may develop and some patients do not respond to treatment.

Neomycin sulfate is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin sulfate may be absorbed from the gut in patients with hepatic failure and, as these patients may also be uraemic, cumulative may occur with resultant ototoxicity.

Once daily dosage
Once daily administration of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded multiple-daily dose regimens (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with endocarditis due to Gram-positive bacteria, HACEK.
endocarditis, burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute. There is insufficient evidence to recommend a once daily, high-dose regimen of an aminoglycoside in pregnancy.

**Serum concentrations**

Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. Serum-aminoglycoside concentrations should be monitored in patients receiving parenteral aminoglycosides and must be determined in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

**Aminoglycosides (by injection)**

- **CONTRA-INDICATIONS** Myasthenia gravis (aminoglycosides may impair neuromuscular transmission)
- **CAUTIONS** Care must be taken with dosage (the main side-effects of the aminoglycosides are dose-related) - conditions characterised by muscular weakness (aminoglycosides may impair neuromuscular transmission) - if possible, dehydration should be corrected before starting an aminoglycoside - whenever possible, parenteral aminoglycosides and must be determined in the elderly.

**SIDE-EFFECTS**

- Common or very common  Skin reactions  tinnitus
- Uncommon  Nausea  vomiting
- Rare or very rare  Anaemia  bronchospasm  eosinophilia  fever  headache  hearing loss  hypomagnesaemia  paraesthesia  renal impairment
- Frequency not known  Confusion  lethargy  nephrotoxicity

**SIDE-EFFECTS, FURTHER INFORMATION**

Ototoxicity and nephrotoxicity are important side-effects to consider with aminoglycoside therapy. Nephrotoxicity occurs most commonly in patients with renal impairment, who may require reduced doses; monitoring is particularly important in the elderly.

**PREGNANCY**

There is a risk of auditory or vestibular nerve damage in the infant when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin. The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential.

**RENAL IMPAIRMENT**

Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment. Ototoxicity and nephrotoxicity occur commonly in patients with renal failure.

- In adults A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with a creatinine clearance less than 20 mL/minute.
- In children A once-daily, high-dose regimen of an aminoglycoside should be avoided in children over 1 month of age with a creatinine clearance less than 20 mL/minute.

**Dose adjustments**

If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well.

**Monitoring**

Serum-aminoglycoside concentrations must be monitored in patients with renal impairment; earlier and more frequent measurement of aminoglycoside concentration may be required.

**MONITORING REQUIREMENTS**

- Serum concentrations Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy.

**INTERACTIONS**

Serum-aminoglycoside concentrations should be measured in all patients receiving parenteral aminoglycosides and must be determined in obesity, if high doses are being given and in cystic fibrosis.

- In adults Serum aminoglycoside concentrations must be determined in the elderly. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen and after a dose change. For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (’peak’ concentration) and also just before the next dose (’trough’ concentration). If the pre-dose (’trough’) concentration is high, the interval between doses must be increased. If the post-dose (’peak’) concentration is high, the dose must be decreased. For once daily dose regimens, consult local guidelines on serum concentration monitoring.

- In children In children with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen. Blood samples should be taken just before the next dose is administered (’trough’ concentration). If the pre-dose (’trough’) concentration is high, the interval between doses must be increased. For multiple daily dose regimens, blood samples should also be taken approximately 1 hour after intramuscular or intravenous administration (’peak’ concentration). If the post-dose (’peak’) concentration is high, the dose must be decreased.

- Renal function should be assessed before starting an aminoglycoside and during treatment.

- Auditory and vestibular function should also be monitored during treatment.

**Amikacin**

- **INDICATIONS AND DOSE**

  **Serious Gram-negative infections resistant to gentamicin (multiple daily dose regimen)**

  - By intramuscular injection, or by slow intravenous injection, or by intravenous infusion

  - Adult: 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses for up to 10 days, higher dose to be used in severe infections; maximum 1.5 g per day; maximum 15 g per course

  **Serious Gram-negative infections resistant to gentamicin (once daily dose regimen)**

  - By intravenous infusion

  - Adult: Initially 15 mg/kg (max. per dose 1.5 g once daily), dose to be adjusted according to serum-amikacin concentration; maximum 15 g per course

**DOSES AT EXTREMES OF BODY-WEIGHT**

- To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum-amikacin concentration closely

**SIDE-EFFECTS**

- Uncommon  Superinfection

- Rare or very rare  Albuminuria  arthralgia  azotaemia  balance impaired  hearing impairment  hypotension  muscle twitching  tremor

- Frequency not known  Apnoea  neuromuscular blockade  paralysis

**MONITORING REQUIREMENTS**

- With intravenous use Multiple daily dose regimen: one-hour (’peak’) serum concentration should not exceed 30 mg/litre; pre-dose (’trough’) concentration should be less than 10 mg/litre. Once daily dose regimen: pre-dose (’trough’) concentration should be less than 5 mg/litre.
DIRECTIONS FOR ADMINISTRATION
- With intravenous use: For intravenous infusion (Amikin®); intermittent in Glucose 5% or Sodium chloride 0.9%. To be given over 30 minutes.

PRESCRIBING AND DISPENSING INFORMATION
- Once daily dose regimen not to be used for endocarditis, febrile neutropenia, or meningitis. Consult local guidelines.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for intravenous injection, powder for reconstitution, and specific preparations for intrathecal or intravenous infusion.

Solution for Injection
- Amikacin (Non-proprietary)
  - Amikacin (as Amikacin sulfate) 250 mg per 1 ml: Amikacin 500mg/2ml solution for injection vials | 5 vial (P) £50.00 (Hospital only)
  - Amikin (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Amikin (as Amikacin sulfate) 50 mg per 1 ml: Amikin 100mg/2ml solution for injection vials | 5 vial (P) £10.33

Gentamicin
DIAGNOSTICS AND DOSE
- Gram-positive bacterial endocarditis or HACEK endocarditis (in combination with other antibacterials)
- By intramuscular injection, or by slow intravenous injection, or by intravenous infusion
- Adult: 1 mg/kg every 12 hours, intravenous injection to be administered over at least 3 minutes, to be given in a multiple daily dose regimen

Septicaemia | Meningitis and other CNS infections | Biliary-tract infection | Acute pyelonephritis | Endocarditis | Pneumonia in hospital patients | Adjunct in infectious meningitis | Prostatitis
- By intravenous infusion, or by slow intravenous injection, or by intramuscular injection
- Adult: 3–5 mg/kg daily in 3 divided doses, to be given in a multiple daily dose regimen, divided doses to be given every 8 hours, intravenous injection to be administered over at least 3 minutes
- By intravenous infusion
- Adult: Initially 5–7 mg/kg, subsequent doses adjusted according to serum-gentamicin concentration, to be given in a once daily dose regimen

CNS infections (administered on expert advice)
- By intrathecal injection
- Adult: 1 mg daily, increased if necessary to 5 mg daily, seek specialist advice

Surgical prophylaxis
- By intravenous infusion
- Adult: 1.5 mg/kg, intravenous injection to be administered over at least 3 minutes, administer dose up to 30 minutes before the procedure, dose may be repeated every 8 hours for high-risk procedures; up to 3 further doses may be given

Surgical prophylaxis in joint replacement surgery
- Adult: 5 mg/kg for 1 dose, administer dose up to 30 minutes before the procedure

DOSES AT EXTREMES OF BODY-WEIGHT
- With intramuscular use or intravenous use To avoid excessive dosage in obese patients, use ideal weight for height to calculate parenteral dose and monitor serum-gentamicin concentration closely.

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: POTENTIAL FOR HISTAMINE-RELATED ADVERSE DRUG REACTIONS WITH SOME BATCHES (NOVEMBER 2017)
Following reports that some batches of gentamicin sulphate active pharmaceutical ingredient (API) used to manufacture gentamicin may contain higher than expected levels of histamine, which is a residual from the manufacturing process, the MHRA advise to monitor patients for signs of histamine-related adverse reactions; particular caution is required in patients taking concomitant drugs known to cause histamine release, in children, and in patients with severe renal impairment.

INTERACTIONS
- Appendix 1: aminoglycosides

SIDE-EFFECTS
- Antibiotic associated colitis | blood disorder | depression | encephalopathy | hallucination | hepatic reaction | neurotoxicity | peripheral neuropathy | seizure | stomatitis | vestibular damage

MONITORING REQUIREMENTS
- With intramuscular use or intravenous use: For multiple daily dose regimen, one-hour (‘peak’) serum concentration should be 5–10 mg/litre; pre-dose (‘trough’) concentration should be less than 2 mg/litre. For multiple daily dose regimen in endocarditis, one-hour (‘peak’) serum concentration should be 3–5 mg/litre; pre-dose (‘trough’) concentration should be less than 1 mg/litre. Serum-gentamicin concentration should be measured after 3 or 4 doses, then at least every 3 days and after a dose change (more frequently in renal impairment).
- With intravenous use: For once-daily dose regimen, consult local guidelines on monitoring serum-gentamicin concentration.

DIRECTIONS FOR ADMINISTRATION
- With intrathecal use: For intrathecal injection, use preservative-free intrathecal preparations only.
- With intravenous use: For intravenous infusion (Cidomycin®); Gentamicin paediatric injection, Beacon; Gentamicin injection Hospira, give intermittently or via drip tubing in Glucose 5% or Sodium Chloride 0.9%. Suggested volume for intermittent infusion 50–100 ml given over 20–30 minutes (given over 60 minutes for once daily dose regimen).

PRESCRIBING AND DISPENSING INFORMATION
- With intravenous use: Local guidelines may vary in the dosing advice provided for once daily administration.
- With intrathecal use: Only preservative-free intrathecal preparation should be used.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Gentamicin (as Gentamicin sulfate) 5 mg per 1 ml: Gentamicin Intrathecal 5mg/1ml solution for injection ampoules | 5 ampoule (P) £36.28 DT + £36.28 (Hospital only)
- Gentamicin (as Gentamicin sulfate) 10 mg per 1 ml Gentamicin 20mg/2ml solution for injection ampoules | 5 ampoule (P) £11.25 DT + £11.25
- Gentamicin Paediatric 20mg/2ml solution for injection vials | 5 vial (P) £11.25 DT + £11.25
- Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Gentamicin 80mg/2ml solution for injection vials | 5 vial (P) £20.00 DT + £6.88 (Hospital only)
- Gentamicin 80mg/2ml solution for injection ampoules | 5 ampoule (P) £6.88 DT + £6.88 | 10 ampoule (P) £12.00
- Cidomycin (Sanofi)
- Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Cidomycin Adult Injectable 80mg/2ml solution for injection vials | 5 vial (P) £6.88 DT + £6.88
Neomycin sulfate

**INDICATIONS AND DOSE**

**Bowel sterilisation before surgery**
- **BY MOUTH**
  - Adult: 1 g every 1 hour for 4 hours, then 1 g every 4 hours for 2–3 days

**Hepatic coma**
- **BY MOUTH**
  - Adult: Up to 4 g daily in divided doses usually for 5–7 days

**SIDE-EFFECTS** Blood disorder - confusion - diarrhoea - drug cross-reactivity - electrolyte imbalance - gastrointestinal disorders - haemolytic anaemia - nausea - nephrotoxicity - ototoxicity - parasthesia - superinfection - vomiting

SIDE-EFFECTS, FURTHER INFORMATION Although neomycin is associated with the same warnings as other aminoglycosides it is generally considered too toxic for systemic use.

**INTERACTIONS** → Appendix 1: neomycin

**CAUTIONS** Avoid prolonged use

**CONTRA-INDICATIONS** Intestinal obstruction - myasthenia gravis (aminoglycosides may impair neuromuscular transmission)

**MEDICINAL FORMS** Forms available from special-order manufacturers include: powder for solution for injection, oral solution, tablet, nebuliser solution, syrup, and liquid

**INDICATIONS AND DOSE**

**Septicaemia | Meningitis and other CNS infections | Biliary-tract infection | Acute pyelonephritis or prostatitis | Pneumonia in hospital patients**

**BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INFUSION**
- Adult: 3 mg/kg daily in 3 divided doses; increased if necessary up to 5 mg/kg daily in 3–4 divided doses, increased dose used in severe infection; dose to be reduced back to 3 mg/kg daily as soon as clinically indicated

**Urinary-tract infection**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 2–3 mg/kg for 1 dose

**Chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis**
- **BY INHALATION OF NEBULISER SOLUTION**
  - Adult: 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

**DOSES AT EXTREMES OF BODY-WEIGHT**
- With intramuscular use or intravenous use  To avoid excessive dosage in obese patients, use ideal weight for height to calculate parental dose and monitor serum-tobramycin concentration closely.

**VANTOBRA NEBULISER SOLUTION**
- Chronic pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis
  - **BY INHALATION OF NEBULISER SOLUTION**
    - Adult: 170 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution
Bacterial infection 521

When used by inhalation Tobramycin dry powder for inhalation is recommended for chronic pulmonary infection caused by Pseudomonas aeruginosa in patients with cystic fibrosis only if there is an inadequate response to colistimethate sodium, or if colistimethate sodium cannot be used because of contra-indications or intolerance. The manufacturer must provide tobramycin dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving tobramycin dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA276

ANTIBACTERIALS > CARBAPENEMS

Carbapenems

Overview
The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; imipenem (imipenem with cilastatin p. 522) and meropenem p. 523 have good activity against Pseudomonas aeruginosa. The carbapenems are not active against meticillin-resistant Staphylococcus aureus and Enterococcus faecium.

Imipenem (imipenem with cilastatin) and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary-tract infections.

Ertaopenem p. 522 is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. It is also licensed for treating foot infections of the skin and soft tissue in patients with diabetes. Unlike the other carbapenems, ertaopenem is not active against Pseudomonas or against Acinetobacter spp.
Imipenem with cilastatin | 07-Feb-2019

● INDICATIONS AND DOSE

Aerobic and anaerobic Gram-positive and Gram-negative infections (not indicated for CNS infections) | Hospital-acquired septicaemia

- **BY INTRAVENOUS INFUSION**
  - Adult: 500 mg every 6 hours, alternatively 1 g every 8 hours

Infection caused by *Pseudomonas* or other less sensitive organisms | Empirical treatment of infection in febrile patients with neutropenia | Life-threatening infection

- **BY INTRAVENOUS INFUSION**
  - Adult: 1 g every 6 hours

Dose equivalence and conversion

- Dose expressed in terms of imipenem.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

ELECTROLYTES: May contain Sodium

- *Ertapenem (Non-proprietary)*
  - Ertapenem (as Ertapenem sodium) 1 gram
  - Ertapenem 1 g powder for concentrate for solution for infusion vials | 10 vial (Hospital only)

- *Invanz* (Merck Sharp & Dohme Ltd)
  - Ertapenem (as Ertapenem sodium) 1 gram
  - Invanz 1 g powder for solution for infusion vials | 1 vial (Hospital)

£31.65 DT + £31.65

● CAUTIONS

CNS disorders—risk of seizures: elderly

● INTERACTIONS

Appendix 1: carbapenems

● SIDE-EFFECTS

- **Common or very common** Diarrhoea, headache, nausea, skin reactions, thrombophlebitis, vomiting
- **Uncommon** Appetite decreased, arthralgia, asthenia, confusion, constipation, dizziness, drowsiness, dry mouth, gastrointestinal discomfort, gastrointestinal disorders, hypotension, increased risk of infection, insomnia, oedema, pseudomembranous enterocolitis, seizure, swelling, taste altered, throat discomfort
- **Rare or very rare** Anxiety, cholecystitis, depression, dysphagia, eye disorder, haemorrhage, hepatic disorders, hypersensitivity, hypoglycaemia, malaise, muscle cramps, nasal congestion, neutropenia, renal impairment, shoulder pain, syncope, thrombocytopenia, tremor
- **Frequency not known** Aggression, delirium, drug reaction with eosinophilia and systemic symptoms (DRESS), gait abnormal, hallucination, level of consciousness decreased, movement disorders, muscle weakness, psychiatric disorder, tooth discoloration

● ALLERGY AND CROSS-SENSITIVITY

Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials.

Use with caution in patients with sensitivity to beta-lactam antibacterials.

● PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk.

● BREAST FEEDING

Present in milk—manufacturer advises avoid.

● RENAL IMPAIRMENT

Dose adjustments

Risk of seizures; max. 500 mg daily if eGFR less than 30 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Invance™), give intermittently in Sodium chloride 0.9%. Reconstitute 1 g with 10 mL Water for injections or Sodium chloride 0.9%; dilute requisite dose in infusion fluid to a final concentration not exceeding 20 mg/mL; give over 30 minutes; incompatible with glucose solutions.

**Dilution**

Dilute to a concentration of 5 mg (as imipenem)/mL in Sodium chloride 0.9%; give up to 500 mg (as imipenem)
over 20–30 minutes, give dose greater than 500 mg (as imipenem) over 40–60 minutes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- **ELECTROLYTES** May contain Sodium
  - Imipenem with cilastatin (Non-proprietary)
  - Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg
  - Imipenem 500mg / Cilastatin 500mg powder for solution for infusion vials | 10 vial
  - Primaxin IV (Merrick Sharp & Dohme Ltd)
  - Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg
  - Primaxin IV 500mg powder for solution for infusion vials | 1 vial

- **UNLICENSED USE** Not licensed for use in endocarditis.

- **INTERACTIONS** Appendix 1: carbapenems

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain, diarrhoea, headache, infection, leucopenia, neutropenia, nausea, pain, skin reactions, vomiting.
  - **Uncommon** Agranulocytosis, antibacterial associated colitis, eosinophilia, haemolytic anaemia, increased risk of infection, leucopenia, neutropenia, paraesthesia, severe cutaneous adverse reactions (SCARs), thrombocytopenia, thrombophlebitis.
  - **Rare or very rare** Seizure
  - **ALLERGY AND CROSS-SENSITIVITY** Avoid if history of immediate hypersensitivity reaction to beta-lactam antibiotics. Use with caution in patients with sensitivity to beta-lactam antibacterials.

- **PREGNANCY** Use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING** Unknown, manufacturer advises avoid.

- **RENAL IMPAIRMENT**
  - **Dose adjustments** Use normal dose every 12 hours if eGFR 26–50 mL/minute/1.73 m².
  - Use half normal dose every 12 hours if eGFR 10–25 mL/minute/1.73 m².
  - Use half normal dose every 24 hours if eGFR less than 10 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Manufacturer advises monitor liver function—risk of hepatotoxicity.

- **EFFECT ON LABORATORY TESTS** Positive Coombs’ test.

- **DIRECTIONS FOR ADMINISTRATION** Intravenous injection to be administered over 5 minutes. For intravenous infusion (Meronem ®), give intermittently in Glucose 5% or Sodium chloride 0.9%.

Dilute dose in infusion fluid to a final concentration of 1–20 mg/mL; give over 15–30 minutes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **ELECTROLYTES** May contain Sodium
  - Meropenem (Non-proprietary)
  - Meropenem (as Meropenem trihydrate) 500 mg
  - Meropenem 500mg powder for solution for injection vials | 10 vial
  - €83.00–€103.14 DT + €88.90 (Hospital only) | 10 vial
  - €88.90–€103.14 DT + €88.90
  - Meropenem (as Meropenem trihydrate) 1 gram
  - Meropenem 1g powder for solution for injection vials | 10 vial
  - €177.80–€206.28 DT + €177.80
  - Meropenem (Pfizer Ltd)
  - Meropenem (as Meropenem trihydrate) 500 mg
  - Meropenem 500mg powder for solution for injection vials | 10 vial
  - €88.90
  - Meropenem (as Meropenem trihydrate) 1 gram
  - Meropenem 1g powder for solution for injection vials | 10 vial
  - €206.28 DT + €177.80

**ANTIBACTERIALS > CEPHALOSPORINS**

**Cephalosporins**

**Overview**

The cephalosporins are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Cefepime penetrates the cerebrospinal fluid poorly unless the meninges are inflamed; ceftriaxone p. 527 and ceftazidime p. 528 are suitable cephalosporins for infections of the CNS (e.g meningitis).

The principal side-effect of the cephalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. If a cephalosporin is essential in patients with a history of immediate hypersensitivity to penicillin, because a suitable alternative antibacterial is not available, then cefixime p. 527, cefotaxime, ceftriaxone p. 528, ceftazidime, or cefuroxime p. 526 can be used with caution; cefaclor p. 525, cefadroxil p. 524, cefalexin p. 524, cefadine p. 525, and cefuroxime axetil p. 531 should be avoided.

The orally active 'first generation' cephalosporins, cefalexin, cefadine, and cefadroxil and the 'second generation' cephalosporin, cefuroxime, have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, and skin and soft-tissue infections. Cefaclor has good activity against *H. influenzae*. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against *H. influenzae*. Cefuroxime axetil, an ester of the 'second generation' cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed and needs to be given with food to maximise absorption.

Cefixime is an orally active 'third generation' cephalosporin. It has a longer duration of action than the other cephalosporins that are active by mouth. It is only licensed for acute infections. Cefotaxime is a 'second generation' cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to the other drugs and has greater activity against *Haemophilus influenzae*.

Cefotaxime, ceftazidime and ceftriaxone are ‘third generation’ cephalosporins with greater activity than the
"second generation" cephalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably Staphylococcus aureus. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

Ceftaroline fosamil is a 'fifth generation' cephalosporin with bactericidal activity similar to cefotaxime; however, ceftaroline fosamil has an extended spectrum of activity against Gram-positive bacteria that includes meticillin-resistant Staphylococcus aureus and multi-drug resistant Streptococcus pneumoniae. Cefaroline fosamil is licensed for the treatment of community-acquired pneumonia and complicated skin and soft-tissue infections, but there is no experience of its use in pneumonia caused by meticillin-resistant S. aureus.

**DRUG ACTION**

Cephalosporins are antibacterials that attach to penicillin binding proteins to interrupt cell wall biosynthesis, leading to bacterial cell lysis and death.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · diarrhoea · dizziness · eosinophilia · headache · increased risk of infection · leucopenia · nausea · neutropenia · skin reactions · thrombocytopenia · vomiting
- **Uncommon** Anaphylactic reaction · antibiotic associated colitis
- **Rare or very rare** Agranulocytosis · angioedema · nephritis tubulointerstitial (reversible) · severe cutaneous adverse reactions (SCARs)
- **Frequency not known** Haemolytic anaemia
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with cephalosporin hypersensitivity.
- **Cross-sensitivity with other beta-lactam antibacterials** About 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin and other beta-lactams should not receive a cephalosporin.
- **Cephalosporins should be used with caution in patients with sensitivity to penicillin and other beta-lactams.**
- **EFFECT ON LABORATORY TESTS** False positive urinary glucose (if tested for reducing substances). False positive Coombs’ test.

**ANTIBACTERIALS** CEFALOSPORINS, FIRST-GENERATION
Bacterial infection

**PROFESSION SPECIFIC INFORMATION**

Adults: 250–500 mg 4 times a day; alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections.

**UNLICENSED USE**

In children. Not licensed for use in children for prevention of *Staphylococcus aureus* lung infection in cystic fibrosis.

**SIDE-EFFECTS**

- Akathisia, aplastic anaemia, arthralgia, blood disorder, chest tightness, confusion, gastrointestinal discomfort, glossitis, hepatitis (transient), hypersensitivity, jaundice cholestatic, muscle tone increased, nervousness, oedema, sleep disorder.

**PREGNANCY**

Not known to be harmful.

**BREAST FEEDING**

Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

Dose adjustments

- In adults: Max. 3 g daily if eGFR 40–50 mL/minute/1.73 m². Max. 1.5 g daily if eGFR 10–40 mL/minute/1.73 m². Max. 750 mg daily if eGFR less than 10 mL/minute/1.73 m².
- In children: Reduce dose in moderate impairment.

**PATIENT AND CARER ADVICE**

- Medicines for Children leaflet: Cefalexin for bacterial infections www.medicinesforchildren.org.uk/cefalexin-bacterial-infections-0

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulation**

Cefalexin Capsules may be prescribed. Cefalexin Tablets may be prescribed.

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS**

9

- Cefalexin (Non-proprietary)
  - Cefalexin 25 mg per 1 ml Cefalexin 125 mg/5 ml oral suspension sugar free sugar-free | 100 ml [POD] £0.94–£1.65
  - Cefalexin 125 mg/5 ml oral suspension | 100 ml [POD] £1.64 DT = £0.84

- Cefalexin 50 mg per 1 ml Cefalexin 250 mg/5 ml oral suspension sugar free sugar-free | 100 ml [POD] £1.72–£2.03

- **Keflex** (Flynn Pharma Ltd)
  - Cefalexin 25 mg per 1 ml Keflex 125 mg/5 ml oral suspension | 100 ml [POD] £0.84 DT = £0.84
  - Cefalexin 50 mg per 1 ml Keflex 250 mg/5 ml oral suspension | 100 ml [POD] £1.40 DT = £1.40

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

9

- Cefalexin (Non-proprietary)
  - Cefalexin 250 mg Cefalexin 250 mg tablets | 28 tablet [POD] £2.55 DT = £1.69
  - Cefalexin 500 mg Cefalexin 500 mg tablets | 21 tablet [POD] £5.35 DT = £2.15

- **Keflex** (Flynn Pharma Ltd)
  - Cefalexin 250 mg Keflex 250 mg tablets | 28 tablet [POD] £1.60 DT = £1.69
  - Cefalexin 500 mg Keflex 500 mg tablets | 21 tablet [POD] £2.08 DT = £2.15

**ANTIBACTERIALS > CEPHALOSPORINS, SECOND-GENERATION**

**Cefradine (Cephadrine)**

**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria | Surgical prophylaxis

- **BY MOUTH**
  - Child 7–11 years: 25–50 mg/kg daily in 2–4 divided doses
  - Child 12–17 years: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections

- Adult: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections.

**INTERACTIONS**

→ Appendix 1: cephalosporins

**CAUTIONARY AND ADVISORY LABELS**

9

**Oral suspension**

There can be variation in the licensing of different medicines containing the same drug.

**CAUTIONARY AND ADVISORY LABELS**

9

- Cefalexin (Non-proprietary)
  - Cefalexin 25 mg per 1 ml Cefalexin 125 mg/5 ml oral suspension sugar free sugar-free | 100 ml [POD] £0.84–£1.65
  - Cefalexin 125 mg/5 ml oral suspension | 100 ml [POD] £1.64 DT = £0.84

- Cefalexin 50 mg per 1 ml Cefalexin 250 mg/5 ml oral suspension sugar free sugar-free | 100 ml [POD] £1.72–£2.03

- **Keflex** (Flynn Pharma Ltd)
  - Cefalexin 25 mg per 1 ml Keflex 125 mg/5 ml oral suspension | 100 ml [POD] £0.84 DT = £0.84
  - Cefalexin 50 mg per 1 ml Keflex 250 mg/5 ml oral suspension | 100 ml [POD] £1.40 DT = £1.40

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

9

- Cefalexin (Non-proprietary)
  - Cefalexin 250 mg Cefalexin 250 mg tablets | 28 tablet [POD] £2.55 DT = £1.69
  - Cefalexin 500 mg Cefalexin 500 mg tablets | 21 tablet [POD] £5.35 DT = £2.15

- **Keflex** (Flynn Pharma Ltd)
  - Cefalexin 250 mg Keflex 250 mg tablets | 28 tablet [POD] £1.60 DT = £1.69
  - Cefalexin 500 mg Keflex 500 mg tablets | 21 tablet [POD] £2.08 DT = £2.15

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

9

- Cefalexin (Non-proprietary)
  - Cefalexin 250 mg Cefalexin 250 mg capsules | 28 capsule [POD] £1.82 DT = £1.82
  - Cefalexin 500 mg Cefalexin 500 mg capsules | 21 capsule [POD] £1.99 DT = £1.99

- **Keflex** (Flynn Pharma Ltd)
  - Cefalexin 250 mg Keflex 250 mg capsules | 28 capsule [POD] £1.46 DT = £1.82
  - Cefalexin 500 mg Keflex 500 mg capsules | 21 capsule [POD] £1.98 DT = £1.99

www.getintopharma.com
526  Bacterial infection

- Adult: 500 mg 3 times a day; maximum 4 g per day

Pneumonia
- BY MOUTH USING MODIFIED-RELEASE TABLETS
- Child 12-17 years: 750 mg every 12 hours, dose to be taken with food
- Adult: 750 mg every 12 hours, dose to be taken with food

Lower urinary-tract infections
- BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Child 12-17 years: 375 mg every 12 hours, dose to be taken with food
- Adult: 375 mg every 12 hours, dose to be taken with food

Asymptomatic carriage of *Haemophilus influenzae* or mild exacerbations in cystic fibrosis
- BY MOUTH

Distaclor
- Child 12
- Child 2
- Child 3 months
- BY MOUTH

Negative bacteria
- Susceptible infections due to Gram-positive and Gram-negative bacteria
- BY MOUTH

Cefuroxime
- **INDICATIONS AND DOSE**
  - Susceptible infections due to Gram-positive and Gram-negative bacteria
  - BY MOUTH

- Adult: 250 mg twice daily, dose may be doubled in severe lower respiratory-tract infections or if pneumonia is suspected
- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
- Child: 20 mg/kg every 8 hours (max. per dose 750 mg); increased to 50–60 mg/kg every 6–8 hours (max. per dose 1.5 g), increased dose used for severe infection and cystic fibrosis
- Adult: 750 mg every 6–8 hours; increased if necessary up to 1.5 g every 6–8 hours, increased dose used for severe infections

Lyme disease
- BY MOUTH
- Adult: 500 mg twice daily for 14–21 days (for 28 days in Lyme arthriitis)

Lower urinary-tract infection
- BY MOUTH
- Child 12-17 years: 125 mg twice daily
- Adult: 125 mg twice daily

**SIDE-EFFECTS, FURTHER INFORMATION**
- Cefaclor is associated with protracted skin reactions, especially in children.
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.
- **RENAI IMPAIRMENT** Manufacturer advises caution.
- **DOSE ADJUSTMENTS** No dose adjustment required.

**INTERACTIONS** → Appendix 1: cephalosporins

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**
- Cefaclor is associated with protracted skin reactions, especially in children.
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.
- **RENAI IMPAIRMENT** Manufacturer advises caution.
- **DOSE ADJUSTMENTS** No dose adjustment required.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Oral suspension**
  - **CAUTIONARY AND ADVISORY LABELS** 9
  - **Distaclor** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 25 mg per 1 ml
  - Distaclor 125mg/5ml oral suspension | 100 ml  £4.13 DT = £4.13
  - **Distaclor** (as Cefaclor monohydrate) 30 mg per 1 ml
  - Distaclor 250mg/5ml oral suspension | 100 ml  £8.26 DT = £8.26

**Modified-release tablet**
- **CAUTIONARY AND ADVISORY LABELS** 9, 21, 25
- **Distaclor** (Flynn Pharma Ltd)
  - **Distaclor** (as Cefaclor monohydrate) 375 mg
  - Distaclor MR 375mg tablets | 14 tablet  £9.10 DT = £9.10

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS** 9
- **Distaclor** (Flynn Pharma Ltd)
  - **Distaclor** (as Cefaclor monohydrate) 500 mg
  - Distaclor 500mg capsules | 21 capsule  £7.50 DT = £7.50

**UNLICENSED USE** Duration of treatment in Lyme disease is unlicensed.

- **INTERACTIONS** → Appendix 1: cephalosporins
- **SIDE-EFFECTS**
  - **Frequency not known**
  - **Common**
  - With oral use Drug fever - hepatic disorders - Jarisch-Herxheimer reaction - serum sickness
  - With parenteral use Cutaneous vasculitis - drug fever
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.
- **RENAI IMPAIRMENT**
  - **DOSE ADJUSTMENTS** With intravenous use in adults
    - Use parenteral dose of 750 mg twice daily if eGFR 10–20 mL/minute/1.73 m². Use parenteral dose of 750 mg once daily if eGFR less than 10 mL/minute/1.73 m².
    - In children Reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².
- **DIRECTIONS FOR ADMINISTRATION**
  - With intramuscular use or intravenous use
    - Single doses over 750 mg should be administered by the intravenous route only.
    - With intravenous use in children Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%; give over 30 minutes.
    - With intravenous use in adults For *intravenous infusion* (*Zinacef*©), give intermittently or via drip tubing in glucose 5% or Sodium chloride 0.9%. Dissolve initially in water for injections (at least 2 mL for each 250 mg,15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes.

- **Surgical prophylaxis**
  - **INITIALLY BY INTRAVENOUS INJECTION**
    - Adult: 1.5 g, to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 750 mg every 8 hours if required for up to 3 doses (in high risk procedures)

- **Open fractures, prophylaxis**
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
    - Adult: 1.5 g every 8 hours until soft tissue closure (maximum duration 72 hours)

- **Frequency not known**
  - **Common**
  - With oral use Drug fever - hepatic disorders - Jarisch-Herxheimer reaction - serum sickness
  - With parenteral use Cutaneous vasculitis - drug fever
  - **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.
- **RENAI IMPAIRMENT**
  - **DOSE ADJUSTMENTS** With intravenous use in adults
    - Use parenteral dose of 750 mg twice daily if eGFR 10–20 mL/minute/1.73 m². Use parenteral dose of 750 mg once daily if eGFR less than 10 mL/minute/1.73 m².
    - In children Reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².
- **DIRECTIONS FOR ADMINISTRATION**
  - With intramuscular use or intravenous use
    - Single doses over 750 mg should be administered by the intravenous route only.
    - With intravenous use in children Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%; give over 30 minutes.
    - With intravenous use in adults For *intravenous infusion* (*Zinacef*©), give intermittently or via drip tubing in glucose 5% or Sodium chloride 0.9%. Dissolve initially in water for injections (at least 2 mL for each 250 mg,15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes.
**PRESCRIBING AND DISPENSING INFORMATION**

- With oral use See Lyme disease p. 577 for information on treatment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion

Tablet

- **CAUTIONARY AND ADVISORY LABELS** 9, 21, 25
  - **Cefuroxime (Non-proprietary)**
    - Cefuroxime (as Cefuroxime axetil) 250 mg 200 mg tablets | 14 tablet [POD] £11.72 DT = £11.72
    - Cefuroxime 250mg tablets | 14 tablet [POD] £11.72 DT = £11.72
  - **Zinnat** (GlasoSmithKline UK Ltd)
    - Cefuroxime (as Cefuroxime axetil) 125 mg Zinnat 125mg tablets | 14 tablet [POD] £4.56 DT = £4.56
    - Cefuroxime (as Cefuroxime axetil) 250 mg Zinnat 250mg tablets | 14 tablet [POD] £8.11 DT = £8.11

**Powder for injection**

- **ELECTROLYTES:** May contain Sodium
  - **Cefuroxime (Non-proprietary)**
    - Cefuroxime (as Cefuroxime sodium) 250 mg Cefuroxime 250mg powder for injection vials | 10 vial [POD] £9.25 (Hospital only)
    - Cefuroxime (as Cefuroxime sodium) 750 mg Cefuroxime 750mg powder for injection vials | 1 vial [POD] £5.22 | 10 vial [POD] £25.20
    - Cefuroxime (as Cefuroxime sodium) 1.5 gram Cefuroxime 1.5g powder for injection vials | 1 vial [POD] £5.05 | 10 vial [POD] £50.50
    - Zinacef (GlasoSmithKline UK Ltd)
    - Cefuroxime (as Cefuroxime sodium) 250 mg Zinacef 250mg powder for injection vials | 5 vial [POD] £4.70
    - Cefuroxime (as Cefuroxime sodium) 750 mg Zinacef 750mg powder for injection vials | 5 vial [POD] £11.72 (Hospital only)
    - Cefuroxime (as Cefuroxime sodium) 1.5 gram Zinacef 1.5g powder for injection vials | 1 vial [POD] £4.70

**Oral suspension**

- **CAUTIONARY AND ADVISORY LABELS** 9, 21
  - **EXCipients:** May contain Aspartame, sucrose
    - **Zinacef** (GlasoSmithKline UK Ltd)
    - Cefuroxime (as Cefuroxime axetil) 25 mg per 1 ml Zinnat 125mg/5ml oral suspension | 70 ml [POD] £5.20 DT = £5.20

**ANTIBACTERIALS**  CEPHALOSPORINS, THIRD-GENERATION

**Cefixime**

- **INDICATIONS AND DOSE**

  **Acute infections due to sensitive Gram-positive and Gram-negative bacteria**
  - **BY MOUTH**
    - Child: 6–11 months: 75 mg daily
    - Child: 1–4 years: 100 mg daily
    - Child: 5–9 years: 200 mg daily
    - Child: 10–17 years: 200–400 mg daily, alternatively 100–200 mg twice daily
    - Adult: 200–400 mg daily in 1–2 divided doses

  **Uncomplicated gonorrhoea**
  - **BY MOUTH**
    - Adult: 400 mg for 1 dose

- **UNLICENSED USE** Use of cefixime for uncomplicated gonorrhoea is an unlicensed indication.
- **INTERACTIONS** → Appendix 1: cefuroxime
- **SIDE-EFFECTS** Acute kidney injury - arthralgia - drug fever - dyspepsia - dysphonia - face oedema - flattulence - genital pruritus - hypereosinophilia - jaundice - serum sickness - like reaction - thrombocytosis
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Manufacturer advises avoid unless essential—no information available.

**Bacterial infection 527**

**Cefotaxime**

- **INDICATIONS AND DOSE**

  **Uncomplicated gonorrhoea**
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: 500 mg for 1 dose

  **Infections due to sensitive Gram-positive and Gram-negative bacteria**
  - **SURGICAL PROPHYLAXIS**
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 1 g every 12 hours

  **Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria**
  - **MENINGITIS**
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 8 g daily in 4 divided doses, increased if necessary to 12 g daily in 3–4 divided doses, intramuscular doses over 1 g should be divided between more than one site

  **Emergency treatment of suspected bacterial meningitis or meningooccal disease, before urgent transfer to hospital, in patients who cannot be given benzylpenicillin (e.g. because of an allergy)**
  - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Child: 1 month–11 years: 50 mg/kg for 1 dose
    - Child: 12–17 years: 1 g for 1 dose
    - Adult: 1 g for 1 dose

- **INTERACTIONS** → Appendix 1: cefuroxime
- **SIDE-EFFECTS**
  - **Uncommon** Drug fever - Jarisch-Herxheimer reaction - renal impairment - seizure
  - **Frequency not known** Arrhythmia (following rapid injection) - bronchospasm - encephalopathy - hepatic disorders
  - **PREGNANCY** Not known to be harmful.
  - **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

- **Dose adjustments** → In adults Reduce dose if eGFR less than 20 mL/minute/1.73 m² (max. 200 mg daily).
  - In children Reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 9
  - **Suprax** (Sanofi)
  - Cefixime 200 mg Suprax 200mg tablets | 7 tablet [POD] £13.23 DT = £13.23

**Suprax** (Sanofi)

- Cefixime 200 mg Suprax 200mg tablets | 7 tablet [POD] £13.23 DT = £13.23

**Cefotaxime**

- **INDICATIONS AND DOSE**

  **Uncomplicated gonorrhoea**
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: 500 mg for 1 dose

  **Infections due to sensitive Gram-positive and Gram-negative bacteria**
  - **SURGICAL PROPHYLAXIS**
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 1 g every 12 hours

  **Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria**
  - **MENINGITIS**
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
    - Adult: 8 g daily in 4 divided doses, increased if necessary to 12 g daily in 3–4 divided doses, intramuscular doses over 1 g should be divided between more than one site

  **Emergency treatment of suspected bacterial meningitis or meningooccal disease, before urgent transfer to hospital, in patients who cannot be given benzylpenicillin (e.g. because of an allergy)**
  - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - Child: 1 month–11 years: 50 mg/kg for 1 dose
    - Child: 12–17 years: 1 g for 1 dose
    - Adult: 1 g for 1 dose

- **INTERACTIONS** → Appendix 1: cefuroxime
- **SIDE-EFFECTS**
  - **Uncommon** Drug fever - Jarisch-Herxheimer reaction - renal impairment - seizure
  - **Frequency not known** Arrhythmia (following rapid injection) - bronchospasm - encephalopathy - hepatic disorders
  - **PREGNANCY** Not known to be harmful.
  - **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

- **Dose adjustments** → In adults If eGFR less than 5 mL/minute/1.73 m², initial dose of 1 g then use half normal dose.
  - In children Usual initial dose, then use half normal dose if estimated glomerular filtration rate less than 5 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**

  **With intravenous use in children** Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute in glucose 5% or sodium chloride 0.9%; administer over 20–60 minutes; incompatible with alkaline solutions.

  **With intravenous use in adults** For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%; Suggested volume 40–100 mL given over 20–60 minutes; incompatible with alkaline solutions.

www.getintopharma.com
Ceftazidime

**INDICATIONS AND DOSE**

**Prophylaxis for transurethral resection of prostate**
- BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION
- Adult: 1 g, single dose to be used up to 30 minutes before procedure and may be repeated if necessary when catheter removed

**Pseudomonal lung infection in cystic fibrosis**
- BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY DEEP INTRAMUSCULAR INJECTION
- Adult: 1–2 g every 8–12 hours

**Septicaemia: Hospital-acquired pneumonia**
- BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
- Adult: 2 g every 8 hours

**Febrile neutropenia**
- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
- Adult: 2 g every 8 hours

**Meningitis**
- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
- Adult: 2 g every 8 hours

**Sepsis**
- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
- Adult: 2 g every 8 hours

**Complicated urinary-tract infection**
- BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION
- Adult: 1–2 g every 8–12 hours

**Gram-negative bacteria**
- BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION
- Adult: 1–2 g every 8 hours

**INTERACTIONS**
- Appendix 1: cephalosporins

**SIDE-EFFECTS**
- Common or very common: Thrombocytopenia
- Very rare: Infection at the site of injection, Intra-abdominal infections
- Rare: Acute kidney injury
- Frequency not known: Coma, encephalopathy, jaundice, lymphopenia
- Neurological effects: Paralysis, seizures, taste alteration, tremor

**PREGNANCY**
- Not known to be harmful.

**BREAST FEEDING**
- Present in milk in low concentration, but appropriate to use.

**HEPATIC IMPAIRMENT**
- Manufacturer advises close monitoring in severe impairment—no information available.

**RENAL IMPAIRMENT**
- Dose adjustments: Manufacturer advises reduce dose if creatinine clearance 50 mL/minute or less—consult product literature.

**DIRECTIONS FOR ADMINISTRATION**
- Intravenous administration used when intravenous administration not possible; single doses over 1 g by intravenous route only.
- With intravenous use: For intravenous infusion give intermittently or via drip tubing in Glucose 5% or 10% or Sodium chloride 0.9%. Dissolve 2 g initially in 10 mL (3 g in 15 mL) infusion fluid. For Fortum® dilute further to a concentration of 40 mg/mL. For Kefadim® dilute further to a concentration of 20 mg/mL. Give over up to 30 minutes.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Cefotaxime (Non-proprietary)**
  - Cefotaxime (as Cefotaxime sodium) 500 mg: 10 vial (£0.30)
  - Cefotaxime (as Cefotaxime sodium) 1 gram: 10 vial (£0.35) (Hospital only)
  - Cefotaxime (as Cefotaxime sodium) 2 gram: 10 vial (£0.75) (Hospital only)

**Electrolytes**
- May contain Sodium

**Ceftazidime (as Ceftazidime pentahydrate)**
- 500 mg: 1 vial (£4.25)
- 1 gram: 1 vial (£3.96) (Hospital only)
- 2 gram: 1 vial (£7.90) (Hospital only)
- 3 gram: 1 vial (£13.50) (Hospital only)
- 5 vial (£19.15) (Hospital only)
Bacterial infection  529

SPECIFIC CAUTIONS
- With intravenous use concomitant treatment with intravenous calcium (including total parenteral nutrition containing calcium) (in adults)
- INTERACTIONS  ➔ Appendix 1: cephalosporins
- SIDE-EFFECTS
  - Uncommon Anaemia - coagulation disorder
  - Rare or very rare Bronchospasm - glycosuria - haematuria - oedema
  - Frequency not known Cholelithiasis - hypersensitivity - nephrolithiasis - oral disorders - pancreatitis - seizure - vertigo

SIDE-EFFECTS, FURTHER INFORMATION
Precipitates of calcium ceftriaxone can occur in the gall bladder and urine (particularly in very young, dehydrated or those who are immobile)—consider discontinuation if symptomatic.

PREGNANCY
Manufacturer advises use only if benefit outweighs risk—limited data available but not known to be harmful in animal studies. (EGG) Specialist sources indicate suitable for use in pregnancy.

- BREAST FEEDING (EGG) Specialist sources advise ceftriaxone is compatible with breastfeeding—present in milk in low concentration but limited effects to breast-fed infant. (EGG)

- RENAL IMPAIRMENT
  - Dose adjustments Manufacturer advises reduce dose and monitor efficacy in patients with severe renal impairment in combination with hepatic impairment—no information available.
  - In adults Manufacturer advises reduce dose if eGFR less than 10 mL/minute/1.73 m² (max. 2 g daily).
  - In children Manufacturer advises reduce dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m² max. 50 mg/kg daily or max. 2 g daily).

- MONITORING REQUIREMENTS
  - Manufacturer advises to monitor full blood count regularly during prolonged treatment.

- DIRECTIONS FOR ADMINISTRATION
  - With intramuscular use or intravenous use Twice daily dosing may be considered for doses greater than 2 g daily.

  - With intravenous use in children For intravenous infusion (preferred route), dilute reconstituted solution with Glucose 5% (or 10% in neonates) or Sodium Chloride 0.9%; give over at least 30 minutes (50 minutes in neonates—may displace bilirubin from serum albumin). Not to be given simultaneously with parenteral nutrition or infusion fluids containing calcium, even by different infusion lines; in children, may be infused sequentially with infusion fluids containing calcium if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with Sodium Chloride 0.9% to avoid precipitation—consult product literature. Displacement value may be significant, consult local guidelines. For intravenous injection, give over 5 minutes.

  - With intramuscular use in children For intramuscular injection, may be mixed with 1% Lidocaine Hydrochloride Injection to reduce pain at intramuscular injection site. Intramuscular injection should only be considered when the intravenous route is not possible or less appropriate. If administered by intramuscular injection, the lower end of the dose range should be used for the shortest time possible; volume depends on the age and size of the child, but doses over 1 g must be divided between more than one site. Displacement value may be significant, consult local guidelines. The maximum single intramuscular dose is 2 g, doses greater than 2 g must be given in divided doses or by intravenous administration (see above).

  - With intravenous use in adults For intravenous infusion (preferred route) (Rocephin®; Ceftriaxone Injection, Genus), give intermittently or via drip tubing in Glucose 5% or 10% or Sodium Chloride 0.9%. Reconstitute 2-g vial with 40 mL


  - In adults (EGG) Dose not licensed for treatment of pelvic inflammatory disease in adults over 18 years. Ceftriaxone is used for Lyme disease affecting the central nervous system, but the dose is not licensed for this indication.

- CAUTIONS
  - GENERAL CAUTIONS History of hypercalciuria - history of kidney stones
530 Bacterial infection

Infection

THIRD-GENERATION WITH BETA-

ANTIBACTERIALS

▶ PRESCRIBING AND DISPENSING INFORMATION

See Lyme disease p. 577 for place in therapy and further information on treatment.

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturer include:

Powder for solution for injection

ELECTROLYTES: May contain Sodium

- Ceftriaxone (Non-proprietary)
  - Ceftriaxone (as Ceftriaxone sodium) 250 mg Ceftriaxone 250mg powder for solution for injection vials 1 vial (Pfizer) $2.30 GT + $2.40 (Hospital only)
  - Ceftriaxone (as Ceftriaxone sodium) 1 gram Ceftriaxone 1g powder for solution for injection vials 1 vial (Pfizer) GT $19.18 10 vial (Pfizer) $191.80
  - Ceftriaxone (as Ceftriaxone sodium) 2 gram Ceftriaxone 2g powder for solution for injection vials 1 vial (Roche) $19.18 GT + $19.18 10 vial (Roche) $191.80
- Rocephin (Roche Products Ltd)
  - Ceftriaxone (as Ceftriaxone sodium) 250 mg Rocephin 250mg powder for solution for injection vials 1 vial (Pfizer) $2.40 GT + $2.40
  - Ceftriaxone (as Ceftriaxone sodium) 1 gram Rocephin 1g powder for solution for injection vials 1 vial (Pfizer) GT $19.58 10 vial (Pfizer) $195.80
- Zavicefta (Pfizer Ltd)
  - Ceftriaxone (as Ceftriaxone sodium) 500 mg, Ceftazidime (as Ceftazidime pentahydrate) 2 gram Zavicefta 2g/0.5g powder for concentrate for solution for injection vials 1 vial (Pfizer) $857.00 (Hospital only)

DOSE EQUIVALENCE AND CONVERSION

- Dose expressed as x/y g ceftazidime/avibactam

INTERACTIONS → Appendix 1: cephalosporins

SIDE-EFFECTS

- Common or very common Thrombocytosis
- Uncommon Acute kidney injury - lymphocytosis - paraesthesia - taste altered
- Frequency not known Coma - encephalopathy - jaundice - myoclonus - neurological effects - seizures - tremor

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies.

BREAST FEEDING

Manufacturer advises avoid — presence of avibactam in milk unknown.

DIRECTIONS FOR ADMINISTRATION

Manufacturer advises for intravenous infusion (Zavicefta®) give in Glucose 5%, or Sodium Chloride 0.9%, or Sodium Chloride 0.45% with Glucose 2.5% combination or Lactated Ringer's solution. Reconstitute each 2 g/0.5 g vial with 10 mL water for injections; dilute requisite dose in an appropriate infusion bag and give over 120 minutes.

PATIENT AND CARER ADVICE

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks — risk of dizziness.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion

ELECTROLYTES: May contain Sodium

- Zavicefta (Pfizer Ltd)
- Avibactam (as Avibactam sodium) 500 mg, Ceftazidime (as Ceftazidime pentahydrate) 2 gram

Ceftolozane with tazobactam

ANTIBACTERIALS > CEPHALOSPORINS, THIRD-GENERATION WITH BETA-LACTAMASE INHIBITOR

Ceftazidime with avibactam

The properties listed below are those particular to the combination only. For the properties of the components please consider, ceftazidime p. 528.

INDICATIONS AND DOSE

Complicated intra-abdominal infection (in combination with metronidazole when anaerobic pathogens suspected)

- BY INTRAVENOUS INFUSION
- Adult: 1/0.5 g every 8 hours for 4–14 days

Complicated urinary tract infection | Acute pyelonephritis

- BY INTRAVENOUS INFUSION
- Adult: 1/0.5 g every 8 hours for 7 days

DOSE EQUIVALENCE AND CONVERSION

- Dose expressed as x/y g where x and y are ceftolozane and tazobactam respectively.

INTERACTIONS → Appendix 1: cephalosporins

SIDE-EFFECTS

- Common or very common Anxiety - constipation - electrolyte imbalance - hypotension - insomnia - thrombocytosis

PREGNANCY

Manufacturer advises to use only if potential benefit outweighs risk — toxicity in animal studies with tazobactam.

BREAST FEEDING

Manufacturer advises avoid — no information available.

RENAL IMPAIRMENT

Manufacturer advises monitor for changes in renal function.

Dose adjustments Manufacturer advises reduce dose to 500/250 mg every 8 hours if eGFR

www.getintopharma.com
Bacterial infection 531

Ceftobiprole 12-Dec-2016

- **INDICATIONS AND DOSE**
  - **Hospital-acquired pneumonia (excluding ventilator-associated pneumonia) / Community-acquired pneumonia**
    - **BY INTRAVENOUS INFUSION**
  - **Adult:** 500 mg every 8 hours

- **CAUTIONS**
  - Pre-existing seizure disorder—increased risk of seizures · super-normal creatinine clearance

- **FURTHER INFORMATION**
  - Super-normal creatinine clearance Manufacturer advises to measure baseline renal function and increase duration of infusion if creatinine clearance greater than 150 mL/minute.

- **INTERACTIONS** → Appendix 1: cephalosporins

**Ceftaroline fosamil**

- **INDICATIONS AND DOSE**
  - **Community-acquired pneumonia**
    - **BY INTRAVENOUS INFUSION**
    - **Adult:** 600 mg every 12 hours for 5–7 days
  - **Complicated skin infections / Complicated soft-tissue infections**
    - **BY INTRAVENOUS INFUSION**
    - **Adult:** 600 mg every 12 hours for 5–14 days

- **CAUTIONS**
  - Seizure disorders
  - **INTERACTIONS** → Appendix 1: cephalosporins

- **SIDE-EFFECTS**
  - **Common or very common**
    - Drowsiness · dyspepsia · electrolyte imbalance · hypersensitivity · taste altered
  - **Uncommon**
    - Anaemia · anxiety · asthma · dyspnoea · laryngeal pain · muscle spasm · peripheral oedema · renal failure · sleep disorders · thrombocytosis
  - **Frequency not known**
    - Seizure
  - **PREGNANCY**
    - Manufacturer advises avoid unless essential—no information available.
  - **BREAST FEEDING**
    - Manufacturer advises avoid—present in milk in animal studies.
  - **RENAL IMPAIRMENT**
    - Manufacturer advises use with caution in severe impairment—limited information available.
  - **Dose adjustments** Reduce dose to 500 mg every 12 hours in moderate impairment and 250 mg every 12 hours in severe impairment.

- **DIRECTIONS FOR ADMINISTRATION**
  - Manufacturer advises for *intravenous infusion* (Zeftera®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute each 500 mg with 10 mL. Water for injections or Glucose 5% dilute in 250 mL infusion fluid and give over 2 hours. Do not mix with calcium-containing solutions (except Lactated Ringer solution) in the same intravenous line—precipitation may occur.

- **HANDLING AND STORAGE**
  - Manufacturer advises store in a refrigerator (2–8°C) and consult product literature for storage after reconstitution and dilution.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks**
    - Manufacturer advises avoid unless reconstituted use within NHS Scotland when metillin-resistant *S. aureus* is suspected in complicated skin and soft-tissue infection and vancomycin cannot be used.

**MEDIINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Zinforo (Pfizer Ltd)**
  - Ceftaroline fosamil (as Ceftaroline fosamil acetic acid solvate monohydrate) 600 mg. Zinforo 600mg powder for concentrate for solution for infusion vials | 10 vial [POM] £375.00 (Hospital only)

- **Ceftriaxone**
  - Ceftriaxone sodium (as Ceftriaxone sodium monohydrate) 1 gram. Ceftriaxone 1g for concentration for solution for infusion vials | 10 vial [POM] £670.30 (Hospital only)

**ANTIBACTERIALS > CEPHALOSPORINS, OTHER**

**Ceftaroline fosamil**

- **INDICATIONS AND DOSE**
  - **Community-acquired pneumonia**
  - **BY INTRAVENOUS INFUSION**
    - **Adult:** 600 mg every 12 hours for 5–7 days
  - **Complicated skin infections / Complicated soft-tissue infections**
    - **BY INTRAVENOUS INFUSION**
    - **Adult:** 600 mg every 12 hours for 5–14 days

- **CAUTIONS**
  - Seizure disorders
  - **INTERACTIONS** → Appendix 1: cephalosporins
  - **SIDE-EFFECTS**
    - **Common or very common**
    - Drowsiness · dyspepsia · electrolyte imbalance · hypersensitivity · taste altered
    - **Uncommon**
    - Anaemia · anxiety · asthma · dyspnoea · laryngeal pain · muscle spasm · peripheral oedema · renal failure · sleep disorders · thrombocytosis
  - **FREQUENCY NOT KNOWN**
    - Seizure
  - **PREGNANCY**
    - Manufacturer advises avoid unless essential—no information available.
  - **BREAST FEEDING**
    - Manufacturer advises avoid—present in milk in animal studies.
  - **RENAL IMPAIRMENT**
    - Manufacturer advises use with caution in severe impairment—limited information available.
  - **Dose adjustments** Reduce dose to 500 mg every 12 hours in moderate impairment and 250 mg every 12 hours in severe impairment.

- **DIRECTIONS FOR ADMINISTRATION**
  - Manufacturer advises for *intravenous infusion* (Zeftera®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute each 500 mg with 10 mL. Water for injections or Glucose 5% dilute in 250 mL infusion fluid and give over 2 hours. Do not mix with calcium-containing solutions (except Lactated Ringer’s solution) in the same intravenous line—precipitation may occur.

- **HANDLING AND STORAGE**
  - Manufacturer advises store in a refrigerator (2–8°C) and consult product literature for storage after reconstitution and dilution.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks**
    - Manufacturer advises avoid unless reconstituted use within NHS Scotland when metillin-resistant *S. aureus* is suspected in complicated skin and soft-tissue infection and vancomycin cannot be used.

**MEDIINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Zinforo (Pfizer Ltd)**
  - Ceftaroline fosamil (as Ceftaroline fosamil acetic acid solvate monohydrate) 600 mg. Zinforo 600mg powder for concentrate for solution for infusion vials | 10 vial [POM] £375.00 (Hospital only)

- **Ceftriaxone**
  - Ceftriaxone sodium (as Ceftriaxone sodium monohydrate) 1 gram. Ceftriaxone 1g for concentration for solution for infusion vials | 10 vial [POM] £670.30 (Hospital only)

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Antibacterials

Antibacterials > Glycopeptide Antibacterials

Dalbavancin

Drug Action
Dalbavancin is a glycopeptide antibiotic; it has bactericidal activity against Gram-positive bacteria including various staphylococci. However, there are reports of Staphylococcus aureus with reduced susceptibility to glycopeptides and increasing reports of glycopeptide-resistant enterococci.

Indications and Dose

- Acute bacterial skin and skin structure infections
  - By Intravenous Infusion
  - Adult: 1500 mg for 1 dose, alternatively 1000 mg, then 500 mg after 1 week

Side Effects
- Common or very common: Diarrhoea, headache, nausea
- Uncommon: Anaemia, antibiotic associated colitis, appetite decreased, constipation, cough, diziness, eosinophilia, flushing, gastrointestinal discomfort, increased risk of infection, infusion related reaction, insomnia, leucopenia, neutropenia, skin reactions, taste altered, thrombocytosis, vomiting, vulvovaginal pruritus
- Rare or very rare: Bronchospasms
- Frequency not known: Ototoxicity

Allergy and Cross-Sensitivity
Manufacturer advises use with caution in patients with other glycopeptide reports of sensitivity.

Pregnancy
Dose adjustments
Manufacturer advises avoid unless essential—toxicity in animal studies.

Breast Feeding
Dose adjustments
Manufacturer advises avoid—present in milk in animal studies.

Hepatic Impairment
Manufacturer advises caution in moderate to severe impairment (no information available).

Renal Impairment
Dose adjustments
Manufacturer advises reduce dose to 1000 mg as a single infusion or reduce dose to 750 mg followed one week later by 375 mg if creatinine clearance <30 mL/minute.

Directions for Administration
Manufacturer advises for intravenous infusion (Xydalba®), reconstitute each 500 mg vial to produce a 20 mg/mL solution with 25 mL water for injections. Dilute reconstituted solution to a concentration of 1–5 mg/mL with Glucose 5%; give intermittently over 30 minutes (avoid rapid infusion—risk of ‘red man’ syndrome).

National Funding/Access Decisions
Scottish Medicines Consortium (SMC) decisions
SMC No. 1105/15
The Scottish Medicines Consortium has advised (January 2017) that dalbavancin (Xydalba®) is accepted for restricted use within NHS Scotland for the treatment of acute bacterial skin and skin structure infections (ABSSSI), only if:
- used as second-line treatment, or
- meticillin-resistant Staphylococcus aureus infection is suspected, or
- under local microbiologist or infectious diseases specialist advice; and
- the patient is initially hospitalised due to ABSSSI requiring intravenous antibiotics but is eligible for early discharge as soon as their medical condition does not require further inpatient treatment.

All Wales Medicines Strategy Group (AWMSG) decisions
AWMSG No. 2001

Teicoplanin

Drug Action
The glycopeptide antibiotic teicoplanin has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of Staphylococcus aureus with reduced susceptibility to glycopeptides and increasing reports of glycopeptide-resistant enterococci. Teicoplanin is similar to vancomycin, but has a significantly longer duration of action, allowing once daily administration after the loading dose.

Indications and Dose

Clostridium difficile infection
- By Mouth
- Adult: 100–200 mg twice daily for 7–14 days

Serious infections caused by Gram-positive bacteria (e.g. complicated skin and soft-tissue infections, pneumonia, complicated urinary tract infections)
- By Intravenous Injection, or By Intravenous Infusion, or By Intramuscular Injection
- Adult: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Streptococcal or enterococcal endocarditis (in combination with another antibacterial) Bone and joint infections
- Initially by Intravenous injection, or by Intravenous infusion
- Adult: 12 mg/kg every 12 hours for 3–5 doses, then (by intravenous injection or by intravenous infusion or by intramuscular injection) 12 mg/kg once daily

Surgical prophylaxis
- By Intravenous Injection
- Adult: 400 mg, to be administered up to 30 minutes before the procedure

Surgical prophylaxis in open fractures
- By Intravenous Infusion
- Adult: 800 mg, to be administered up to 30 minutes before skeletal stabilisation and definitive soft-tissue closure

Peritonitis associated with peritoneal dialysis (added to dialysis fluid)
- By Intrapерitoneal Infusion
- Adult: (consult local protocol)

Pharmacokinetics
- Teicoplanin should not be given by mouth for systemic infections because it is not absorbed significantly.

Unlicensed Use
Not licensed for surgical prophylaxis.
**Telavancin**

**DRUG ACTION** Telavancin is a glycopeptide antibiotic; it has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci.

**INDICATIONS AND DOSE**

- **Hospital-acquired pneumonia, known or suspected to be caused by meticillin-resistant *Staphylococcus aureus***
- **when other antibacterials cannot be used**
  - **BY INTRAVENOUS INFUSION**
  - Adult: 10 mg/kg once daily for 7–21 days

**CAUTIONS** Conditions that predispose to renal impairment: predisposition to QT interval prolongation (including electrolyte disturbances, congenital long QT syndrome, uncompensated heart failure, severe left ventricular hypertrophy)

**INTERACTIONS** → Appendix 1: telavancin

**SIDE-EFFECTS**

- **Common or very common** Asthenia - constipation - diarrhoea - dizziness - headaches - increased risk of infection - insomnia - nausea - renal impairment - skin reactions - taste altered - urine abnormalities - vomiting
- **Rare or very rare** Deafness

**ALLERGY AND CROSS-SENSITIVITY** Use with caution in patients with vancomycin or teicoplanin sensitivity.

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

**PREGNANCY** Avoid (teratogenic in animal studies).

**BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (no information available).

**RENAL IMPAIRMENT** Avoid in acute renal failure—risk of mortality increased. In chronic renal failure, avoid if eGFR less than 30 mL/minute/1.73 m².

**SIDE-EFFECTS, FURTHER INFORMATION** Telavancin is associated with a lower incidence of nephrotoxicity than vancomycin.

**MEDICINAL FORMS**

- **Powder and solvent for solution for injection**
  - **Electrolytes**: May contain Sodium
  - **Teicoplanin (non-proprietary)** 
    - **Teicoplanin 200 mg**: Teicoplanin 200 mg powder and solvent for solution for injection vials | 1 vial | £3.93
    - **Teicoplanin 400 mg**: Teicoplanin 400 mg powder and solvent for solution for injection vials | 1 vial | £7.32
    - **Targocid (Sanofi)**
      - **Teicoplanin 200 mg**: Targocid 200 mg powder and solvent for solution for injection vials | 1 vial | £3.93
      - **Teicoplanin 400 mg**: Targocid 400 mg powder and solvent for solution for injection vials | 1 vial | £7.32
  - **Dose adjustments** In chronic renal failure, use 7.5 mg/kg once daily if eGFR 30–50 mL/minute/1.73 m².
  - **Monitoring requirements** Monitor renal function daily for at least the first 3–5 days, then every 2–3 days thereafter.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Vibutiv®). Avoid rapid infusion (can cause ‘red man’ syndrome). Give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 750 mg with 45 mL glucose 5%, sodium chloride 0.9%, or water for injections to produce a 15 mg/mL solution; for doses of 150–800 mg, dilute requisite dose in 100 to 250 mL infusion fluid; for doses outside this range, dilute to a final concentration of 0.5–8 mg/mL; give over at least 60 minutes.
Vancomycin

11-May-2018

**DRUG ACTION** The glycopeptide antibiotic vancomycin has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci. Penetration into cerebrospinal fluid is poor.

**Medical Forms** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- **Vibativ** (Clinigen Healthcare Ltd)
  - Telavancin (as Telavancin hydrochloride) 750 mg
  - **Vibativ 750mg powder for solution for infusion vials** | 1 vial **£665.00** (Hospital only)

**INDICATIONS AND DOSE**

- **Clostridium difficile infection**
  - **[first episode]**
    - **By mouth**
      - Adult: 125 mg every 6 hours for 10 days; increased if necessary to 500 mg every 6 hours for 10 days, increased dose if severe or complicated infection
  - **[multiple recurrences]**
    - **By mouth**
      - Adult: 125 mg every 6 hours for 10 days, followed by, either tapering the dose (gradually reducing until 125 mg daily) or a pulse regimen (125–500 mg every 2–3 days for at least 3 weeks)

- **Complicated skin and soft tissue infections**
- **Bone infections**
- **Joint infections**
- **Community-acquired pneumonia**
- **Hospital-acquired pneumonia**
- **[including ventilator-associated pneumonia]**
- **[infective endocarditis]**
- **Acute bacterial meningitis**
- **Bacteraemia**

- **[occurring in association with or suspected to be associated with the licensed indications]**
  - **By intravenous infusion**
    - Adult: 15 mg/kg, to be given prior to induction of anaesthesia, a second dose may be required depending on duration of surgery
  - **Surgical prophylaxis**
    - **By intravenous infusion**
      - Adult: 1 g for 1 dose
  - **Peritonitis associated with peritoneal dialysis**
    - **By intraperitoneal administration**
      - Adult: (consult local protocol)

**Pharmacokinetics**

- Vancomycin should not be given by mouth for systemic infections because it is not absorbed significantly.

**UNLICENSED USE** Vancomycin doses in BNF publications may differ from those in product literature. Use of vancomycin (added to dialysis fluid) for the treatment of peritonitis associated with peritoneal dialysis is an unlicensed route.

**CONTRA-INDICATIONS**

- With intravenous use Previous hearing loss

**CAUTIONS**

- With oral use systemic absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridium difficile*-induced pseudomembranous colitis (increased risk of adverse reactions)

**INTERACTIONS** → Appendix 1: vancomycin

**SIDE-EFFECTS**

**General Side-effects**

- Agranulocytosis - dizziness - drug fever - eosinophilia - hypersensitivity - nausea - nephritis - tubulointerstitial - neutropenia (more common after 1 week or cumulative dose of 25g) - renal failure - severe cutaneous adverse reactions (SCARs) - skin reactions - thrombocytopenia - tinnitus (discontinue) - vasculitis - vertigo

**Specific Side-effects**

- With intravenous use Back pain - bradycardia - cardiac arrest (on rapid intravenous injection) - cardiogenic shock (on rapid intravenous injection) - chest pain - dyspnoea - hearing loss - hypotension - muscle complaints - pseudomembranous enterocolitis - red man syndrome - wheezing

**SIDE-EFFECTS, FURTHER INFORMATION** Vancomycin is associated with a higher incidence of nephrotoxicity than teicoplanin.

**Allergy and Cross-Sensitivity**

- Caution if teicoplanin sensitivity.

**Pregnancy**

- Manufacturer advises use only if potential benefit outweighs risk.

**Monitoring**

- Plasma-vancomycin concentration monitoring with intravenous use
- Monitoring of renal function.

**Breast Feeding**

- Present in milk—significant absorption following oral administration unlikely.

**Renal Impairment**

- Manufacturer advises serial monitoring of renal function.

- With intravenous use Manufacturer advises use with caution—increased risk of toxic effects with prolonged high blood concentration.

**Dose Adjustments**

- With oral use Manufacturer advises dose adjustment is unlikely to be required unless substantial oral absorption occurs in inflammatory disorders of the intestinal mucosa or with *Clostridium difficile*-induced pseudomembranous colitis, see Monitoring.

- With intravenous use Manufacturer advises initial dose must not be reduced—consult product literature.

**Monitoring Requirements**

- With intravenous use Manufacturer advises initial doses should be based on body-weight; subsequent dose adjustments should be based on serum-vancomycin concentrations to achieve targeted therapeutic concentrations. All patients require serum-vancomycin measurement (on the second day of treatment, immediately before the next dose if renal function normal, earlier if renal impairment—consult product literature).

- Frequency of monitoring depends on the clinical situation and response to treatment; regular monitoring indicated in high-dose therapy and longer-term use, particularly in patients with impaired renal function, impaired hearing, or concurrent use of nephrotoxic or ototoxic drugs.

- Manufacturer advises pre-dose (‘trough’) concentration should normally be 10–20 mg/litre depending on the site of infection and the susceptibility of the pathogen; trough concentration of 15–20 mg/litre is usually recommended to cover susceptible pathogens with MIC greater than or equal to 1 mg/litre—consult product literature.

- Manufacturer advises periodic testing of auditory function.

www.getintopharma.com
**Antibacterials**

**Clindamycin**

- **Drug Action**: Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides fragilis*. It is well concentrated in bone and excreted in bile and urine.

**INDICATIONS AND DOSE**

**Staphylococcal bone and joint infections such as osteomyelitis | Peritonitis | Intra-abdominal sepsis | Meticillin-resistant *Staphylococcus aureus* (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections | Erysipelas or cellulitis in penicillin-allergic patients (alternative to macrolides)**

- **By Mouth**
  - Child: 3–6 mg/kg 4 times a day (max. per dose 450 mg)
  - Adult: 150–300 mg every 6 hours; increased if necessary up to 450 mg every 6 hours if required, increased dose used in severe infection

- **By Deep Intramuscular Injection, or by Intravenous Infusion**
  - Adult: 0.6–2.7 g daily in 2–4 divided doses; increased if necessary up to 4.8 g daily, increased dose used in life-threatening infection, single doses above 600 mg to be administered by intravenous infusion only, single doses by intravenous infusion not to exceed 1.2 g

**Treatment of mild to moderate pneumonia**

- **By Mouth**
  - Child: 7–13 mg/kg every 8 hours (max. per dose 450 mg) for 7 days
  - Adult: 450 mg every 8 hours for 7 days

**SIDE-EFFECTS**

**General Side-effects**

- **Common or very common** Skin reactions

**Specific Side-effects**

- **Common or very common**
  - With oral use: Abdominal pain | Antibiotic-associated colitis | Diarrhoea (discontinue)
  - Uncommon
  - With oral use: Nausea | Vomiting
  - Frequency not known

- **With oral use: Agranulocytosis | angioedema | eosinophilia | gastrointestinal disorders | Jaundice | Leucopenia | Neutropenia | Severe cutaneous adverse reactions (SCARs) | Taste altered | Thrombocytopenia | Vulvovaginal infection

- **With parenteral use: Abdominal pain | Agranulocytosis | Antibiotic-associated colitis | Cardiac arrest | Diarrhoea | Eosinophilia | Hypotension | Jaundice | Leucopenia | Nausea | Neutropenia | Severe cutaneous adverse reactions (SCARs) | Taste altered | Thrombocytopenia | Thrombophlebitis | Vomiting | Vulvovaginal infection

**Side-effects, Further Information**

**Antibiotic-associated colitis**

Clindamycin has been associated with antibiotic-associated colitis, which may be fatal. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. If *Clostridium difficile* infection is suspected or confirmed, discontinue the antibiotic if appropriate. Seek specialist advice if the antibiotic cannot be stopped and the diarrhoea is severe.

**Medicinal Forms**

- **There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection, infusion.

**Powder for solution for infusion**

- **Vancomycin** *(Non-proprietary)*
  - Vancomycin (as Vancomycin hydrochloride) 500 mg: Vancomycin 500 mg powder for solution for infusion vials | 1 vial (PN) £7.25 DT + £5.49 | 10 vial (PN) £62.50 DT + £62.50
  - Vancomycin 500 mg powder for concentrate for solution for infusion vials | 1 vial (PN) £5.49–£8.50 DT + £5.49 (Hospital only) | 10 vial (PN) £62.50 DT + £62.50 (Hospital only) | 10 vial (PN) £62.50–£72.50 DT + £62.50
  - Vancomycin (as Vancomycin hydrochloride) 1 gram: Vancomycin 1g powder for solution for infusion vials | 1 vial (PN) £11.25 DT + £10.00 | 10 vial (PN) £125.00 DT + £125.00
  - Vancomycin 1g powder for concentrate for solution for infusion vials | 1 vial (PN) £11.25–£17.25 DT + £11.25 (Hospital only) | 10 vial (PN) £125.00 DT + £125.00 (Hospital only) | 10 vial (PN) £125.00 DT + £125.00

- **Vancomycin** *(Flynn Pharma Ltd)*
  - Vancomycin (as Vancomycin hydrochloride) 500 mg: Vancomycin 500 mg powder for solution for infusion vials | 1 vial (PN) £6.25 DT + £5.49
  - Vancomycin (as Vancomycin hydrochloride) 1 gram: Vancomycin 1g powder for solution for infusion vials | 1 vial (PN) £11.25 DT + £10.00

**Capsule**

- **Vancomycin** *(Non-proprietary)*
  - Vancomycin (as Vancomycin hydrochloride) 50 mg: Vancomycin 50 mg capsules | 28 capsule (PN) £132.47 DT + £112.47
  - Vancomycin (as Vancomycin hydrochloride) 125 mg: Vancomycin 125 mg capsules | 28 capsule (PN) £264.94 DT + £224.94

- **Vancomycin Matrigel** *(Flynn Pharma Ltd)*
  - Vancomycin (as Vancomycin hydrochloride) 125 mg: Vancomycin Matrigel 125 mg capsules | 28 capsule (PN) £88.31 DT + £132.47

**Medications**

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use: Avoid rapid infusion (risk of anaphylactoid reactions) and rotate infusion sites.
  - For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 500 mg with 10 mL water for injections and dilute with infusion fluid to a concentration of up to 5 mg/mL (10 mg/mL in fluid restriction but increased risk of infusion-related effects); give over at least 60 minutes (rate not to exceed 10 mg/minute for doses over 500 mg); use continuous infusion only if intermittent not feasible.
  - With oral use: Injection can be used to prepare solution for oral administration—consult product literature.

**Contraindications**

- Avoid use in Acute porphyrias p. 132
  - With parenteral use: Agranulocytosis | angioedema | eosinophilia | gastrointestinal disorders | Jaundice | Leucopenia | Neutropenia | Severe cutaneous adverse reactions (SCARs) | Taste altered | Thrombocytopenia | Vulvovaginal infection

- **UNLICENSED USE**
  - Not licensed for treatment of mild to moderate pneumococcal infection.

- **CONTRA-INDICATIONS**
  - Diarrhoeal states

- **CAUTIONS**
  - Avoid in Acute porphyrias p. 1058 | middle-aged and elderly women, especially after an operation (antibiotic-associated colitis more common)

- **INTERACTIONS**
  - Appendix 1: clindamycin

**UNLICENSED USE**

- Not licensed for treatment of mild to moderate pneumococcal infection. Not licensed for treatment of falciparum malaria.

- **SIDE-EFFECTS**
  - **Common or very common** Skin reactions
  - **Specific Side-effects**
  - **Common or very common**
  - With oral use: Abdominal pain | Antibiotic-associated colitis | Diarrhoea (discontinue)
  - **Uncommon**
  - With oral use: Nausea | Vomiting
  - **Frequency not known**
  - With oral use: Agranulocytosis | Angioedema | Eosinophilia | Gastrointestinal disorders | Jaundice | Leucopenia | Neutropenia | Severe cutaneous adverse reactions (SCARs) | Taste altered | Thrombocytopenia | Vulvovaginal infection
  - With parenteral use: Abdominal pain | Agranulocytosis | Antibiotic-associated colitis | Cardiac arrest | Diarrhoea (discontinue) | Eosinophilia | Hypotension | Jaundice | Leucopenia | Nausea | Neutropenia | Severe cutaneous adverse reactions (SCARs) | Taste altered | Thrombocytopenia | Thrombophlebitis | Vomiting | Vulvovaginal infection

**SIDE-EFFECTS, FURTHER INFORMATION**

**Antibiotic-associated colitis**

Clindamycin has been associated with antibiotic-associated colitis, which may be fatal. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. If *Clostridium difficile* infection is suspected or confirmed, discontinue the antibiotic if appropriate. Seek specialist advice if the antibiotic cannot be stopped and the diarrhoea is severe.
**Macrolides**

### Overview

The macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin; they are thus an alternative in penicillin-allergic patients. They are active against many - penicillin-resistant staphylococci, but some are now also resistant to the macrolides.

Indications for the macrolides include campylobacter enteritis, respiratory infections (including pneumonia, whooping cough, Legionella, chlamydia, and mycoplasma infection), and skin infections.

Erythromycin p. 539 is also used in the treatment of early syphilis, uncomplicated genital chlamydial infection, and non-gonococcal urethritis. Erythromycin has poor activity against *Haemophilus influenzae*. Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose, but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed.

Azithromycin below is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria, but enhanced activity against some Gram-negative organisms including *H. influenzae*. Plasma concentrations are very low, but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of uncomplicated genital chlamydial infection, non-gonococcal urethritis, uncomplicated gonorrhea, typhoid [unlicensed indication], trachoma [unlicensed indication], and Lyme disease [unlicensed indication].

Clarithromycin p. 538 is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. Clarithromycin is also used in regimens for *Helicobacter pylori* eradication. Spiramycin is also a macrolide which is used for the treatment of toxoplasmosis.

### Macrolides

#### CAUTIONS
- With intravenous use or oral use electrolyte disturbances (predisposition to QT interval prolongation) - may aggravate myasthenia gravis - predisposition to QT interval prolongation
- **SIDE EFFECTS**
  - **Common or very common** Appetite decreased - diarrhoea - dizziness - gastrointestinal discomfort - gastrointestinal disorders - headache - hearing impairment - insomnia - nausia - pancreatitis - paraesthesia - skin reactions - taste altered - vasodilation - vision disorders - vomiting
  - **Uncommon** Angioedema - anxiety - arrhythmias - candida infection - chest pain - constipation - drowsiness - eosinophilia - hepatic disorders - leucopenia - neutropenia - palpitations - QT interval prolongation - severe cutaneous adverse reactions (SCARs) - tinnitus - vertigo
  - **Rare or very rare** Antibiotic associated colitis - myasthenia gravis - nephritis tubulo-intertstitial
  - **Frequency not known** Hallucination - hypotension - seizure - smell altered - thrombocytopenia - tongue discolouration

#### Azithromycin

#### INDICATIONS AND DOSE

*Prevention of secondary case of invasive group A streptococcal infection in patients who are allergic to penicillin*
- **BY MOUTH**
  - Child 6 months-11 years: 12 mg/kg once daily (max. per dose 500 mg) for 5 days
  - Child 12-17 years: 500 mg once daily for 5 days
  - Adult: 500 mg once daily for 5 days

#### Macrolides

**BY MOUTH**
- Clindamycin (as Clindamycin hydrochloride) 75 mg Dalacin C 75mg capsules | 24 capsule (Pﬁzer Ltd) £7.45 DT £7.45 Clindamycin (as Clindamycin hydrochloride) 150 mg Dalacin C 150mg capsules | 24 capsule (Pﬁzer Ltd) £13.72 DT £13.08 | 100 capsule (Pﬁzer Ltd) £12.83-£55.08 Clindamycin (as Clindamycin hydrochloride) 300 mg Dalacin C 300mg capsules | 30 capsule (Pﬁzer Ltd) £42.00 DT £38.26

**INJECTION**
- Dalacin C (Pﬁzer Ltd) Clindamycin (as Clindamycin phosphate) 150 mg per 1 ml Dalacin C Phosphate 300mg/2ml solution for injection ampoules | 5 amouple (Pﬁzer Ltd) £31.01 | 5 amouple (Hospital only) £33.01 (Hospital only)

#### Patanjali Ayurveda TLimited

- Clindamycin (as Clindamycin hydrochloride) 150 mg Dalacin C 150mg capsules | 24 capsule (Patanjali Ayurveda TLimited) £6.75 DT £6.13

#### Clarithromycin

- Clarithromycin (as Clarithromycin hydrochloride) 100 mg Zithromax 100mg capsules | 21 capsule (Pﬁzer Ltd) £27.20 DT £25.90

#### Spiramycin

- Spiramycin (as Spiramycin phosphate) 600 mg/4ml solution for injection ampoules | 5 ampoule (Pﬁzer Ltd) £14.61 (Hospital only)

#### Cautionary and Advisory Labels

- 9, 27

<table>
<thead>
<tr>
<th>Item</th>
<th>Property</th>
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<tr>
<td><strong>Clindamycin</strong></td>
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<tr>
<td>Clindamycin (as Clindamycin phosphate) 150 mg</td>
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<tr>
<td>Clindamycin (as Clindamycin hydrochloride) 150 mg</td>
<td>Dalacin C 150mg capsules</td>
</tr>
<tr>
<td>Clindamycin (as Clindamycin hydrochloride) 300 mg</td>
<td>Dalacin C 300mg capsules</td>
</tr>
</tbody>
</table>

#### Paediatric Dosing

- Child 12 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 11 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 10 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 9 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 8 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 7 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 6 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 5 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 4 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 3 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 2 years:
  - Erythromycin 500 mg once daily for 5 days
  - Child 1 year:
  - Erythromycin 500 mg once daily for 5 days
  - Child 12 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 6 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 5 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 4 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 3 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 2 months:
  - Erythromycin 500 mg once daily for 5 days
  - Child 1 month:
  - Erythromycin 500 mg once daily for 5 days
  - Child 6 weeks:
  - Erythromycin 500 mg once daily for 5 days
  - Child 5 weeks:
  - Erythromycin 500 mg once daily for 5 days
  - Child 4 weeks:
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  - Child 3 weeks:
  - Erythromycin 500 mg once daily for 5 days
  - Child 2 weeks:
  - Erythromycin 500 mg once daily for 5 days
  - Child 1 week:
  - Erythromycin 500 mg once daily for 5 days
  - Child 6 days:
  - Erythromycin 500 mg once daily for 5 days
  - Child 5 days:
  - Erythromycin 500 mg once daily for 5 days
  - Child 4 days:
  - Erythromycin 500 mg once daily for 5 days
  - Child 3 days:
  - Erythromycin 500 mg once daily for 5 days
  - Child 2 days:
  - Erythromycin 500 mg once daily for 5 days
  - Child 1 day:
  - Erythromycin 500 mg once daily for 5 days

### Clindamycin

- Clindamycin (as Clindamycin hydrochloride) 75 mg Dalacin C 75mg capsules | 24 capsule (Pﬁzer Ltd) £7.45 DT £7.45 Clindamycin (as Clindamycin hydrochloride) 150 mg Dalacin C 150mg capsules | 24 capsule (Pﬁzer Ltd) £13.72 DT £13.08 | 100 capsule (Pﬁzer Ltd) £12.83-£55.08 Clindamycin (as Clindamycin hydrochloride) 300 mg Dalacin C 300mg capsules | 30 capsule (Pﬁzer Ltd) £42.00 DT £38.26

#### Clarithromycin

- Clarithromycin (as Clarithromycin hydrochloride) 100 mg Dalacin C 100mg capsules | 20 capsule (Pﬁzer Ltd) £30.90 DT £27.80

#### Clarithromycin

- Clarithromycin (as Clarithromycin hydrochloride) 100 mg Dalacin C 100mg capsules | 20 capsule (Pﬁzer Ltd) £30.90 DT £27.80

### Spiramycin

- Spiramycin (as Spiramycin phosphate) 600 mg/4ml solution for injection ampoules | 5 ampoule (Pﬁzer Ltd) £14.61 (Hospital only)
**Respiratory-tract infections, otitis media, skin and soft-tissue infections**
- With oral use
  - Adult: 500 mg once daily for 3 days
  - Child 6 months-17 years (body-weight 40–65 kg): 250 mg once daily for 3 days
  - Child 6 months-17 years (body-weight 30–39 kg): 200 mg once daily for 3 days
  - Child 6 months-17 years (body-weight 20–29 kg): 150 mg once daily for 3 days
  - Child 6 months-17 years (body-weight 10–19 kg): 100 mg once daily for 3 days
  - Child 6 months-17 years (body-weight 5–9 kg): 50 mg once daily for 3 days
  - Child 6 months-17 years (body-weight ≤ 5 kg): 25 mg once daily for 3 days
- With intravenous use
  - Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

**Uncomplicated genital chlamydial infections | Non-gonococcal urethritis**
- With oral use
  - Adult: 1 g for 1 dose
  - Child 12-17 years: 1 g for 1 dose
- With intravenous use
  - Adult: 1 g for 1 dose

**Lyme disease [erythema migrans and/or non-focal symptoms]**
- With oral use
  - Adult: 500 mg daily for 17 days
  - Child 6 months-17 years: 250 mg once daily for 7 days

**Mild to moderate typhoid due to multiple-antibacterial resistant organisms**
- With oral use
  - Adult: 500 mg once daily for 7 days
  - Child 6 months-17 years: 250 mg once daily for 7 days

**Community-acquired pneumonia, low to moderate severity**
- With oral use
  - Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

**Community-acquired pneumonia, high severity**
- Initially by intravenous infusion
  - Adult: Initially 500 mg once daily for at least 2 days, then (by mouth) 500 mg once daily for a total duration of 7–10 days

**Antibacterial prophylaxis for insertion of intra-uterine device**
- With oral use
  - Adult: 1 g for 1 dose

**Unlicensed use**
- In children Not licensed for prevention of group A streptococcal infection.
- With oral use in adults Azithromycin may be used as detailed below, although these situations are considered outside the scope of its licence:
  - Prevention of group A streptococcal infection;
  - Uncomplicated gonorrhoea;
  - Lyme disease;
  - Mild to moderate typhoid due to multiple-antibacterial resistant organisms;
  - Community-acquired pneumonia (high severity) when oral treatment continues for more than 3 days.

**Interactions**
- Appendix 1: macrolides

**Side-effects**
- Common or very common
  - With oral use Arthralgia
  - Uncommon
  - With oral use Numbness · oedema · photosensitivity reaction
  - With parenteral use Numbness · oedema · photosensitivity reaction

**Frequency not known**
- With oral use Acute kidney injury · aggression · akathisia · haemolytic anaemia · syncope
- With parenteral use Acute kidney injury · aggression · akathisia · haemolytic anaemia · syncope

**Pregnancy**
- Manufacturers advise use only if adequate alternatives not available.

**Breast feeding**
- Present in milk; use only if no suitable alternatives.

**Hepatic impairment**
- Manufacturer advises caution; consider avoiding in severe impairment (no information available).

**Renal impairment**
- In adults Use with caution if eGFR less than 10 mL/minute/1.73 m².
- With oral use in children Use with caution if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use in adults For intravenous infusion (Zedbac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 500 mg with 4.8 mL water for injections to produce a 100 mg/mL solution, then dilute 5 mL of solution with infusion fluid to a final concentration of 1 or 2 mg/mL; give the 1 mg/mL solution over 3 hours or give the 2 mg/mL solution over 1 hour.

**Prescribing and dispensing information**
- With oral use See Lyme disease p. 577 for place in therapy and further information on treatment. Flavours of oral liquid formulations may include cherry or banana.

**Patient and carer advice**
- Medicines for Children leaflet: Azithromycin for bacterial infections www.medicinesforchildren.org.uk/azithromycin-bacterial-infections-0

**Profession specific information**
- Dental practitioners’ formulary
  - With oral use Azithromycin Capsules may be prescribed. Azithromycin Tablets may be prescribed.
  - Azithromycin Oral Suspension 200 mg/5 mL may be prescribed.

**Exceptions to legal category**
- With oral use Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic Chlamydia trachomatis genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to maximum single dose of 1 g, maximum daily dose 1 g, and a pack size of 1 g.

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

<table>
<thead>
<tr>
<th>Table</th>
<th>Pack size</th>
<th>Price</th>
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<tbody>
<tr>
<td>Tablet</td>
<td></td>
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<tr>
<td>Azithromycin (Non-proprietary)</td>
<td>Azithromycin 250 mg</td>
<td>£10.11 DT = £1.124</td>
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<tr>
<td>Azithromycin 500 mg</td>
<td>£9.80 DT = £1.09</td>
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<tr>
<td>Oral suspension</td>
<td></td>
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<tr>
<td>Azithromycin 40 mg per 1 ml</td>
<td>Azithromycin 200mg/5ml oral suspension</td>
<td>15 ml (PBO) £6.18 DT = £4.06</td>
</tr>
<tr>
<td>Zithromax (Pfizer Ltd)</td>
<td>Azithromycin 40 mg per 1 ml</td>
<td>Zithromax 200mg/5ml oral suspension</td>
</tr>
</tbody>
</table>

**Powder for solution for infusion**
- Electrolytes: May contain Sodium
- Zedbac (Aspire Pharma Ltd)
  - Azithromycin (as Azithromycin dihydrate) 500 mg Zedbac 500mg powder for solution for infusion vials | 1 vial (PBO) £3.50 (Hospital only)
Clarithromycin

INDICATIONS AND DOSE

Respiratory-tract infections | Mild to moderate skin and soft-tissue infections

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily
  - Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily
  - Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily
  - Child 1 month–11 years (body-weight 30–40 kg): 250 mg twice daily for 5 days
  - Child 12–17 years: 250–500 mg twice daily for 5 days
  - Adult: 250–500 mg twice daily for 5 days

- **By intravenous infusion**
  - Adult: 500 mg every 12 hours maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein

Acute exacerbation of chronic obstructive pulmonary disease

- **By mouth using immediate-release medicines**
  - Adult: 500 mg twice daily for 5 days
  - By intravenous infusion
  - Adult: 500 mg every 12 hours, to be administered into a large proximal vein

Acute exacerbation of bronchiectasis

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 7–14 days
  - Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily for 7–14 days
  - Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily for 7–14 days
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 7–14 days
  - Child 1 month–11 years (body-weight 30–40 kg): 250 mg twice daily for 7–14 days
  - Child 12–17 years: 250–500 mg twice daily for 7–14 days
  - Adult: 500 mg twice daily for 7–14 days

Acute cough [if systemically very unwell or at higher risk of complications]

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 5 days

Acute otitis media

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 5–7 days
  - Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily for 5–7 days
  - Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily for 5–7 days
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 5–7 days
  - Child 12–17 years: 250–500 mg twice daily for 5–7 days
  - Adult: 250 mg twice daily usually for 7–14 days, increased to 500 mg twice daily, if required in severe infections

- **By intravenous infusion**
  - Adult: 500 mg every 12 hours maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein

Prevention of pertussis

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 7 days
  - Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily for 7 days
  - Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily for 7 days
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 7 days
  - Child 1 month–11 years (body-weight 30–49 kg): 250 mg twice daily for 7 days
  - Child 12–17 years: 500 mg twice daily for 7 days
  - Adult: 500 mg twice daily for 7 days

Helicobacter pylori eradication in combination with a proton pump inhibitor and amoxicillin

- **By mouth**
  - Adult: 500 mg twice daily

Helicobacter pylori eradication in combination with a proton pump inhibitor and metronidazole

- **By mouth**
  - Adult: 250 mg twice daily

Acute sinusitis

- **By mouth using immediate-release medicines**
  - Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 5 days
  - Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily for 5 days
  - Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily for 5 days
  - Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 5 days
  - Child 1 month–11 years (body-weight 30–40 kg): 250 mg twice daily for 5 days
  - Child 12–17 years: 250 mg twice daily for 5 days, alternatively 500 mg twice daily for 5 days
  - Adult: 500 mg twice daily for 5 days

UNLICENSED USE

Duration of treatment for acute sinusitis differs from product literature and adheres to
Granules

CAUTIONARY AND ADVISORY LABELS 9, 13

- Klaricid (Mylan)
- Clarithromycin 250 mg Klaricid Adult 250mg granules sachets | 14 sachets | £11.48

Tablet

CAUTIONARY AND ADVISORY LABELS 9

- Clarithromycin (Non-proprietary)
- Clarithromycin 250 mg Clarithromycin 250mg tablets | 14 tablet (Pos) £10.50 DT = £1.29
- Clarithromycin 500 mg Clarithromycin 500mg tablets | 14 tablet (Pos) £21.50 DT = £1.20

Oral suspension

CAUTIONARY AND ADVISORY LABELS 9

- Clarithromycin (Non-proprietary)
- Clarithromycin 25 mg per 1 ml Clarithromycin 125mg/5ml oral suspension | 70 ml (Pos) £3.75 DT = £3.36
- Clarithromycin 50 mg per 1 ml Clarithromycin 250mg/5ml oral suspension | 70 ml (Pos) £5.25 DT = £4.46

- Klaricid (Mylan)
- Clarithromycin 25 mg per 1 ml Klaricid Paediatric 125mg/5ml oral suspension | 70 ml (Pos) £5.25 DT = £3.36 | 100 ml (Pos) £9.04
- Clarithromycin 50 mg per 1 ml Klaricid Paediatric 250mg/5ml oral suspension | 70 ml (Pos) £10.51 DT = £4.46

Powder for solution for infusion

ELECTROLYTES: May contain Sodium

- Clarithromycin (Non-proprietary)
- Clarithromycin 500 mg Clarithromycin 500mg powder for solution for infusion vials | 1 vial (Pos) £11.25 DT = £9.45 (Hospital only)
- Clarithromycin 500 mg Clarithromycin 500mg powder for concentrate for solution for infusion vials | 1 vial (Pos) £11.25 DT = £9.45 | 10 vial (Pos) £111.50

- Klaricid (Mylan)
- Clarithromycin 500 mg Klaricid IV 500mg powder for solution for infusion vials | 1 vial (Pos) £9.45 = £9.45

Erythromycin

- INDICATIONS AND DOSE
  Susceptible infections in patients with penicillin hypersensitivity (e.g. respiratory-tract infections (including Legionella infection), skin and oral infections, and campylobacter enteritis)
  - BY MOUTH
    - Child 1-23 months: 125 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 250 mg 4 times a day, dose increase may be used in severe infections
    - Child 2-7 years: 250 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500 mg 4 times a day, dose increase may be used in severe infections
    - Child 8-17 years: 250-500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500–1000 mg 4 times a day, dose increase may be used in severe infections
    - Adult: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 500–1000 mg 4 times a day, dose increase may be used in severe infections
  - BY INTRAVENOUS INFUSION
    - Child: 12.5 mg/kg every 6 hours (max. per dose 1 g)
    - Adult: 6.25 mg/kg every 6 hours, for mild infections when oral treatment not possible, increased to 12.5 mg/kg every 6 hours, dose increase may be used in severe infections

  Acute cough (if systemically very unwell or at higher risk of complications)
  - BY MOUTH
    - Child 1-23 months: 125 mg 4 times a day for 5 days, alternatively 250 mg twice daily for 5 days
    - Child 2-7 years: 250 mg 4 times a day for 5 days, alternatively 500 mg twice daily for 5 days

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 9, 21, 25

- Clarie XL (Teva UK Ltd)
  Clarithromycin 500 mg Clarie XL 500mg tablets | 7 tablet (Pos) £6.72 DT = £6.72 | 14 tablet (Pos) £11.23

- Klaricid XL (Mylan)
  Clarithromycin 500 mg Klaricid XL 500mg tablets | 7 tablet (Pos) £6.72 DT = £6.72 | 14 tablet (Pos) £11.23

- Xetinin XL (Morningside Healthcare Ltd)
  Clarithromycin 500 mg Xetinin XL 500mg tablets | 7 tablet (Pos) £6.72 DT = £6.72 | 14 tablet (Pos) £11.23
### Bacterial infection

#### 540

**Unlicensed use** Duration of treatment for acute otitis media differs from product literature and adheres to national guidelines. See Ear infections, antibacterial therapy p. 511 for further information.

- In adults Erythromycin may be used for gastrointestinal stasis, but it is not licensed for this indication.
- **Caution** Avoid in Acute porphyrias p. 1058
- **Interactions** Appendix 1: macrolides
- **Side-effects**
  - General side-effects
  - Rare or very rare
- **Special side-effects**
- **Pregnancy** Not known to be harmful.
- **Breast-feeding** Only small amounts in milk—not known to be harmful.
- **Hepatic impairment** May cause idiiosyncratic hepatotoxicity.
- **Renal impairment**
  - Dose adjustments In adults Max. 1.5 g daily in severe renal impairment (ototoxicity).
  - In children Reduce dose in severe renal impairment (ototoxicity).
- **Directions for administration**
  - With intravenous use in children Dilute reconstituted solution further in glucose 5% (neutralised with Sodium bicarbonate) or sodium chloride 0.9% to a concentration of 1–5 mg/mL; give over 20–60 minutes. Concentration of up to 10 mg/mL may be used in fluid-restriction if administered via a central venous catheter.
  - With intravenous use in adults For intravenous infusion (as lactobionate), give intermittently in Glucose 5% (neutralised with sodium bicarbonate) or Sodium chloride 0.9%; dissolve initially in water for injections (1 g in 20 mL) then dilute to a concentration of 1–5 mg/mL; give over 20–60 minutes.
- **Prescribing and dispensing information** Flavours of oral liquid formulations may include banana.
- **Patient and carer advice**
  - **Profession specific information**
  - **Dental practitioners’ formulary**
    - With oral use Erythromycin tablets e/c may be prescribed. Erythromycin ethyl succinate oral suspension may be prescribed. Erythromycin stearate tablets may be prescribed. Erythromycin ethyl succinate tablets may be prescribed.
  - **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.
  - **Gastro-resistant tablet**
  - See Ear infections, antibacterial therapy p. 511 for further information.

### Acne

**By mouth**

- Adult: 500 mg twice daily

### Gastro-intestinal stasis

**By mouth**

- Adult: 250–500 mg 3 times a day for up to 4 weeks, to be taken before food
- **By intravenous infusion**
- **Child**: 3 mg/kg 3 times a day

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#### Prevention and treatment of pertussis

**By mouth**

- **Adult**: 4–8 mg/kg every 6 hours, to be increased to 12.5 mg/kg every 6 hours, dose increase may be used in severe infections

#### Prevention of secondary case of diphtheria in non-immune patient

**By mouth**

- **Adult**: 500 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment

#### Prevention of secondary case of invasive group A streptococcal infection in penicillin allergic patients

**By mouth**

- **Adult**: 250–500 mg every 6 hours for 10 days

#### Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease (if penicillin-allergic)

**By mouth**

- **Adult**: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

#### Rosacea

**By mouth**

- **Adult**: 500 mg twice daily courses usually last 6–12 weeks and are repeated intermittently

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### By mouth

- **Child 8–17 years**: 250–500 mg 4 times a day for 5 days, alternatively 500–1000 mg twice daily for 5 days
- **Adult**: 250–500 mg 4 times a day for 5 days, alternatively 500–1000 mg twice daily for 5 days

#### Acute otitis media

**By mouth**

- **Child 1–3 months**: 125 mg 4 times a day for 5–7 days, alternatively 250 mg 4 times daily for 5–7 days
- **Child 2–7 years**: 250 mg 4 times a day for 5–7 days, alternatively 500 mg twice daily for 5–7 days
- **Child 8–17 years**: 250–500 mg 4 times a day for 5–7 days, alternatively 500–1000 mg twice daily for 5–7 days

### Early syphilis

**By mouth**

- **Adult**: 500 mg 4 times a day for 14 days

#### Uncomplicated genital chlamydia | Non-gonococcal urethritis

**By mouth**

- **Adult**: 500 mg twice daily for 14 days

#### Chronic prostatitis

**By mouth**

- **Adult**: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses, increased to 4 g daily in divided doses, dose increase may be used in severe infections
- **By intravenous infusion**
  - **Adult**: 6.25 mg/kg every 6 hours, for mild infections when oral treatment is not possible, increased to 12.5 mg/kg every 6 hours, dose increase may be used in severe infections

#### Prevention of secondary case of diphtheria in non-immune patient

**By mouth**

- **Adult**: (consult local protocol)

#### Prevention of secondary case of invasive group A streptococcal infection in penicillin allergic patients

**By mouth**

- **Adult**: 250–500 mg every 6 hours for 10 days

#### Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease (if penicillin-allergic)

**By mouth**

- **Adult**: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

#### Rosacea

**By mouth**

- **Adult**: 500 mg twice daily courses usually last 6–12 weeks and are repeated intermittently
Aztreonam

**Drug Action**

Aztreonam is a monocyclic beta-lactam ('monobactam') antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Neisseria meningitidis*, and *Haemophilus influenzae*; it should not be used alone for 'blind' treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection).

**Indications and Dose**

Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*:

- **BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
- Adult: 1 g every 8 hours, alternatively 2 g every 12 hours, single doses over 1 g intravenous route only

**Severe gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria meningitidis*, and lung infections in cystic fibrosis**

- **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: 2 g every 6–8 hours

**Gonorrhoea | Cystitis**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 1 g for 1 single dose

**Urinary-tract infections**

- **BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: 0.5–1 g every 8–12 hours

**Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis**

- **BY INHALATION OF NEBULISED SOLUTION**
  - Adult: 75 mg 3 times a day for 28 days, doses to be administered at least 4 hours apart, subsequent courses repeated after 28-day interval without aztreonam nebuliser solution

**Caution**

- When used by inhalation Haemoptysis— risk of further haemorrhage

**Side-effects**

**General side-effects**

- Common or very common Dyspnoea | respiratory disorders

**Specific side-effects**

- Common or very common Cough | haemoptysis | joint disorders | laryngeal pain | nasal complaints | rash

- Rare or very rare Abdominal pain | angioedema | chest pain | confusion | diplopia | dizziness | eosinophilia | haemorrhage | headache | hepatic disorders | hypotension | insomnia | leucocytosis | myalgia | nasal congestion | neutropenia | oral disorders | pancytopenia | paraesthesia | pseudomembranous enterocolitis | seizure | thrombocytopenia | thrombocytosis | tinnitus | vertigo | vulvovaginal candidiasis

**Frequency not known**

- With parental use Anaemia | asthenia | breast tenderness | chest pain | confusion | diplopia | dizziness | eosinophilia | haemorrhage | headache | hepatic disorders | hypotension | insomnia | leucocytosis | myalgia | nasal congestion | neutropenia | oral disorders | pancytopenia | paraesthesia | pseudomembranous enterocolitis | seizure | thrombocytopenia | thrombocytosis | tinnitus | vertigo | vulvovaginal candidiasis

**Allergy and cross-sensitivity**

Contra-indicated in aztreonam hypersensitivity. Use with caution in patients with hypersensitivity to other beta-lactam antibiotics (although aztreonam may be less likely than other beta-lactams to cause hypersensitivity in penicillin-sensitive patients).

**Pregnancy**

- With systemic use No information available; manufacturer of injection advises avoid.
  - When used by inhalation No information available; manufacturer of powder for nebuliser solution advises avoid unless essential.

**Breast feeding**

Amount in milk probably too small to be harmful.

**Hepatic impairment**

- With systemic use Manufacturer advises caution in chronic impairment with cirrhosis.

**Dose adjustments**

- With systemic use Manufacturer advises dose reduction of 20–25% for long term treatment of patients with chronic impairment with cirrhosis, especially in alcoholic cirrhosis and concomitant renal impairment.

**Renal impairment**

- With systemic use If eGFR 10–30 mL/minute/1.73 m², usual initial dose of injection, then half normal dose. If eGFR less than 10 mL/minute/1.73 m², usual initial dose of injection, then one-quarter normal dose.
Bacterial infection

**DERIVATIVES**

**NATIONAL FUNDING/ACCESS DECISIONS**

When used by inhalation

**DIRECTIONS FOR ADMINISTRATION**

With intravenous use For *intravenous injection*, give over 3–5 minutes. For *intravenous infusion* (Azactam®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Dissolve initially in water for injections (1 g per 3 mL) then dilute to a concentration of less than 20 mg/mL; to be given over 20–60 minutes.

When used by inhalation Other inhaled drugs should be administered before aztreonam; a bronchodilator should be administered before each dose.

**MONITORING REQUIREMENTS**

When used by inhalation Measure lung function before and after initial dose of aztreonam and monitor for bronchospasm.

**MEDICATIONS**

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 753/12

The Scottish Medicines Consortium has advised (January 2015) that aztreonam powder for nebuliser solution (Cayston®) is accepted for restricted use within NHS Scotland when inhaled colistimethate sodium and inhaled tobramycin are not tolerated or are not providing satisfactory therapeutic benefit (measured as >2% decline in forced expiratory volume in 1 second). This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

**DOSE EQUIVALENCE AND CONVERSION**

**AntibacteriaLs > Nitroimidazole derivatives**

**Metronidazole**

**DRUG ACTION** Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

**INDICATIONS AND DOSE**

**Anaerobic infections**

By mouth

- Child 1 month: 7.5 mg/kg every 12 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
- Child 2 months-11 years: 7.5 mg/kg every 8 hours (max. per dose 400 mg) usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
- Child 12-17 years: 400 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
- Adult: 400 mg every 8 hours, alternatively 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)

By rectum

- Child 1-11 months: 125 mg 3 times a day for 3 days, then 125 mg twice daily, for usual total treatment duration of 7 days
- Child 1-4 years: 250 mg 3 times a day for 3 days, then 250 mg twice daily, for usual total treatment duration of 7 days

- Child 5–9 years: 500 mg 3 times a day for 3 days, then 500 mg twice daily, for usual total treatment duration of 7 days
- Child 10–17 years: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days
- Adult: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days

By intravenous infusion

- Adult: 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection), to be given over 20 minutes

**Helicobacter pylori eradication; in combination with clarithromycin and esomeprazole; or in combination with clarithromycin and lansoprazole; or in combination with amoxicillin and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole**

By mouth

- Adult: 400 mg twice daily

**Helicobacter pylori eradication; in combination with amoxicillin and omeprazole**

By mouth

- Adult: 400 mg 3 times a day

**Fistulating Crohn’s disease**

By mouth

- Adult: 10–20 mg/kg daily in divided doses, usual dose 400–500 mg 3 times a day usually given for 1 month but no longer than 3 months because of concerns about peripheral neuropathy

**Leg ulcers and pressure sores**

By mouth

- Adult: 400 mg every 8 hours for 7 days

**Bacterial vaginosis (notably *Gardnerella vaginalis* infection)**

By mouth

- Adult: 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Bacterial vaginosis**

By vagina using vaginal gel

- Adult: 1 applicatorful daily for 5 days, dose to be administered at night

**DOSE EQUIVALENCE AND CONVERSION**

1 applicatorful of vaginal gel delivers a 5 g dose of metronidazole 0.75%

**Pelvic inflammatory disease**

By mouth

- Adult: 400 mg twice daily for 14 days

**Acute ulcerative gengivitis**

By mouth

- Adult: 1 applicatorful daily for 5 days, dose to be administered at night

**Dose equivalence and conversion**

1 applicatorful of vaginal gel delivers a 5 g dose of metronidazole 0.75%

**Surgical prophylaxis**

By mouth

- Adult: 400–500 mg, to be administered 2 hours before surgery, then 400–500 mg every 8 hours if required for up to 3 doses (in high-risk procedures)
**Invasive intestinal amoebiasis | Extra-intestinal amoebiasis (including liver abscess)**

- **BY MOUTH**
  - Child 1–2 years: 200 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 3–6 years: 200 mg 4 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 7–9 years: 400 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 10–17 years: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Adult: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)

**Urogenital trichomoniasis**

- **BY MOUTH**
  - Child 1–2 years: 50 mg 3 times a day for 7 days
  - Child 3–6 years: 100 mg twice daily for 7 days
  - Child 7–9 years: 100 mg 3 times a day for 7 days
  - Child 10–17 years: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose
  - Adult: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Giardiasis**

- **BY MOUTH**
  - Child 1–2 years: 500 mg once daily for 3 days
  - Child 3–6 years: 600–800 mg once daily for 3 days
  - Child 7–9 years: 1 g once daily for 3 days
  - Child 10–17 years: 2 g once daily for 3 days, alternatively 400–500 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days
  - Adult: 2 g once daily for 3 days, alternatively 400 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days

**Established case of tetanus**

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

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**SIDE-EFFECTS**

- Rare or very rare
  - With systemic use: Agranulocytosis, angioedema, appetite decreased, ataxia, cerebellar syndrome, confusion, diarrhoea, dizziness, drowsiness, encephalopathy, epigastric pain, epileptiform seizure (with long term or intensive therapy), flushing, hallucination, hepatic disorders, meningitis aseptic, mucositis, nerve disorders, neutropenia, pancreatitis, pancytopenia, peripheral neuropathy (with long term or intensive therapy), psychotic disorder, seizure, severe cutaneous adverse reactions (SCARs), skin reactions, thrombocytopenia, urinae dark, vision disorders

- Frequency not known
  - With systemic use: Depressed mood, gastrointestinal disorder, hearing impairment, tinnitus

- PREGNANCY
  - With systemic use: Manufacturer advises avoidance of high-dose regimens; use only if potential benefit outweighs risk.

- BREAST FEEDING
  - With systemic use: Significant amount in milk; manufacturer advises avoid large single doses though otherwise compatible; may give milk a bitter taste.

- HEPATIC IMPAIRMENT
  - With systemic use: Use with caution in hepatic encephalopathy.

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**PRESCRIBING AND DISPENSING INFORMATION**

- With systemic use: In severe liver disease reduce total daily dose to one-third, and give once daily.

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**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use: For intravenous infusion, give over 20–30 minutes.

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**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, suppository.
**Tinidazole**

- **DRUG ACTION** Tinidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa; it has a longer duration of action than metronidazole.

- **INDICATIONS AND DOSE**

**Anaerobic infections**
- **BY MOUTH**
  - Adult: Initially 2 g, followed by 1 g daily usually for 5–6 days, alternatively 500 mg twice daily usually for 5–6 days

**Bacterial vaginosis / Acute ulcerative gingivitis**
- **BY MOUTH**
  - Adult: 2 g for 1 single dose

**Abdominal surgery prophylaxis**
- **BY MOUTH**
  - Adult: 2 g once daily for 2–3 days

**Intestinal amoebiasis**
- **BY MOUTH**
  - Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 3 days
  - Child 12–17 years: 2 g once daily for 2–3 days
  - Adult: 2 g once daily for 2–3 days

**Amoebic involvement of liver**
- **BY MOUTH**
  - Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 5 days
  - Child 12–17 years: 1.5–2 g once daily for 3–6 days
  - Adult: 1.5–2 g once daily for 3–6 days

**Urogenital trichomoniasis / Giardiasis**
- **BY MOUTH**
  - Child 1 month–11 years: 50–75 mg/kg (max. per dose 2 g) for 1 single dose, dose may be repeated once if necessary
  - Child 12–17 years: 2 g for 1 single dose, dose may be repeated once if necessary
  - Adult: 2 g for 1 single dose

**Helicobacter pylori eradication**
- **BY MOUTH**
  - Adult: (consult local protocol)

- **INTERACTIONS** Appendix 1: tinidazole

- **SIDE-EFFECTS**

**Common or very common** Abdominal pain - appetite decreased - diarrhoea - headache - nausea - skin reactions - vertigo - vomiting

**Frequency not known** Angioedema - ataxia - dizziness - fatigue - flushing - Leucopenia - oral disorders - peripheral neuropathy - seizure - sensation abnormal - taste altered - tongue discolouration - urine discolouration

- **Pregnancy** Manufacturer advises avoid in first trimester.

- **Breast Feeding** Present in milk—manufacturer advises avoid breast-feeding during and for 3 days after stopping treatment.

- **Monitoring Requirements** Clinical and laboratory monitoring advised if treatment exceeds 10 days.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**
  - 4, 9, 21, 25

- **Fasigyn (Pfizer Ltd)**
  - Tinidazole 500 mg Fasigyn 500mg tablets £11.04
  - 16 tablet pack

**Antibacterials**

- **Penicillins**

**Benzylpenicillin and phenoxymethylpenicillin**

Benzylpenicillin sodium p. 547 (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax, diphtheria, gas-gangrene, and leptospirosis. Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; benzylpenicillin sodium is no longer the drug of first choice for pneumococcal meningitis. Although benzylpenicillin sodium is effective in the treatment of tetanus, tinidazole p. 542 is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gastro-intestinal tract is low; therefore it must be given by injection.

**Benazathine benzylpenicillin** is used for the treatment of early syphilis and late latent syphilis; it is given by intramuscular injection.

Phenoxymethylpenicillin p. 548 (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin sodium, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin sodium when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.

**Penicillinase-resistant penicillins**

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. Flucloxacillin p. 554, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection. Flucloxacillin is well absorbed from the gut.

Temocillin p. 555 is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against *Pseudomonas aeruginosa* or *Acinetobacter* spp.

**Broad-spectrum penicillins**

Ampicillin p. 550 is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by
common Gram-negative bacilli such as *Escherichia coli*. Almost all staphylococci, approx. 60% of *E. coli* strains and approx. 20% of *Haemophilus influenzae* strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the ‘blind’ treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin is well excreted in the bile and urine. It is principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to *Streptococcus pneumoniae* and *H. influenzae*, and for urinary-tract infections.

Ampicillin can be given by mouth but less than half the dose is absorbed, and absorption is further decreased by the presence of food in the gut.

Maculopapular rashes commonly occur with ampicillin (and amoxicillin p. 548) but are not usually related to true penicillin allergy. They almost always occur in patients with glandular fever; broad-spectrum penicillins should not therefore be used for ‘blind’ treatment of a sore throat. The risk of rash is also increased in patients with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.

Amoxicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach. Amoxicillin is also used for the treatment of Lyme disease.

Co-amoxiclav p. 551 consists of amoxicillin with the beta-lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of *Staph. aureus*, *E. coli*, and *H. influenzae*, as well as many *Bacteroides* and *Klebsiella* species that would otherwise be resistant. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains.

A combination of ampicillin with flucloxacillin (as co-fluampicil p. 550) is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

**Antipseudomonal penicillins**

Piperacillin, a ureidopenicillin, is only available in combination with the beta-lactamase inhibitor tazobactam.

Ticarcillin, a carboxypenicillin, is only available in combination with the beta-lactamase inhibitor clavulanic acid. Both preparations have a broad spectrum of activity against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam below has activity against a wider range of Gram-negative organisms than ticarcillin with clavulanic acid p. 546 and it is more active against *Pseudomonas aeruginosa*. These antibacterials are not active against MRSA. They are used in the treatment of septicaemia, hospital-acquired pneumonia, and complicated infections involving the urinary tract, skin and soft tissues, or intra-abdomen. For severe pseudomonas infections these antipseudomonal penicillins can be given with an aminoglycoside (e.g. gentamicin p. 519) since they have a synergistic effect.

**Mecillinams**

Pivmecillinam hydrochloride p. 554 has significant activity against many Gram-negative bacteria including *Escherichia coli*, klebsiella, enterobacter, and salmonellae. It is not active against *Pseudomonas aeruginosa* or enterococci.

Pivmecillinam hydrochloride is hydrolysed to mecillinam, which is the active drug.

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**Penicillins**

- **DRUG ACTION** The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

- **CAUTIONS** History of allergy

- **SIDE-EFFECTS**
  - Common or very common Diarrhoea - hypersensitivity - nausea - skin reactions - thrombocytopenia - vomiting
  - Uncommon Antibiotic associated colitis - leucopenia
  - Rare or very rare Agranulocytosis - angioedema - haemolytic anaemia - hepatic disorders - nephritis - tubulointerstitial - neutropenia - seizure - severe cutaneous adverse reactions (SCARs)

- **ALLERGY AND CROSS-SENSITIVITY** The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive a penicillin. Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other beta-lactam antibiotics (including cephalosporins) can be used in these patients.

Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. Patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics. If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity.

**ANTIBACTERIALS > PENICILLINS, ANTIPSEUDOMONAL WITH BETALACTAMASE INHIBITOR**

**Piperacillin with tazobactam**

- **INDICATIONS AND DOSE** Hospital-acquired pneumonia | Septicaemia | Complicated infections involving the urinary-tract | Complicated infections involving the skin | Complicated infections involving the soft-tissues | Acute exacerbation of chronic obstructive pulmonary disease | Acute exacerbation of bronchiectasis
  - By intravenous infusion
  - Adult: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections
Infections in neutropenic patients

- **BY INTRAVENOUS INFUSION**
- Adult: 4.5 g every 6 hours

**UNLICENSED USE** Piperacillin with tazobactam is used for the treatment of acute exacerbation of chronic obstructive pulmonary disease, but is not licensed for this indication. See Respiratory system infections, antibacterial therapy p. 515 for further information.

**CAUTIONS** High doses may lead to hypernatraemia (owing to sodium content of preparations)

**INTERACTIONS** → Appendix 1: penicillins

**SIDE-EFFECTS**
- **Common or very common** Anaemia - candida infection - constipation - gastrointestinal discomfort - headache - insomnia
- **Uncommon** Arthralgia - flushing - hypokalaemia - hypotension - myalgia - thrombophlebitis
- **Frequency not known** Eosinophilia - pancytopenia - pneumonia eosinophilic - renal failure - thrombocytosis

**PREGNANCY** Manufacturers advise use only if potential benefit outweighs risk.

**BREAST FEEDING** Trace amount in milk, but appropriate to use.

**RENA L IMPAIRMENT**
- **Dose adjustments** Max. 4.5 g every 8 hours if eGFR 20–40 mL/minute/1.73 m². Max. 4.5 g every 12 hours if eGFR less than 20 mL/minute/1.73 m².

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION** For **intravenous infusion**, give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially (2.25 g in 10 mL, 4.5 g in 20 mL) with water for injections, or glucose 5% (Tazocin® brand only), or sodium chloride 0.9%, then dilute to 50–150 mL with infusion fluid; give over 30 minutes.

**PRESCRIBING AND DISPENSING INFORMATION** Dose expressed as a combination of piperacillin and tazobactam (both as sodium salts) in a ratio of 8:1.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Powder for solution for infusion**

- **ELECTROLYTES:** May contain Sodium
- **Piperacillin with tazobactam (Non-proprietary)**
  - **Tazocin (Pfizer Ltd)**
    - **Tazocin (as Tazobactam sodium) 250 mg, Piperacillin (as Piperacillin sodium) 2 gram** Tazocin 2g/0.25g powder for solution for infusion vials | 1 vial £7.65 DT = £7.65

**Tazocin with clavulanic acid**

**INDICATIONS AND DOSE**

Infections due to *Pseudomonas* and *Proteus spp.*

- **BY INTRAVENOUS INFUSION**
- Adult: 3.2 g every 6–8 hours; increased if necessary to 3.2 g every 4 hours, increased frequency used for more severe infections

**CAUTIONS** High doses may lead to hypernatraemia (owing to sodium content of preparations)

**CAUTIONS, FURTHER INFORMATION**

- **Choledonic jaundice** Choledonic jaundice is possibly associated with clavulanic acid. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav (amoxicillin, clavulanic acid) than with amoxicillin. Choledonic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

**INTERACTIONS** → Appendix 1: clavulanic acid - penicillins

**SIDE-EFFECTS** Eosinophilia - haemorrhage - hypokalaemia - thrombophlebitis

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Trace amounts in milk, but appropriate to use.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.

**RENA L IMPAIRMENT** Accumulation of electrolytes contained in preparation can occur in patients with renal failure.

- **Dose adjustments** Reduce dose to 3.2 g every eight hours if eGFR 30–60 mL/minute/1.73 m²; 1.6 g every eight hours if eGFR 10–30 mL/minute/1.73 m²; 1.6 g every twelve hours if eGFR less than 10 mL/minute/1.73 m².

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION** For **intravenous infusion** (Timentin®), give intermittently in Glucose 5%. Suggested volume (depending on dose) 100–150 mL; give over 30–40 minutes.

**PRESCRIBING AND DISPENSING INFORMATION** Dose expressed as a combination of ticarcillin (as sodium salt) and clavulanic acid (as potassium salt) in a ratio of 15:1.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Powder for solution for infusion**

- **ELECTROLYTES:** May contain Potassium, sodium
- **Timentin (GSK/SmithKline UK Ltd)**
  - **Clavulanic acid (as Potassium clavulanate) 200 mg, Ticarcillin (as Ticarcillin sodium) 3 gram** Timentin 3.2g powder for solution for infusion vials | 4 vial £21.32
**ANTIBACTERIALS > PENICILLINS, BETA-LACTAMASE SENSITIVE**

**Benzylpenicillin sodium (Penicillin G)**

- **INDICATIONS AND DOSE**

  - **Mild to moderate susceptible infections**
    - **Throat infections**
    - **Otitis media**
    - **Cellulitis**
    - **Pneumonia**
    - **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - **Adult:** 0.6–1.2 g every 6 hours, dose may be increased if necessary in more serious infections (consult product literature), single doses over 1.2 g to be given by intravenous route only

  - **Endocarditis (in combination with other antibacterials if necessary)**
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** 1.2 g every 4 hours, increased if necessary to 2.4 g every 4 hours, dose may be increased in infections such as enterococcal endocarditis

  - **Anthrax (in combination with other antibacterials)**
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** 2.4 g every 4 hours

  - **Intrapartum prophylaxis against group B streptococcal infection**
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** Initially 3 g for 1 dose, then 1.5 g every 4 hours until delivery

  - **Meningitis / Meningococcal disease**
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** 2.4 g every 4 hours
    - **BY INTRAMUSCULAR INJECTION**
    - **Neonate up to 7 days:** 50 mg/kg every 12 hours.
    - **Neonate 7 days to 28 days:** 50 mg/kg every 8 hours.
    - **Child:** 50 mg/kg every 4–6 hours (max. per dose 2.4 g every 4 hours)

  - **Suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) prior to urgent transfer to hospital**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - **Child 1–11 months:** 300 mg, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
    - **Child 1–9 years:** 600 mg, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
    - **Child 10–17 years:** 1.2 g, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer
    - **Adult:** 1.2 g, administer as single dose prior to urgent transfer to hospital so long as does not delay transfer

  - **Suspected bacterial meningitis without non-blanching rash where patient cannot be transferred to hospital urgently**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
    - **Child 1–11 months:** 300 mg, administer as single dose prior to transfer to hospital
    - **Child 1–9 years:** 600 mg, administer as single dose prior to transfer to hospital

- **UNLICENSED USE**
  - In adults Benzylpenicillin doses in the BNF may differ from those in product literature.

- **IMPORTANT SAFETY INFORMATION**
  - Intrathecal injection of benzylpenicillin is not recommended.

- **CAUTIONS**
  - Accumulation of sodium from injection can occur with high doses
  - **INTERACTIONS > Appendix 1: penicillins**
  - **SIDE-EFFECTS**
    - **Fever**
    - **Jarisch-Herxheimer reaction**
    - **Coma**
  - **PREGNANCY**
  - **BREAST FEEDING**
  - **RENAI IMPAIRMENT**
  - **DIRECTIONS FOR ADMINISTRATION**
    - With intravenous use in children Intravenous route recommended in neonates and infants. **For intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes. Longer administration time is particularly important when using doses of 50 mg/kg (or greater) to avoid CNS toxicity.**
    - With intravenous use in adults **For intravenous infusion (Crystapen), give intermittently in Glucose 5% or Sodium chloride 0.9%; suggested volume 100 mL given over 30–60 minutes. Continuous infusion not usually recommended.**

- **MEDICINAL FORMS**
  - There may be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

- **Powder for solution for injection**
  - **ELECTROLYTES:** May contain Sodium
  - **Benzy|penicillin sodium (Non-proprietary)**
    - Benzylpenicillin sodium 600 mg Benzylpenicillin 600mg powder for solution for injection vials | 2 vial | £6.01–£6.08 DT = £6.08 | 25 vial | £75.12–£76.00
    - Benzylpenicillin sodium 1.2 gram Benzylpenicillin 1.2g powder for solution for injection vials | 25 vial | £109.49–£113.92 DT = £113.92

www.getintopharma.com
Phenoxymethylpenicillin
(Penicillin V)

**INDICATIONS AND DOSE**

**Oral infections | Tonsillitis | Otitis media | Erysipelas | Cellulitis**

- **BY MOUTH**
  - Child 1-11 months: 62.5 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day
  - Child 1-5 years: 125 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day
  - Child 6-11 years: 250 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day
  - Child 12-17 years: 500 mg 4 times a day; increased if necessary up to 1 g 4 times a day
  - Adult: 500 mg every 6 hours, increased if necessary up to 1 g every 6 hours

**Prevention of recurrence of rheumatic fever**

- **BY MOUTH**
  - Child 1-month–5 years: 125 mg twice daily
  - Child 6-17 years: 250 mg twice daily
  - Adult: 250 mg twice daily

**Prevention of secondary case of invasive group A streptococcal infection**

- **BY MOUTH**
  - Child 1-11 months: 62.5 mg every 6 hours for 10 days
  - Child 1-5 years: 125 mg every 6 hours for 10 days
  - Child 6-11 years: 250 mg every 6 hours for 10 days
  - Child 12-17 years: 250–500 mg every 6 hours for 10 days
  - Adult: 250–500 mg every 6 hours for 10 days

**Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease**

- **BY MOUTH**
  - Child 1-11 months: 62.5 mg twice daily
  - Child 1-4 years: 125 mg twice daily
  - Child 5-17 years: 250 mg twice daily
  - Adult: 250 mg twice daily

**Acute sinusitis**

- **BY MOUTH**
  - Child 1-11 months: 62.5 mg 4 times a day for 5 days
  - Child 1-5 years: 125 mg 4 times a day for 5 days
  - Child 6-11 years: 250 mg 4 times a day for 5 days
  - Child 12-17 years: 500 mg 4 times a day for 5 days
  - Adult: 500 mg 4 times a day for 5 days

**UNLICENSED USE**

Duration of treatment for acute sinusitis adheres to national guidelines. See Sinusitis (acute) p. 1203 for further information.

**INTERACTIONS**

- Appendix 1: penicillins

**SIDE-EFFECTS**

- Arthralgia, circulatory collapse, coagulation disorder, eosinophilia, faeces soft, fever, increased risk of infection, neurotoxicity, oral disorders, paraesthesia

**PREGNANCY**

Not known to be harmful.

**BREAST FEEDING**

Trace amounts in milk, but appropriate to use.

**EFFECT ON LABORATORY TESTS**

False-positive urinary glucose (if tested for reducing substances).

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Penicillin V for bacterial infections

www.medicinesforchildren.org.uk/penicillin-v-bacterial-infections

Medicines for Children leaflet: Penicillin V for prevention of pneumococcal infection

www.medicinesforchildren.org.uk/penicillin-v-prevention-pneumococcal-infection

**PROFESSIONAL INFORMATION**

Dental practitioners’ formulary

Phenoxymethylpenicillin Tablets may be prescribed. Phenoxymethylpenicillin Oral Solution may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- **Phenoxymethylpenicillin (as Phenoxymethylpenicillin potassium)**
  - 25 mg per 1 ml
  - Phenoxymethylpenicillin 125mg/5ml oral solution | 100 ml (PSt) £34.00 DT + £4.28
  - Phenoxymethylpenicillin 125mg/5ml oral solution sugar free | 100 ml (PSt) £25.00 DT + £7.10

- **Phenoxymethylpenicillin (as Phenoxymethylpenicillin potassium)**
  - 50 mg per 1 ml
  - Phenoxymethylpenicillin 250mg/5ml oral solution | 100 ml (PSt) £35.00 DT + £5.23
  - Phenoxymethylpenicillin 250mg/5ml oral solution sugar free | 100 ml (PSt) £35.00 DT + £7.72

**Tablet**

- **Phenoxymethylpenicillin (Non-proprietary)**
  - Phenoxymethylpenicillin (as Phenoxymethylpenicillin potassium)
  - 250 mg
  - Phenoxymethylpenicillin 250mg tablets | 28 tablet (PSt) £5.00 DT + £10.93

**ANTIBACTERIALS | PENICILLINS, BROAD-SPECTRUM**

Amoxicillin
(Amoxyccillin)

**INDICATIONS AND DOSE**

Susceptible infections (including urinary-tract infections, sinusitis, uncomplicated community acquired pneumonia, salmonellosis, oral infections)

- **BY MOUTH**
  - Child 1-11 months: 125 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
  - Child 1-4 years: 250 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
  - Child 5-11 years: 500 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day (max. per dose 1 g)
  - Child 12-17 years: 500 mg 3 times a day; increased if necessary up to 1 g 3 times a day, use increased dose in severe infections
  - Adult: 500 mg every 8 hours, increased if necessary to 1 g every 8 hours, increased dose used in severe infections

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 500 mg every 8 hours

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 500 mg every 8 hours, increased to 1 g every 6 hours, use increased dose in severe infections

**Acute exacerbation of bronchiectasis**

- **BY MOUTH**
  - Child 1-11 months: 125 mg 3 times a day for 7–14 days
  - Child 1-4 years: 250 mg 3 times a day for 7–14 days
  - Child 5-17 years: 500 mg 3 times a day for 7–14 days
  - Adult: 500 mg every 3 times a day for 7–14 days

**Acute exacerbation of chronic obstructive pulmonary disease**

- **BY MOUTH**
  - Adult: 500 mg 3 times a day for 5 days, increased if necessary to 1 g 3 times a day, increased dose used in severe infections

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 500 mg every 8 hours, increased to 1 g every 6 hours, increased dose used in severe infections
Acute cough [if systemically very unwell or at higher risk of complications]
- **BY MOUTH**
  - Child 1-11 months: 125 mg 3 times a day for 5 days
  - Child 1-4 years: 250 mg 3 times a day for 5 days
  - Child 5-17 years: 500 mg 3 times a day for 5 days
  - Adults: 500 mg 3 times a day for 5 days

**Acute otitis media**
- **BY MOUTH**
  - Child 1-11 months: 125 mg 3 times a day for 5–7 days
  - Child 1-4 years: 250 mg 3 times a day for 5–7 days
  - Child 5-17 years: 500 mg 3 times a day for 5–7 days

**Lyme disease** (erythema migrans and/or non-focal symptoms) [Lyme disease (affecting cranial nerves or peripheral nervous system)]
- **BY MOUTH**
  - Adult: 1 g 3 times a day for 21 days

**Lyme arthritis** | **Acrodermatitis chronica atrophicans**
- **BY MOUTH**
  - Adult: 1 g 3 times a day for 28 days

**Anthrax (treatment and post-exposure prophylaxis)**
- **BY MOUTH**
  - Adult: 500 mg 3 times a day

**Dental abscess (short course)**
- **BY MOUTH**
  - Adult: 3 g, then 3 g after 8 hours

**Urinary-tract infections (short course)**
- **BY MOUTH**
  - Adult: 3 g, then 3 g after 10–12 hours

**Listerial meningitis** (in combination with another antibiotic)
- **BY INTRAVENOUS INFUSION**
  - Adult: 2 g every 4 hours

**Endocarditis** (in combination with another antibiotic if necessary)
- **BY INTRAVENOUS INFUSION**
  - Adult: 2 g every 4 hours

**Helicobacter pylori eradication** in combination with metronidazole and omeprazole
- **BY MOUTH**
  - Adult: 500 mg 3 times a day

**Helicobacter pylori eradication** in combination with clarithromycin and esomeprazole; or in combination with clarithromycin and lansoprazole; or in combination with metronidazole and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole
- **BY MOUTH**
  - Adult: 1 g twice daily

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**SPECIFIC CAUTIONS**
- With intravenous use accumulation of sodium can occur with high parenteral doses
- **INTERACTIONS** → Appendix 1: penicillins
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Rare or very rare: Colitis haemorrhagic - crystalluria - dizziness - hyperkinesia - hypersensitivity vasculitis - mucocutaneous candidiasis
    - Frequency not known: Jarisch-Herxheimer reaction
  - **SPECIFIC SIDE-EFFECTS**
    - Rare or very rare: With oral use Black hairy tongue
    - **PREGNANCY** Not known to be harmful.
    - **BREAST FEEDING** Trace amount in milk, but appropriate to use.

**RENAL IMPAIRMENT** Risk of crystalluria with high doses (particularly during parenteral therapy). With intravenous use accumulation of sodium from injection can occur in patients with renal failure. Dose adjustments Reduce dose in severe impairment; rashes more common.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use in adults For intravenous infusion (Amoxil®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes or give via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.

**PRESCRIBING AND DISPENSING INFORMATION** See Lyme disease p. 577 for place in therapy and further information on treatment.
- Flavours of oral liquid formulations and sachets may include peach, strawberry, or lemon.

**PATIENT AND CARER ADVICE** Patient counselling is advised for Amoxicillin (Amoxil®) paediatric suspension (use of pipette).

**PROFESSION SPECIFIC INFORMATION**
- Dental practitioners’ formulary
- Amoxicillin capsules may be prescribed.
- Amoxicillin sachets may be prescribed as Amoxicillin Oral Powder.
- Amoxicillin Oral Suspension may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **ELECTROLYTES:** May contain Sodium
  - **Amoxicillin (as Amoxicillin sodium) 250 mg**
    - 10 vial £4.80
    - 10 vial [Pmax] £4.50
  - **Amoxicillin (as Amoxicillin sodium) 500 mg**
    - 10 vial £9.60 DT = £5.48
    - 10 vial [Pmax] £12.00 DT = £5.48 (Hospital only)
  - **Amoxicillin (as Amoxicillin sodium) 1 gram**
    - 1 vial £1.92
    - 10 vial [Pmax] £16.50 DT = £10.96 (Hospital only)
  - **Amoxil®** (GlaxoSmithKline UK Ltd)
    - **Amoxicillin (as Amoxicillin sodium) 500 mg**
      - 10 vial £5.48 DT = £5.48
    - **Amoxicillin (as Amoxicillin sodium) 1 gram**
      - 10 vial [Pmax] £10.96 DT = £10.96

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**UNLICENSED USE** Amoxicillin doses in BNF Publications may differ from those in product literature. Duration of treatment for acute otitis media differs from product literature and adheres to national guidelines. See Ear infections, antibacterial therapy p. 511 for further information.

Amoxicillin is used for the treatment of acute exacerbation of bronchiectasis, but is not licensed for this indication. See Respiratory system infections, antibacterial therapy p. 515 for further information.

**CAUTIONS**
- **GENERAL CAUTIONS**
  - Acute lymphocytic leukaemia (increased risk of erythematous rashes).
  - Chronic lymphocytic leukaemia (increased risk of erythematous rashes). Cytomegalovirus infection (increased risk of erythematous rashes).
  - Glandular fever (erythematous rashes). Maintain adequate hydration with high doses (particularly during parenteral therapy).
Oral suspension

CAUTIONARY AND ADVISORY LABELS 9

EXCipients: May contain Sucrose

Ampicillin (Non-proprietary)
Ampicillin (as Ampicillin trihydrate) 25 mg per 1 ml Ampicillin 125mg/5ml oral suspension sugar-free sugar-free 100 ml PSt £25.00 DT = £1.13
Ampicillin 125mg/5ml oral suspension | 100 ml PSt £35.00 DT = £1.59

Ampicillin (as Ampicillin trihydrate) 50 mg per 1 ml Ampicillin 250mg/5ml oral suspension sugar-free sugar-free 100 ml PSt £35.00 DT = £1.26
Ampicillin 250mg/5ml oral suspension | 100 ml PSt £35.00 DT = £1.59

Ampicillin 250mg/5ml oral suspension | 20 ml PSt £3.18 DT = £1.38

Ampicillin (as Ampicillin trihydrate) 100 mg per 1 ml Ampicillin 125mg/1.25ml paediatric oral suspension | 20 ml PSt £3.18 DT = £1.38

Ampicillin (as Ampicillin trihydrate) 3 gram Ampicillin 3g oral powder sachets sugar-free sugar-free 2 sachet PSt £15.00 DT = £9.90

Ampicillin (Non-proprietary)
Ampicillin (as Ampicillin trihydrate) 100 mg capsules | 15 capsule PSt £5.99 DT = £0.75 | 2 sachet PSt £15.00 DT = £9.90

Ampicillin (as Ampicillin trihydrate) 250 mg Ampicillin 250mg capsules | 1 capsule PSt £8.99 DT = £1.05 | 500 capsule PSt £16.60-£12.00

Ampicillin (as Ampicillin trihydrate) 500 mg Ampicillin 500mg capsules | 15 capsule PSt £17.50 DT = £0.77 | 21 capsule PSt £15.99 DT = £1.08 | 100 capsule PSt £5.00-£7.50

Combinations available: Co-amoxiclav, p. 551

SPECIFIC CAUTIONS

▶ With intravenous use accumulation of electrolytes contained in parenteral preparations can occur with high doeses

SIDE-EFFECTS

Colitis haemorrhagic

PREGNANCY

Not known to be harmful.

BREAST FEEDING

Trace amounts in milk, but appropriate to use.

RENAL IMPAIRMENT

With intravenous use Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

Dose adjustments

In adults Reduce dose if eGFR less than 10 mL/minute/1.73 m²; rashes more common.

In children If estimated glomerular filtration rate less than 10 mL/minute/1.73 m² reduce dose or frequency; rashes more common.

DIRECTIONS FOR ADMINISTRATION

With oral use Administer at least 30 minutes before food.

With intravenous use in adults For intravenous infusion (Penbritin®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes via drip tubing in Glucose 5% or Sodium chloride 0.9%. Continuous infusion not usually recommended.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Ampicillin for bacterial infection

www.medicinesforchildren.org.uk/ampicillin-bacterial-infection

MEDIcINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

ORAL SUSPENSION

CAUTIONARY AND ADVISORY LABELS 9, 23

Ampicillin 25 mg per 1 ml Ampicillin 125mg/5ml oral suspension | 100 ml PSt £29.86 DT = £29.86
Ampicillin 50 mg per 1 ml Ampicillin 250mg/5ml oral suspension | 100 ml PSt £38.86 DT = £38.86

CAPSULE

CAUTIONARY AND ADVISORY LABELS 9, 23

Ampicillin 250 mg Ampicillin 250mg capsules | 28 capsule PSt £40.30 DT = £40.30

Ampicillin 500 mg Ampicillin 500mg capsules | 28 capsule PSt £78.30

POWDER FOR SOLUTION FOR INJECTION

Ampicillin (Non-proprietary)
Ampicillin (as Ampicillin sodium) 500 mg Ampicillin 500mg powder for solution for injection vials | 10 vial PSt £78.30

Co-fluampicil

INDICATIONS AND DOSE

Mixed infections involving beta-lactamase-producing staphylococci

BY MOUTH

Child 1 month–9 years: 125/250 mg every 6 hours
Child 10–17 years: 250/500 mg every 6 hours
Adult: 250/500 mg every 6 hours

BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION

Adult: 250/500 mg every 6 hours

SEVERE MIXED INFECTIONS INVOLVING Beta-lactamase-producing staphylococci

BY MOUTH

Child 1 month–9 years: 250/500 mg every 6 hours
Adult: 500/500 mg every 6 hours

www.getintopharma.com
Capsule  
**CAUTIONARY AND ADVISORY LABELS 9, 22**  
Co-fluampicil (Non-proprietary)  
Ampicillin (as Ampicillin trihydrate) 250 mg, Flucloxacillin (as Flucloxacillin sodium) 250 mg  
Co-fluampicil 250mg/250mg capsules  | 28 capsule (-Pack) £2.27 DT + £1.95  
100 capsule (Pack) £6.96

**ANTIBACTERIALS > PENICILLINS, BROAD-SPECTRUM WITH BETA-LACTAMASE INHIBITOR**

**Co-amoxiclav**

**INDICATIONS AND DOSE**  
Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites  
**BY MOUTH USING TABLETS**  
Child 12-17 years: 250/125 mg every 8 hours; increased to 500/125 mg every 8 hours, increased dose used for severe infection  
Adult: 250/125 mg every 8 hours; increased to 500/125 mg every 8 hours, increased dose used for severe infection  
**BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**  
Child 1-2 months: 30 mg/kg every 12 hours, intravenous infusion recommended in children less than 3 months  
Child 3 months-17 years: 30 mg/kg every 8 hours (max. per dose 1.2 g every 8 hours)  
Adult: 1.2 g every 8 hours  
**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites (doses for 125/31 suspension)**  
**BY MOUTH USING ORAL SUSPENSION**  
Child 1-11 months: 0.25 mg/kg 3 times a day, dose doubled in severe infection  
Child 1-5 years: 0.25 mg/kg 3 times a day, alternatively 5 ml 3 times a day, dose doubled in severe infection  
**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites (doses for 250/62 suspension)**  
**BY MOUTH USING ORAL SUSPENSION**  
Child 6-11 years: 0.15 mg/kg 3 times a day, alternatively 5 ml 3 times a day, dose doubled in severe infection  
**Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites (doses for 400/57 suspension)**  
**BY MOUTH USING ORAL SUSPENSION**  
Child 2-23 months: 0.15 mg/kg twice daily, doubled in severe infection  
Child 2-6 years (body-weight 13-21 kg): 2.5 ml twice daily, doubled in severe infection  
Child 7-12 years (body-weight 22-40 kg): 5 ml twice daily, doubled in severe infection  
Child 12-17 years (body-weight 41 kg and above): 10 ml twice daily; increased if necessary to 10 ml 3 times a day, increased frequency to be used in severe infection  
Adult: 10 ml twice daily; increased if necessary to 10 ml 3 times a day, increased frequency to be used in severe infection  

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**Bacterial infection 551**

**BNF 78**

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**IMPORTANT SAFETY INFORMATION**

**HEPATIC DISORDERS**  
Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:  
- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;  
- flucloxacillin should be used with caution in patients with hepatic impairment;  
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibiotics.

**CAUTIONS**

**GENERAL CAUTIONS**  
Acute lymphocytic leukaemia (increased risk of erythematous rashes).  
Chronic lymphocytic leukaemia (increased risk of erythematous rashes).  
Cytomegalovirus infection (increased risk of erythematous rashes).  
Glandular fever (erythematous nodosum).  
Musculoskeletal disorder: Jarisch-Herxheimer reaction.  
Respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites.

**SPECIFIC CAUTIONS**

- With intravenous use accumulation of electrolytes contained in parenteral preparations can occur with high doses.
- **INTERACTIONS**  
  - Appendix 1: penicillins
- **SIDE-EFFECTS**  
- **PREGNANCY**  
  - Not known to be harmful.
- **BREAST FEEDING**  
  - Not appropriate to use.
- **HEPATIC IMPAIRMENT**  
  - Manufacturer advises use with caution in hepatic dysfunction.
- **RENAL IMPAIRMENT**  
  - With intravenous use accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.
  - **Dose adjustments**  
    - In adults: Reduce dose if eGFR less than 10 ml/minute/1.73 m²; rashes more common.
    - In children: Reduce dose or frequency if estimated glomerular filtration rate less than 10 ml/minute/1.73 m²; rashes more common.
- **EFFECT ON LABORATORY TESTS**  
  - False-positive urinary glucose (if tested for reducing substances).
- **PRESCRIBING AND DISPENSING INFORMATION**  
  - Dose expressed as a combination of equal parts by mass of flucloxacillin and ampicillin.

**MEDICINAL FORMS**  
There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS 9, 22**  
Co-fluampicil (Non-proprietary)  
Ampicillin (as Ampicillin trihydrate) 25 mg per 1 ml Flucloxacillin (as Flucloxacillin magnesius) 25 mg per 1 ml (Co-fluampicil 125mg/125mg/5ml oral suspension)  
100 ml (Pack) £23.93 DT + £23.93

**Powder for solution for injection**

**ELECTROLYTES:** May contain Sodium

Co-fluampicil (Non-proprietary)  
Ampicillin (as Ampicillin sodium) 250 mg, Flucloxacillin (as Flucloxacillin sodium) 250 mg (Co-fluampicil 250mg/250mg powder for solution for injection vials)  
10 vial (Pack) £13.33

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Severe dental infection with spreading cellulitis | Dental infection not responding to first-line antibacterial

- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 250/125 mg every 8 hours for 5 days
  - Adult: 250/125 mg every 8 hours for 5 days

Surgical prophylaxis

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 1.2 g, to be administered up to 30 minutes before the procedure, then 1.2 g every 8 hours for up to 2–3 further doses in high risk procedures

Acute exacerbation of bronchiectasis (doses for 125/31 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 1-11 months: 0.25 mL/kg/3 times a day for 7–14 days
  - Child 1–5 years: 5 mL 3 times a day for 7–14 days, alternatively 0.25 mL/kg/3 times a day for 7–14 days

Acute exacerbation of bronchiectasis (doses for 250/62 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6-11 years: 5 mL 3 times a day for 7–14 days, alternatively 0.15 mL/kg/3 times a day for 7–14 days
  - Adult: 500/125 mg 3 times a day for 7–14 days
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Child 1–2 months: 30 mg/kg every 12 hours, intravenous infusion is recommended in children less than 3 months
  - Child 3 months-17 years: 30 mg/kg every 8 hours (max. per dose 1.2 g every 8 hours)
  - Adult: 1.2 g every 8 hours

Acute exacerbation of chronic obstructive pulmonary disease

- **BY MOUTH USING TABLETS**
  - Adult: 500/125 mg 3 times a day for 5 days
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 1.2 g every 8 hours

Acute sinusitis (doses for 125/31 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 1-11 months: 0.25 mL/kg/3 times a day for 5 days
  - Child 1–5 years: 5 mL 3 times a day for 5 days, alternatively 0.25 mL/kg/3 times a day for 5 days

Acute sinusitis (doses for 250/62 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6–11 years: 5 mL 3 times a day for 5 days, alternatively 0.15 mL/kg/3 times a day for 5 days

Acute sinusitis

- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 250/125 mg 3 times a day for 5 days, alternatively 500/125 mg 3 times a day for 5 days
  - Adult: 500/125 mg 3 times a day for 5 days

Acute otitis media (doses for 125/31 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 1-11 months: 0.25 mL/kg/3 times a day for 5–7 days
  - Child 1–5 years: 5 mL 3 times a day for 5–7 days, alternatively 0.25 mL/kg/3 times a day for 5–7 days

Acute otitis media (doses for 250/62 suspension)

- **BY MOUTH USING ORAL SUSPENSION**
  - Child 6–11 years: 5 mL 3 times a day for 5–7 days, alternatively 0.15 mL/kg/3 times a day for 5–7 days

Acute otitis media

- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 250/125 mg 3 times a day for 5–7 days, alternatively 500/125 mg 3 times a day for 5–7 days

Dose equivalence and conversion

- Doses are expressed as co-amoxiclav.
- A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form \( x/y \) where \( x \) and \( y \) are the strengths in milligrams of amoxicillin and clavulanic acid respectively.

**UNLICENSED USE** Duration of treatment for acute sinusitis differs from product literature and adheres to national guidelines. See Sinusitis (acute) p. 1203 for further information.

**CONTRA-INDICATIONS** History of co-amoxiclav-associated jaundice or hepatic dysfunction - history of penicillin-associated jaundice or hepatic dysfunction.

**CAUTIONS**

- **GENERAL CAUTIONS** Acute lymphocytic leukaemia (increased risk of erythematous rashes) - chronic lymphocytic leukaemia (increased risk of erythematous rashes) - cytomegalovirus infection (increased risk of erythematous rashes) - glandular fever (erythematous rashes common) - maintain adequate hydration with high doses (particularly during parental therapy)

**SPECIFIC CAUTIONS**

- With intravenous use accumulation of electrolytes contained in parenteral preparations can occur with high doses

**INTERACTIONS** → Appendix 1: clavulanic acid - penicillins

**SIDE-EFFECTS**

- **GENERAL SIDE-EFFECTS**
  - Common or very common: Increased risk of infection
  - Uncommon: Dizziness - dyspepsia - headache
  - **Frequency not known**
    - Colitis haemorrhagic - crystalluria - hypersensitivity vasculitis - meningitis aseptic

**SPECIFIC SIDE-EFFECTS**

- With oral use: Akathisia - black hairy tongue
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Trace amount in milk, but appropriate to use.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution.

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**RENAIL IMPAIRMENT** Risk of crystalluria with high doses (particularly during parenteral therapy).

**With intravenous use** Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

**Dose adjustments** With oral use in adults Co-amoxiclav 250/125 tablets or 500/125 tablets: if eGFR 10–30 mL/minute/1.73 m², one 250/125 strength tablet every 12 hours or one 500/125 strength tablet every 12 hours; if eGFR less than 10 mL/minute/1.73 m², one 250/125 strength tablet every 24 hours or one 500/125 strength tablet every 24 hours. Co-amoxiclav 400/57 suspension: avoid if eGFR less than 30 mL/minute/1.73 m².

With intravenous use in adults Co-amoxiclav injection (expressed as co-amoxiclav): If eGFR 10–30 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 12 hours; if eGFR less than 10 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 24 hours.

With oral use in children Co-amoxiclav 125/31 suspension, 250/62 suspension, 250/125 tablets, or 500/125 tablets: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Use the normal dose recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

Co-amoxiclav 400/57 suspension: avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

With intravenous use in children Co-amoxiclav injection: use normal initial dose and then use half normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; use normal initial dose and then use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

With intravenous use in children For intravenous infusion, dilute reconstituted solution to a concentration of 10 mg/mL with Sodium Chloride 0.9%; give intermittently over 30–40 minutes. For intravenous injection, administer over 3–4 minutes.

With intravenous use in adults For intravenous infusion (Augmentin®), give intermittently in Sodium Chloride 0.9%. Reconstitute 600 mg initially with 10 mL water for injections, then dilute with 50 mL infusion fluid; reconstitute 1.2 g initially with 20 mL water for injections, then dilute with 100 mL infusion fluid; give over 30–40 minutes. For intravenous injection, administer over 3–4 minutes. Via drip tubing in Sodium Chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION** Doses are expressed as co-amoxiclav: a mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively.

With oral use Flavours of oral liquid formulations may include raspberry and orange.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Co-amoxiclav for bacterial infections www.medicinesforchildren.org.uk/co-amoxiclav-bacterial-infections-0

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners' formulary Co-amoxiclav 250/125 Tablets may be prescribed. Co-amoxiclav 125/31 Suspension may be prescribed. Co-amoxiclav 250/62 Suspension may be prescribed.

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**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Oral suspension**

- **Augmentin (Non-proprietary)**
  - Clavulanic acid (as Potassium clavulanate) 6.25 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 25 mg per 1 mL Co-amoxiclav 125mg/31mg/5ml oral suspension | 100 ml | £5.00 DT = £5.00
  - Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free sugar-free | 100 ml | £1.65 DT = £1.65
  - Clavulanic acid (as Potassium clavulanate) 2.5 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 50 mg per 1 mL Co-amoxiclav 250mg/62mg/5ml oral suspension | 100 ml | £5.00 DT = £5.00
  - Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free sugar-free | 70 ml | £2.05 sugar-free | 100 ml | £1.68 DT = £1.67
  - Clavulanic acid (as Potassium clavulanate) 1.4 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 80 mg per 1 mL Co-amoxiclav 400mg/75mg/5ml oral suspension sugar free sugar-free | 35 ml | £4.13 DT = £4.13 sugar-free | 70 ml | £6.97 DT = £5.79
  - **Augmentin (GlaxoSmithKline UK Ltd)**
    - Clavulanic acid (as Potassium clavulanate) 6.25 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 25 mg per 1 mL Augmentin 125/31 SF oral suspension sugar-free | 100 ml | £3.54 DT = £1.65
  - Clavulanic acid (as Potassium clavulanate) 1.25 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 50 mg per 1 mL Augmentin 250/62 SF oral suspension sugar-free | 100 ml | £3.60 DT = £1.67
  - **Augmentin-Duo (GlaxoSmithKline UK Ltd)**
    - Clavulanic acid (as Potassium clavulanate) 1.4 mg per 1 mL, Amoxicillin (as Amoxicillin trihydrate) 80 mg per 1 mL Augmentin-Duo 400/57 oral suspension sugar-free | 35 ml | £4.13 DT = £4.13 sugar-free | 70 ml | £5.79 DT = £5.79

**Tablet**

- **Augmentin (Non-proprietary)**
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 250 mg Co-amoxiclav 250mg/125mg tablets | 21 tablet | £6.00 DT = £1.79
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 500 mg Co-amoxiclav 500mg/125mg tablets | 21 tablet | £13.00 DT = £2.11
  - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 875 mg Co-amoxiclav 875mg/125mg tablets | 14 tablet | £18.00 DT = £13.00
  - **Augmentin (GlaxoSmithKline UK Ltd)**
    - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 250 mg Augmentin 375mg tablets | 21 tablet | £5.03 DT = £1.79
    - Clavulanic acid (as Potassium clavulanate) 125 mg, Amoxicillin (as Amoxicillin trihydrate) 500 mg Augmentin 625mg tablets | 21 tablet | £9.60 DT = £3.31

**Powder for solution for injection**

**ELECTROLYTES** May contain Potassium, sodium

- **Co-amoxiclav (Non-proprietary)**
  - Clavulanic acid (as Potassium clavulanate) 100 mg, Amoxicillin (as Amoxicillin sodium) 500 mg Co-amoxiclav 500mg/100mg powder for solution for injection vials | 10 vial | £10.60–14.90 | 10 vial | £13.50 (Hospital only)
  - **Augmentin (GlaxoSmithKline UK Ltd)**
    - Clavulanic acid (as Potassium clavulanate) 200 mg, Amoxicillin (as Amoxicillin sodium) 1000 mg Co-amoxiclav 1000mg/200mg powder for solution for injection vials | 10 vial | £10.60–22.70 | 10 vial | £27.50 (Hospital only)
    - **Augmentin Intravenous (GlaxoSmithKline UK Ltd)**
      - Clavulanic acid (as Potassium clavulanate) 100 mg, Amoxicillin (as Amoxicillin sodium) 500 mg Augmentin Intravenous 600mg powder for solution for injection vials | 10 vial | £10.60
      - Clavulanic acid (as Potassium clavulanate) 200 mg, Amoxicillin (as Amoxicillin sodium) 1000 mg Augmentin Intravenous 1.2g powder for solution for injection vials | 10 vial | £10.60

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**ANTIBACTERIALS > PENICILLINS, MECILLINAM-TYPE**

**Pivmecillinam hydrochloride**

- **INDICATIONS AND DOSE**
  - **Acute uncomplicated cystitis**
    - **BY MOUTH**
      - Child (body-weight 40 kg and above): Initially 400 mg for 1 dose, then 200 mg every 8 hours to a total of 10 tablets.
      - Adult (body-weight 40 kg and above): Initially 400 mg for 1 dose, then 200 mg every 8 hours to a total of 10 tablets.
  - **Chronic or recurrent bacteriuria**
    - **BY MOUTH**
      - Child (body-weight 40 kg and above): 400 mg every 6–8 hours.
      - Adult (body-weight 40 kg and above): 400 mg every 6–8 hours.
  - **Urinary-tract infections**
    - **BY MOUTH**
      - Child (body-weight up to 40 kg): 5–10 mg/kg every 6 hours, alternatively 20–40 mg/kg daily in 3 divided doses.

- **UNLICENSED USE**
  - In children Not licensed for use in children under 3 months.
  - **CONTRA-INDICATIONS** Carnitine deficiency; gastrointestinal obstruction; infants under 3 months; oesophageal strictures.
  - **CAUTIONS** Avoid in Acute porphyrias p. 1058.
  - **INTERACTIONS** → Appendix 1: penicillins.
  - **SIDE-EFFECTS**
    - Common or very common Vulvovaginal fungal infection
    - Uncommon Dizziness; fatigue; gastrointestinal discomfort; gastrointestinal disorders; headache; oral ulceration; vertigo.
  - **PREGNANCY** Not known to be harmful, but manufacturer advises avoid.
  - **BREAST FEEDING** Trace amount in milk, but appropriate to use.
  - **MONITORING REQUIREMENTS** Liver and renal function tests required in long-term use.
  - **EFFECT ON LABORATORY TESTS** False positive urinary glucose (if tested for reducing substances).
  - **DIRECTIONS FOR ADMINISTRATION** Tablets should be swallowed whole with plenty of fluid during meals while sitting or standing.
  - **PATIENT AND CARER ADVICE** Patient counselling is advised on administration of pivmecillinam hydrochloride tablets (posture).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 9, 21, 27
  - **Pivmecillinam hydrochloride (Non-proprietary)**
    - Pivmecillinam hydrochloride 200 mg Pivmecillinam 200mg tablets 10 tablet £5.40 DT = £5.40
    - Selexid (LEO Pharma)
    - Pivmecillinam hydrochloride 200 mg Selexid 200mg tablets 10 tablet £5.40 DT = £5.40 18 tablet £9.72

**Flucloxacillin**

- **INDICATIONS AND DOSE**
  - **Infections due to beta-lactamase-producing staphylococci including otitis externa**
  - **Adjunct in pneumonia**
  - **Adjunct in impetigo**
  - **Adjunct in cellulitis**
    - **BY MOUTH**
      - Child 1 month–1 year: 6.25–125 mg 4 times a day.
      - Child 2–9 years: 125–250 mg 4 times a day.
      - Child 10–17 years: 250–500 mg 4 times a day.
      - Adult: 250–500 mg 4 times a day.
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: 250–500 mg every 6 hours.
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 0.25–2 g every 6 hours.
  - **Endocarditis (in combination with other antibacterial if necessary)**
    - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: Up to 8 g daily in 3–4 divided doses.
  - **Surgical prophylaxis**
    - **INITIALLY BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 1–2 g, to be administered up to 30 minutes before the procedure, then (by mouth or by intramuscular injection or by slow intravenous injection or by intravenous infusion) 500 mg every 6 hours if required for up to 4 further doses in high risk procedures.
  - **Staphylococcal lung infection in cystic fibrosis**
    - **BY MOUTH**
      - Child: 25 mg/kg 4 times a day (max. per dose 1 g), alternatively 100 mg/kg daily in 3 divided doses; maximum 4 g per day.
  - **Prevention of Staphylococcus aureus lung infection in cystic fibrosis—primary prevention**
    - **BY MOUTH**
      - Child 1 month–3 years: 125 mg twice daily.
  - **Prevention of Staphylococcus aureus lung infection in cystic fibrosis—secondary prevention**
    - **BY MOUTH**
      - Child: 50 mg/kg twice daily (max. per dose 1 g twice daily).

- **UNLICENSED USE**
  - In adults Flucloxacillin doses in the BNF may differ from those in product literature.

**IMPORTANT SAFETY INFORMATION**

**HEPATIC DISORDERS**

Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:

- Flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin.
Flucloxacillin should be used with caution in patients with hepatic impairment.
- Careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.

**Cautions**
- With intravenous use, accumulation of electrolytes can occur with high doses.
- **Interactions** → Appendix 1: penicillins.

**Side-effects**
**General side-effects**
- Rare or very rare: Arthralgia; fever.
- Common or very common: With oral use, Gastrointestinal disorder.
- Rare or very rare: With oral use, Eosinophilia; myalgia.
- Frequency not known:
  - With parenteral use, bronchospasm; coma; dyspnoea; electrolyte imbalance; erythema nodosum; hallucination; Jarisch-Herxheimer reaction; nephropathy; neurotoxicity; oral candidiasis; platelet dysfunction; purpura; non-thrombocytopenic; vasculitis.
- **Pregnancy** Not known to be harmful.

**Breastfeeding**
Trace amounts in milk, but appropriate to use.

**Hepatic impairment**
Manufacturer advises caution; including in those with risk factors for hepatic reactions.

**Renal impairment**
- With intravenous use: Accumulation of electrolytes can occur in patients with renal failure.
  - **Dose adjustments**:
    - In adults: Reduce dose if eGFR less than 10 mL/minute/1.73 m².
    - In children: Use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**Effect on laboratory tests**
False-positive urinary glucose (if tested for reducing substances).

**Directions for administration**
- With intravenous use in adults:
  - For intravenous infusion (Fluospen®), give intermittently in Glucose 5% or Sodium chloride 0.9%; suggested volume 100 mL given over 30–60 minutes. Via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.

**Patient and carer advice**

**Medicinal forms**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion.

**Oral solution**
CAUTIONARY AND ADVISORY LABELS 9, 23
- **Flucloxacillin (Non-proprietary)**
- **Flucloxacillin (as Flucloxacillin sodium) 25 mg per 1 ml Flucloxacillin 125mg/5ml oral solution:** 100 ml Flucloxacillin (Non-proprietary) £20.99 + £6.37
  - Flucloxacillin 125mg/5ml oral solution sugar-free sugar-free: 100 ml Flucloxacillin (Non-proprietary) £26.70 + £21.05
- **Flucloxacillin (as Flucloxacillin sodium) 50 mg per 1 ml Flucloxacillin 250mg/5ml oral solution sugar-free sugar-free:** 100 ml Flucloxacillin (Non-proprietary) £33.09 + £31.71

**Capsule**
CAUTIONARY AND ADVISORY LABELS 9, 23
- **Flucloxacillin (Non-proprietary)**
- **Flucloxacillin (as Flucloxacillin sodium) 250 mg Flucloxacillin 250mg capsules:** 28 capsule Flucloxacillin (Non-proprietary) £1.42 + £1.42
  - 100 capsule Flucloxacillin (Non-proprietary) £4.50 + £1.80

**Powder for solution for injection**
- **Flucloxacillin (Non-proprietary)**
- **Flucloxacillin (as Flucloxacillin sodium) 500 mg Flucloxacillin 500 mg capsules:** 28 capsule Flucloxacillin (Non-proprietary) £10.50 + £2.34
  - 100 capsule Flucloxacillin (Non-proprietary) £18.36 + £17.50

**Powder for solution for injection**
- **Flucloxacillin (Non-proprietary)**
- **Flucloxacillin (as Flucloxacillin sodium) 250 mg Flucloxacillin 250 mg powder for solution for injection.vials:** 10 vial Flucloxacillin (Non-proprietary) £8.60 + £8.60
  - Hospital only)
- **Flucloxacillin (as Flucloxacillin sodium) 500 mg Flucloxacillin 500 mg powder for solution for injection.vials:** 10 vial Flucloxacillin (Non-proprietary) £12.25 + £12.25
  - Hospital only)
- **Flucloxacillin (as Flucloxacillin sodium) 1 gram Flucloxacillin 1g powder for solution for injection.vials:** 10 vial Flucloxacillin (Non-proprietary) £34.50 + £34.50
  - Hospital only)
- **Flucloxacillin (as Flucloxacillin sodium) 2 gram Flucloxacillin 2g powder for solution for injection.vials:** 1 vial Flucloxacillin (Non-proprietary) £6.00 + £6.00
  - Hospital only)

**Combinations available:** Co-fluampicil, p. 550

**Temocillin**

- **Indications and dose**
  - Septicaemia brakes
  - **By intramuscular injection, or by slow intravenous injection**, or by intravenous infusion.
  - Adult: 2 g every 12 hours, alternatively 2 g every 8 hours, higher daily dose to be used in critically ill patients.
  - **By continuous intravenous infusion.**
  - Adult: (consult product literature).

**Cautions**
Accumulation of sodium from injection can occur with high doses.

**Interactions** → Appendix 1: penicillins.

**Side-effects**
Arthralgia; fever; myalgia; nervous system disorder; thrombophlebitis.

**Pregnancy**
Not known to be harmful.

**Breastfeeding**
Trace amounts in milk.

**Renal impairment**
Accumulation of sodium from injection can occur in patients with renal failure.

**Dose adjustments**
Manufacturer advises reduce usual dose to 1 g every 12 hours if creatinine clearance 30–60 mL/min; reduce usual dose to 1 g every 24 hours if creatinine clearance 30–50 mL/min.; reduce usual dose to 1 g every 48 hours or 500 mg every 24 hours if creatinine clearance less than 10 mL/min; no information available to recommend dose adjustments with higher daily dose for use in critically ill patients.

**Effect on laboratory tests**
False-positive urinary glucose (if tested for reducing substances).

**Directions for administration**
Manufacturer advises for intramuscular injection, reconstitute 1 g with 2 mL water for injections or Sodium chloride 0.9% (or 0.5 or 1% lidocaine solution, if pain is experienced at injection site). Manufacturer advises for slow intravenous injection, reconstitute 1 g with 10 mL water for injections or Sodium chloride 0.9%; give over 3–4 minutes. Manufacturer advises for intermittent intravenous infusion, give in Glucose 5% or 10% or Sodium chloride 0.9% or Ringer’s solution or Lactated Ringer’s solution. Reconstitute 1 g with 10 mL water for injections or infusion fluid, then dilute in up to 150 mL infusion fluid; give over 30–40 minutes. For continuous intravenous infusion, consult product literature.
**Bacterial infection**

**Colistimethate sodium**

**Drug action** The polymyxin antibiotic, colistimethate sodium (colistin sulfomethate sodium), is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. It is not absorbed by mouth and thus needs to be given by injection for a systemic effect.

**Indications and dose**

**Serious infections due to selected aerobic Gram-negative bacteria in patients with limited treatment options**

- **By intravenous infusion**
  - Adult: 9 million units daily in 2–3 divided doses, an initial loading dose of 9 million units should be used in those who are critically ill, loading and maintenance doses of up to 12 million units may be required in some cases, however clinical experience is limited and safety has not been established — consult product literature for details.

**Management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis**

- **By inhalation of nebulised solution**
  - Adult: 9 million units daily in 2–3 divided doses, an initial loading dose of 9 million units should be used in those who are critically ill, loading and maintenance doses of up to 12 million units may be required in some cases, however clinical experience is limited and safety has not been established — consult product literature for details.

**Contra-indications** Myasthenia gravis

**Cautions**

**General cautions** Children under 1 year of age (effects of immature renal and metabolic function on conversion to active colistin not known) (in children)

**Specific cautions**

- When used by inhalation Severe haemoptysis — risk of further haemorrhage

**Interactions**

- Appendix 1: colistimethate

**Side-effects**

**Common or very common**

- Arthralgia, asthenia, asthma, balance impaired, chest discomfort, cough, dysphonia, dysphagia, fever, haemorrhage, headache, lower respiratory tract infection, nausea, respiratory disorders, taste altered, throat complaints, tinnitus, vomiting

**Uncommon**

- Anxiety, appetite decreased, diarrhoea, drowsiness, ear congestion, flatulence, oral disorders, proteinuria, seizure, sputum purulent, thirst, weight change

**Rare or very rare**

- With parental use Confusion, nephrotoxicity, presyncope, psychosis, speech slurred, visual impairment

**Frequency not known**

- With parental use Apnoea, neurological effects, neurotoxicity, renal disorder, sensory disorder

**Side-effects, further information** Neurotoxicity and nephrotoxicity are dose-related.

**Pregnancy**

- When used by inhalation Clinical use suggests probably safe.

- When used by inhalation Manufacturer advises use only if potential benefit outweighs risk.

**Breast feeding** Present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk).

**Hepatic impairment**

- With intravenous use. Manufacturer advises caution (no information available).

**Renal impairment**

- When used by inhalation. Manufacturer advises caution.

**Dose adjustments**

- With intravenous use. Manufacturer advises reduce maintenance dose if creatinine clearance less than 50 mL/minute — consult product literature.

**Monitoring**

- With intravenous use. Monitor renal function.

- With intravenous use. Measure lung function before and after initial dose of colistimethate sodium and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium.

**Directions for administration**

- When used by inhalation. Manufacturer advises if other treatments are being administered, they should be taken in the order recommended by the physician. For nebulisation, consult product literature for information on reconstitution and dilution.

- With intravenous use. For intravenous infusion, manufacturer advises following reconstitution, dilute requisite dose, usually with 50 mL Sodium Chloride 0.9%; give over 30–60 minutes. Patients fitted with a totally implantable venous access device may tolerate an injection. For slow intravenous injection into a totally implantable venous access device, dilute to a concentration of 200 000 units/mL with Sodium Chloride 0.9%; give over at least 5 minutes.

**Prescribing and dispensing information**

Colistimethate sodium is included in some preparations for topical application.

**Patient and carer advice**

- When used by inhalation Patient should be advised to rinse mouth with water after each dose of dry powder inhalation. Patients or carers should be given advice on how to administer colistimethate sodium; first dose should be given under medical supervision.

- Driving and skilled tasks. Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks — increased risk of dizziness, confusion and visual disturbances.

**National funding/access decisions**

**NICE decisions**

- Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (March 2013) NICE TA276

Colistimethate sodium dry powder for inhalation is recommended for chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis who would benefit from continued treatment, but do not tolerate the drug in its nebulised form. The manufacturer must provide colistimethate sodium dry powder for
inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving colistimethate sodium dry powder for inhalation can continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta276

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

- Powder for solution for injection
  - ELECTROLYTES: May contain Sodium
    - Colistimethate sodium (Non-proprietary)
      - Colistimethate sodium 1000000 unit powder for solution for injection vials | 10 vial | £30.00 DT + £18.00 DT = £18.00 (Hospital only)
    - Colomycin (Teva UK Ltd)
      - Colistimethate sodium 1000000 unit powder for solution for injection vials | 10 vial | £32.40 DT + £18.00 DT = £18.00
    - Colistimethate sodium 2000000 unit powder for solution for injection vials | 10 vial | £37.50 DT + £18.00 (Hospital only)
  - Inhalation powder
    - Colobreathe (Teva UK Ltd)
      - Colistimethate sodium 1662500 unit inhalation powder capsules | 36 capsule | £66.80 DT + £968.80
  - Powder for nebuliser solution
    - Promixin (Profile Pharma Ltd)
      - Colistimethate sodium 1000000 unit powder for nebuliser solution unit dose vials | 30 unit dose | £240.00

ANTIBACTERIALS > QUINOLONES

Quinolones

31-Oct-2017

- MHRA/CHM advice: Systemic and inhaled fluoroquinolones (November 2018, and March 2019)

  The MHRA and CHM have released important safety information regarding the use of systemic and inhaled fluoroquinolones. For restrictions and precautions, see Important safety information for all quinolones. Ciprofloxacin p. 558, levofloxacin p. 559, moxifloxacin p. 560, and ofloxacin p. 561.

  Overview

  In the UK, only fluoroquinolones are available; the recommendations below therefore refer to the use of fluoroquinolones.

  Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including Salmonella, Shigella, Campylobacter, Neisseria, and Pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as Streptococcus pneumoniae and Enterococcus faecalis; it should not be used for pneumococcal pneumonia. It is active against Chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), infections of the gastrointestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

  Ofloxacin is licensed for urinary-tract infections, lower respiratory-tract infections, gonorrhoea, and non-gonococcal urethritis and cervicitis.

  Levofloxacin is active against Gram–positive and Gram-negative organisms. It has greater activity against Pseudomonas than ciprofloxacin.

  Many Staphylococci are resistant to quinolones and their use should be avoided in MRSA infections.

  Moxifloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against Gram-positive organisms, including Pseudomonas, than ciprofloxacin. Moxifloxacin is not active against Pseudomonas aeruginosa or meticillin-resistant Staphylococcus aureus (MRSA).

Quinolones

IMPORTANT SAFETY INFORMATION

The CSM has warned that quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them.

Tendon damage

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- patients over 60 years of age are more prone to tendon damage;
- the risk of tendon damage is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

MHRA/CHM ADVICE: SYSTEMIC AND INHALED FLUOROQUINOLONES: SMALL INCREASED RISK OF AORTIC ANEURYSM AND DISSECTION; ADVICE FOR PRESCRIBING IN HIGH-RISK PATIENTS (NOVEMBER 2018)

The MHRA advises that benefit-risk should be assessed and other therapeutic options considered before using fluoroquinolones in patients at risk of aortic aneurysm and dissection. Patients (particularly the elderly and those at risk) and their carers should be informed about rare events of aortic aneurysm and dissection, and advised to seek immediate medical attention if sudden-onset severe abdominal, chest, or back pain develops.

MHRA/CHM ADVICE: FLUOROQUINOLONE ANTIBIOTICS: NEW RESTRICTIONS AND PRECAUTIONS FOR USE DUE TO VERY RARE REPORTS OF DISABLING AND POTENTIALLY LONG-LASTING OR IRREVERSIBLE SIDE EFFECTS (MARCH 2019)

Disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely with fluoroquinolone antibiotics. Healthcare professionals are advised to inform patients to stop treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and CNS effects, and to contact their doctor immediately. Fluoroquinolones should not be prescribed for non-severe or self-limiting infections, or non-bacterial conditions. Unless other commonly recommended antibiotics are inappropriate, fluoroquinolones should not be prescribed for some mild to moderate infections, such as acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease, and ciprofloxacin or levofloxacin should not be prescribed for uncomplicated cystitis. Fluoroquinolones should be avoided in patients who have previously had serious adverse reactions. Use of fluoroquinolones with corticosteroids should also be avoided as it may exacerbate fluoroquinolone-induced tendinitis and tendon rupture. Fluoroquinolones should be prescribed with caution in patients older than 60 years and in...
patients with renal impairment or solid-organ transplants as they are at a higher risk of tendon injury.

**CONTRA-INDICATIONS** History of tendon disorders related to quinolone use

**CAUTIONS** Can prolong the QT interval; children or adolescents (arthropathy has developed in weight-bearing joints in young animals) in children; conditions that predispose to seizures - diabetes (may affect blood glucose); exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs); G6PD deficiency - history of epilepsy - myasthenia gravis (risk of exacerbation)

**CAUTIONS, FURTHER INFORMATION**

- Use in children: Quinolones cause arthropathy in the weight-bearing joints of immature animals and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of ciprofloxacin may be justified in children.

**SIDE-EFFECTS**

- **Common or very common** Appetite decreased - arthralgia - asthenia - constipation (in adults) - diarrhoea - dizziness - dyspnoea - eye discomfort - eye disorders - fever - gastrointestinal discomfort - headache - muscle complaints - nausea - QT interval prolongation - skin reactions - sleep disorders - taste altered - tinnitus - vision disorders - vomiting


- **Rare or very rare** Agranulocytosis - angioedema - arthritis - cardiac arrest (in adults) - gait abnormal - haemolytic anaemia - hyperglycaemia - hypoglycaemia - idiopathic intracranial hypertension - muscle weakness - myasthenia gravis aggravated - nephritis tubulointerstitial - pancreatitis - pancytopenia - peripheral neuropathy (sometimes irreversible) - photosensitivity reaction - polyneuropathy - psychotic disorder - severe cutaneous adverse reactions (SCARs) - stomatitis (in adults) - suicidal tendencies - syncope - vasculitis

- **Frequency not known** Corneal deposits (reversible after completion of treatment) - hypoglycaemic coma - increased risk of aortic aneurysm (more common in elderly) - increased risk of aortic dissection (more common in elderly) - ligament rupture - rhabdomyolysis (in adults) - self-endangering behaviour

**SIDE-EFFECTS, FURTHER INFORMATION** The drug should be discontinued if neurological, psychiatric, tendon disorders or hypersensitivity reactions (including severe rash) occur. For more information regarding the safety of fluoroquinolones, please see Important Safety Information.

**ALLERGY AND CROSS-SENSITIVITY** Use of quinolones contra-indicated in quinolone hypersensitivities.

**PREGNANCY** Avoid in pregnancy—shown to cause arthropathy in animal studies; safer alternatives are available.

**PATIENT AND CARER ADVICE** The MHRA has produced an advice sheet on serious adverse reactions affecting musculoskeletal and nervous systems associated with fluoroquinolone use, which should be provided to patients and their carers.

## Ciprofloxacin

**INDICATIONS AND DOSE**

**Fistulating Crohn’s disease**
- **BY MOUTH**
  - Adult: 500 mg twice daily

**Respiratory-tract infections**
- **BY MOUTH**
  - Adult: 500–750 mg twice daily
- **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Pseudomonal lower respiratory-tract infection in cystic fibrosis**
- **BY MOUTH**
  - Adult: 750 mg twice daily

**Urinary-tract infections**
- **BY MOUTH**
  - Adult: 250–750 mg twice daily
- **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Acute uncomplicated cystitis in women**
- **BY MOUTH**
  - Adult: 250 mg twice daily for 3 days

**Acute or chronic prostatitis**
- **BY MOUTH**
  - Adult: 500 mg twice daily for 28 days
- **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Gonorrhoea**
- **BY MOUTH**
  - Adult: 500 mg for 1 dose

**Most other infections**
- **BY MOUTH**
  - Adult: Initially 500 mg twice daily; increased to 750 mg twice daily, in severe or deep-seated infection
- **BY INTRAVENOUS INFUSION**
  - Adult: 400 mg every 8–12 hours, to be given over 60 minutes

**Surgical prophylaxis**
- **BY MOUTH**
  - Adult: 750 mg, to be taken 60 minutes before procedure

**Anthrax (treatment and post-exposure prophylaxis)**
- **BY MOUTH**
  - Child 1 month–4 years: 30 mg/kg (max. per dose 125 mg) for 1 dose
  - Child 5–11 years: 250 mg for 1 dose
  - Child 12–17 years: 500 mg for 1 dose
  - Adult: 500 mg for 1 dose

**Prevention of secondary case of meningococcal meningitis**
- **BY MOUTH**
  - Child 1 month–4 years: 30 mg/kg (max. per dose 125 mg) for 1 dose
  - Child 5–11 years: 250 mg for 1 dose
  - Child 12–17 years: 500 mg for 1 dose
  - Adult: 500 mg for 1 dose

**UNLICENSED USE** Not licensed for use in children for prophylaxis of meningococcal meningitis.

**CAUTIONS** Acute myocardial infarction (risk factor for QT interval prolongation) - avoid excessive alkalinity of urine (risk of crystalluria) - bradycardia (risk factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) -...
ensure adequate fluid intake (risk of crystalluria) · heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) · history of symptomatic arrhythmias (risk factor for QT interval prolongation)

- INTERACTIONS → Appendix 1: quinolones

- SIDE-EFFECTS
  - Common or very common  Arthropathy (in children)
  - Rare or very rare  Bone marrow depression · crystalluria · erythema nodosum · haematuria · intracranial pressure increased · leucocytosis · migraine · muscle tone increased · status epilepticus
  - Frequency not known  Mood altered

- PREGNANCY  A single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.

- BREAST FEEDING  Amount too small to be harmful but manufacturer advises avoid.

- RENAL IMPAIRMENT
  - Dose adjustments
    - With oral use in adults  Give 250–500 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m² (every 24 hours if eGFR less than 30 mL/minute/1.73 m²).
    - With intravenous use in adults  Give (200 mg over 30 minutes), 200–400 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m² (every 24 hours if eGFR less than 30 mL/minute/1.73 m²).
    - In children  Reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—consult product literature.

- PRESCRIBING AND DISPENSING INFORMATION
  - With oral use  Flavours of oral liquid formulations may include strawberry.

- PATIENT AND CARER ADVICE
  - Medicines for Children leaflet: Ciprofloxacin for bacterial infections (Bayer Plc)
  - Driving and skilled tasks  May impair performance of skilled tasks (e.g. driving); effects enhanced by alcohol.

- MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  - CAUTIONARY AND ADVISORY LABELS  T, 9, 25
  - Ciprofloxacin (Non-proprietary)
    - Ciprofloxacin (as Ciprofloxacin hydrochloride)
      - 100 mg Ciprofloxacin 100mg tablets 6 tablet [PO] £2.11 DT + £2.11
      - Ciprofloxacin (as Ciprofloxacin hydrochloride)
    - 250 mg Ciprofloxacin 250mg tablets 10 tablet [PO] £5.60 DT + £0.74 20 tablet [PO] £1.18–£11.20 100 tablet [PO] £5.90–£7.90
    - Ciprofloxacin (as Ciprofloxacin hydrochloride)
      - 500 mg Ciprofloxacin 500mg tablets 10 tablet [PO] £10.62 DT + £0.91 20 tablet [PO] £1.64–£21.23 100 tablet [PO] £8.20–£9.10
    - Ciprofloxacin (as Ciprofloxacin hydrochloride)
      - 750 mg Ciprofloxacin 750mg tablets 10 tablet [PO] £15.11 DT + £8.00 20 tablet [PO] £15.99
    - Ciprofloxacin (Bayer PK)
      - Ciprofloxacin (as Ciprofloxacin hydrochloride) 500 mg Ciprofloxacin 500mg tablets 10 tablet [PO] £2.09 DT + £0.91

  **Oral suspension**
  - CAUTIONARY AND ADVISORY LABELS  T, 9, 25
  - Ciprofloxacin (Bayer PK)
    - Ciprofloxacin 50 mg per 1 ml Ciprofloxacin 250mg/5ml oral suspension 100 ml [PO] £21.29 DT + £21.29

  **Solution for infusion**
  - ELECTROLYTES: May contain Sodium
    - Ciprofloxacin (Non-proprietary)
      - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciprofloxacin 200mg/100ml solution for infusion vials 1 vial [PO] £10.00
      - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciprofloxacin 200mg/100ml solution for infusion vials 10 bottle [PO] £124.80–£144.50

Bacterial infection 559

Ciprofloxacin 100mg/50ml solution for infusion vials 1 vial [PO] £10.00–£13.00
Ciprofloxacin 400mg/200ml solution for infusion bottles 1 bottle [PO] £10.00 10 bottle [PO] £139.70–£195.90
Ciprofloxacin 400mg/200ml solution for infusion vials 1 vial [PO] £10.00

- Ciproxin (Bayer Plc)
  - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciproxin Infusion 100mg/50ml solution for infusion bottles 1 bottle [PO] £7.61 (Hospital only)
  - Ciproxin Infusion 400mg/200ml solution for infusion bottles 5 bottle [PO] £114.23 (Hospital only)
  - Ciproxin Infusion 200mg/100ml solution for infusion bottles 5 bottle [PO] £75.06 (Hospital only)

**Infusion**

- Ciprofloxacin (Non-proprietary)
  - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciprofloxacin 200mg/100ml infusion bags 5 bag [PO] £60.00 (Hospital only)
  - Ciprofloxacin 400mg/200ml infusion bags 5 bag [PO] £85.00 (Hospital only) 10 bag [PO] £200.00–£228.46 (Hospital only)

Levofloxacin

- INDICATIONS AND DOSE
  - Acute sinusitis
    - BY MOUTH
      - Adult: 500 mg once daily for 10–14 days

  - Acute exacerbation of chronic obstructive pulmonary disease
    - BY MOUTH
      - Adult: 500 mg once daily for 5 days

  - Acute exacerbation of bronchiectasis
    - BY MOUTH
      - Adult: 500 mg 1–2 times a day for 7–14 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes

  - Community-acquired pneumonia
    - BY MOUTH
      - Adult: 500 mg 1–2 times a day for 7–14 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes

  - Urinary-tract infections
    - BY MOUTH
      - Adult: 500 mg once daily for 7–14 days

  - Urinary-tract infections (uncomplicated infection)
    - BY MOUTH
      - Adult: 250 mg once daily for 3 days

  - Complicated urinary-tract infections
    - BY INTRAVENOUS INFUSION
      - Adult: 500 mg once daily, to be given over at least 60 minutes

  - Chronic prostatitis
    - BY MOUTH
      - Adult: 500 mg once daily for 28 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg once daily, to be given over at least 60 minutes

  - Complicated skin infections / Complicated soft-tissue infections
    - BY MOUTH
      - Adult: 500 mg 1–2 times a day for 7–14 days
      - BY INTRAVENOUS INFUSION
      - Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes

  - Inhalation of anthrax (treatment and post-exposure prophylaxis)
    - BY MOUTH
      - Adult: 500 mg once daily for 8 weeks

www.getintopharma.com
unlicensed use \(^{212}\) Duration of treatment for acute exacerbation of chronic obstructive pulmonary disease differs from product literature and adheres to national guidelines. \(^{212}\) See Respiratory system infections, antibacterial therapy p. 515 for further information.

interactions \(^{212}\) \(^{212}\) Levofoxacin is used for the treatment of acute exacerbation of bronchiectasis, \(^{212}\) but is not licensed for this indication. See Respiratory system infections, antibacterial therapy p. 515 for further information.

cautions History of psychiatric illness \(^{212}\) risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, bradycardia, congenital long QT syndrome, history of symptomatic arrhythmias)

interactions \(^{212}\) Side-effects

common or very common

- When used by inhalation: Bronchial secretion changes 
- Dysphonia 
- Haemoptysis 
- Weight decreased

uncommon

- When used by inhalation: Costochondritis 
- Hyperbilirubinaemia 
- Joint stiffness

rare or very rare

- With oral and intravenous use: Paranoia

frequency not known

- With oral and intravenous use: Diarrhoea haemorrhagic

side-effects, further information Systemic side-effects may occur with nebulised levofloxacin.

bronchospasm Manufacturer advises if acute symptomatic bronchospasm occurs after receiving nebulised levofloxacin, patients may benefit from the use of a short-acting inhaled bronchodilator at least 15 minutes to 4 hours prior to subsequent doses.

breast feeding Manufacturer advises avoid.

renal impairment

Dose adjustments

- With intravenous use or oral use: usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m\(^2\); consult product literature if eGFR less than 20 mL/minute/1.73 m\(^2\).

- When used by inhalation: Manufacturer advises avoid if creatinine clearance less than 20 mL/minute.

patient and carer advice

- When used by inhalation: Manufacturer advises patients and carers should be given advice on how to administer levofloxacin.

- Missed doses: When used by inhalation: Manufacturer advises if a dose is more than 4 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- Driving and skilled tasks: May impair performance of skilled tasks (e.g. driving).

national funding/access decisions

Scottish medicines consortium (SMC) decisions

The Scottish medicines consortium has advised (August 2016) that levofloxacin (Quinsair®) is accepted for restricted use within NHS Scotland for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis, as a third-line treatment option after colistimethate sodium (first line) and tobramycin (second line). This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

All Wales medicines strategy Group (AWMSG) decisions

The All Wales medicines strategy Group has advised (November 2016) that levofloxacin (Quinsair®) is recommended as an option for restricted use within NHS Wales as third-line therapy for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis, who do not respond to, or are intolerant of, second-line treatment with tobramycin, only if the approved Wales patient access scheme (WPAS) is used or where the list price is equivalent or lower.

medicinal forms There can be variation in the licensing of different medicines containing the same drug.

tablet

Cautionary and advisory labels 6, 9, 25

- Levofloxacin (Non-proprietary)

- Levofloxacin (as Levofloxacin hemihydrate) 250 mg

- 250 mg tablets | 5 tablet | £1.19-1.74 | 10 tablet | £4.84

- DT = £3.80

- Levofloxacin (as Levofloxacin hemihydrate) 500 mg

- 500 mg tablets | 5 tablet | £7.90-£12.93 | 10 tablet | £25.85

- DT = £23.10

solution for infusion

Electrolytes: May contain Sodium

- Levofloxacin (Non-proprietary)

- Levofloxacin (as Levofloxacin hemihydrate) 5 mg per

- 1 ml Levofloxacin 500 mg/100 ml solution for infusion vials | 1 vial | £11.80 (Hospital only)

- Levofloxacin 500 mg/100 ml solution for infusion bottles | 1 bottle | £12.00 | 10 bottle | £26.00

Nebuliser liquid

- Quinsair (Chiesi Ltd)

- Levofloxacin (as Levofloxacin hemihydrate) 100 mg per

- 1 ml Quinsair 240 mg nebuliser solution ampoules | 16 ampoule | £2.18

Infusion

- Levofloxacin (Non-proprietary)

- Levofloxacin (as Levofloxacin hemihydrate) 5 mg per

- 1 ml Levofloxacin 500 mg/100 ml infusion bags | 10 bag | £250.00 (Hospital only)

- 20 bag | £502.00 (Hospital only)

Moxifloxacin

- Indications and dose

  Sinusitis

  - By mouth

  - adult: 400 mg once daily for 7 days

Community-acquired pneumonia

- By mouth

- adult: 400 mg once daily for 7–14 days

- By intravenous infusion

- adult: 400 mg once daily for 7–14 days, to be given over 60 minutes

Exacerbations of chronic bronchitis

- By mouth

- adult: 400 mg once daily for 5–10 days

Mild to moderate pelvic inflammatory disease

- By mouth

- adult: 400 mg once daily for 14 days

Complicated skin and soft-tissue infections which have failed to respond to other antibiotics or for patients who cannot be treated with other antibiotics

- By mouth

- adult: 400 mg once daily for 7–21 days

- By intravenous infusion

- adult: 400 mg once daily for 7–21 days, to be given over 60 minutes

- Contra-indications Acute myocardial infarction (risk factor for QT interval prolongation), bradycardia (risk factor for QT interval prolongation), sick sinus syndrome, long QT syndrome, QT interval prolongation.
factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) - heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) - history of symptomatic arrhythmias (risk factor for QT interval prolongation)

INTERACTIONS  ➔ Appendix 1: quinolones

SIDE-EFFECTS

With oral and intravenous use  Angina pectoris - dehydration - gastritis - hyperlipidaemia - malaise - pelvic pain

Rare or very rare

With oral and intravenous use  Concentration impaired - depersonalisation - dysphagia - emotional lability - generalised tonic-clonic seizure - hypertension - hyperuricaemia - memory loss - self-injurious behaviour - speech disorder

BREAST FEEDING  Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT  Manufacturer advises avoid in severe impairment or increased transaminases (5 times upper limit of normal).

PATIENT AND CARER ADVICE

Driving and skilled tasks  May impair performance of skilled tasks (e.g. driving).

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS  6, 9

Moxifloxacin (Non-proprietary)

Moxifloxacin (as Moxifloxacin hydrochloride) 400 mg Moxifloxacin 400mg tablets  5 tablet  £11.81 DT = £9.54

Avelox (Bayer Plc)

Moxifloxacin (as Moxifloxacin hydrochloride) 400 mg Avelox 400mg tablets  5 tablet  £12.43 DT = £9.54

Solution for infusion

ELECTROLYTES: May contain Sodium

Moxifloxacin (Non-proprietary)

Moxifloxacin (as Moxifloxacin hydrochloride) 1.6 mg per 1 ml Moxifloxacin 400mg/250ml solution for infusion bottles  10 bottle  £399.50-£509.90 (Hospital only)

Avelox (Bayer Plc)

Moxifloxacin (as Moxifloxacin hydrochloride) 1.6 mg per 1 ml Avelox 400mg/250ml solution for infusion bottles  1 bottle  £39.95 (Hospital only)  5 bottle  £199.75 (Hospital only)

Ofloxacin

INDICATIONS AND DOSE

Urinary-tract infections

BY MOUTH

Adult: 200–400 mg daily, preferably taken in the morning; increased if necessary to 400 mg twice daily, in upper urinary tract infections

Complicated urinary-tract infection

BY INTRAVENOUS INFUSION

Adult: 200 mg daily, increased if necessary to 400 mg twice daily, dose increased for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

Acute or chronic prostatitis

BY MOUTH

Adult: 200 mg twice daily for 28 days

Lower respiratory-tract infections

BY MOUTH

Adult: 400 mg daily, dose preferably taken in the morning, then increased if necessary to 400 mg twice daily

BY INTRAVENOUS INFUSION

Adult: 200 mg twice daily, increased to 400 mg twice daily, dose to be increased for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

Skin and soft-tissue infections

BY MOUTH

Adult: 400 mg twice daily

BY INTRAVENOUS INFUSION

Adult: 400 mg twice daily, to be given over at least 30 minutes for each 200 mg

Uncomplicated gonorrhoea

BY MOUTH

Adult: 400 mg as a single dose

Uncomplicated genital chlamydial infection  Non-gonococcal urethritis

BY MOUTH

Adult: 400 mg daily for 7 days, dose may be taken as a single daily dose or in divided doses

Pelvic inflammatory disease

BY MOUTH

Adult: 400 mg twice daily for 14 days

CAUTIONS  Acute myocardial infarction (risk factor for QT interval prolongation) - bradycardia (risk factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) - heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) - history of psychiatric illness - history of symptomatic arrhythmias (risk factor for QT interval prolongation)

INTERACTIONS  ➔ Appendix 1: quinolones

SIDE-EFFECTS

Rare or very rare

With oral and intravenous use  Enterocolitis - enterocolitis haemorrhagic

Frequency not known

With oral and intravenous use  Bone marrow failure - myopathy - nephritis acute interstitial

BREAST FEEDING  Amount probably too small to be harmful but manufacturer advises avoid.

HEPATIC IMPAIRMENT  Manufacturer advises caution.

Dose adjustments  Manufacturer advises maximum 400 mg daily in hepatic failure (risk of decreased elimination).

RENAL IMPAIRMENT  usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m²; 100 mg every 24 hours if eGFR less than 20 mL/minute/1.73 m²

PATIENT AND CARER ADVICE

Driving and skilled tasks  May impair performance of skilled tasks (e.g. driving); effects enhanced by alcohol.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS  6, 9, 11

Ofloxacin 200 mg Ofloxacin 200mg tablets  10 tablet  £6.75 DT = £6.73

Ofloxacin 400 mg Ofloxacin 400mg tablets  5 tablet  £12.80 DT = £11.86  10 tablet  £45.92-£23.72

www.getintopharma.com
Infection

ANTIBACTERIALS

Co-trimoxazole

- **DRUG ACTION** Sulfamethoxazole and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity (the importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic).

- **INDICATIONS AND DOSE**
  - **Treatment of susceptible infections**
    - **BY MOUTH**
      - Child: 120 mg twice daily, alternatively 24 mg/kg twice daily
      - Child: 240 mg twice daily, alternatively 24 mg/kg twice daily
      - Child 6–11 years: 480 mg twice daily, alternatively 24 mg/kg twice daily
      - Child 12–17 years: 960 mg twice daily
      - Adult: 960 mg twice daily
    - **BY INTRAVENOUS INFUSION**
      - Adult: 960 mg every 12 hours, increased to 1.44 g every 12 hours, increased dose used in severe infection

  - **Acute exacerbation of chronic obstructive pulmonary disease**
    - **BY MOUTH**
      - Adult: 960 mg twice daily for 5 days
    - **BY INTRAVENOUS INFUSION**
      - Adult: 960 mg every 12 hours, increased if necessary to 1.44 g every 12 hours, increased dose used in severe infection

  - **Treatment of Pneumocystis jiroveci (Pneumocystis carinii) infections** (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature)
    - **BY MOUTH**
      - Child: 120 mg/kg daily in 2–4 divided doses for 14–21 days, oral route preferred for children
      - Adult: 120 mg/kg daily in 2–4 divided doses for 14–21 days

  - **Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections**
    - **BY MOUTH**
      - Child: 450 mg/m² twice daily (max. per dose 960 mg twice daily) for 3 days of the week (either consecutively or on alternate days), dose regimens may vary, consult local guidelines
      - Adult: 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily on alternate days, alternate day dose to be given 3 times weekly, alternatively 960 mg twice a day on alternate days, alternate day dose to be given 3 times weekly

  - **DOSE EQUIVALENCE AND CONVERSION**
    - 480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg.

- **SIDE-EFFECTS**
  - Common or very common: Diarrhoea, electrolyte imbalance, fungal overgrowth, headache, nausea, skin reactions
  - Uncommon: Vomiting
  - Rare or very rare: Agranulocytosis, angioedema, aplastic anaemia, appetite decreased, arthralgia, ataxia, cough, depression, dizziness, dyspnoea, eosinophilia, fever, haemolysis, haemolytic anaemia, hallucination, hepatic disorders, hypoglycaemia, leucopenia, lung infiltration, megaloblastic anaemia, meningitis, aseptic meningitis, metabolic acidosis, methaemoglobinemia, myalgia, myocarditis, allergic, nephritis, tubulointerstitial, neutropenia, oral disorders, pancreatitis, peripheral neuritis, photosensitivity reaction, pseudomembranous enterocolitis, renal impairment, renal tubular acidosis, seizure, serum sickness, severe cutaneous adverse reactions (SCARs), systemic lupus erythematosus (SLE), thrombocytopenia, tinnitus, urticaria, vasculitis, vertigo

- **INTERACTIONS**
  - Appendix 1: sulfonamides, trimethoprim

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Co-trimoxazole is associated with rare but serious side effects. Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) develop.

- **PREGNANCY**
  - Teratogenic risk in first trimester (trimethoprim is a folate antagonist). Neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.

- **BREAST FEEDING**
  - Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole).

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid in severe liver disease.

- **RENAL IMPAIRMENT**
  - In adults Avoid if eGFR less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored.
  - In children Avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored.

- **IN CHILDREN**
  - Not licensed for use in children under 6 weeks.

- **IMPORTANT SAFETY INFORMATION**
  - **RESTRICTIONS ON THE USE OF CO-TRIMOXAZOLE**
    - Co-trimoxazole is the drug of choice in the prophylaxis and treatment of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia; it is also indicated for nocardiosis, Stenotrophomonas maltophilia infection [unlicensed indication], and toxoplasmosis. It should only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract where there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it. Co-trimoxazole is also used for the treatment of infections caused by Burkholderia cepacia in cystic fibrosis [unlicensed indication].

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 1058
  - **CAUTIONS**
    - Asthma - avoid in blood disorders (unless under specialist supervision) - avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus - elderly (increased risk of serious side-effects) - G6PD deficiency (risk of haemolytic anaemia) - maintain adequate fluid intake - predisposition to folate deficiency - predisposition to hyperkalaemia

- **UNLICENSED USE**
  - Not licensed for Burkholderia cepacia infections in cystic fibrosis. Not licensed for Stenotrophomonas maltophilia infections.
**Dose adjustments**

- In adults: Use half normal dose if eGFR 15–30 mL/minute/1.73 m².
- In children: Use half normal dose if estimated glomerular filtration rate 15–30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor blood counts on prolonged treatment.
- In children: Plasma concentration monitoring may be required with high doses; seek expert advice.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in adults: For intermittent intravenous infusion, may be further diluted in glucose 5% and 10% or sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and the required dose infused over max. 60 minutes; check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.
- With intravenous use in children: For intermittent intravenous infusion (Septrin® for infusion), give intermittently in Glucose 5% or 10% or Sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and infused over max. 60 minutes.

**PRESCRIBING AND DISPENSING INFORMATION**

- Co-trimoxazole is a mixture of trimethoprim and sulfamethoxazole (sulphamethoxazole) in the proportions of 1 part to 5 parts. Flavours of oral liquid formulations may include banana, or vanilla.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Excipients:** May contain Alcohol, propylene glycol, sulfites
- **Electrolytes:** May contain Sodium
- **Co-trimoxazole (Non-proprietary)**
  - Trimethoprim 16 mg per 1 ml, Sulfamethoxazole 80 mg per 1 ml Co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules | 10 ampoule | £35.00 DT + £35.00

**Oral suspension**

- CAUTIONARY AND ADVISORY LABELS
- **Co-trimoxazole (Non-proprietary)**
  - Trimethoprim 8 mg per 1 ml, Sulfamethoxazole 40 mg per 1 ml Co-trimoxazole 40mg/200mg/5ml oral suspension sugar free | 100 ml [Pip] £3.95–£3.96 DT + £3.96
  - Trimethoprim 16 mg per 1 ml, Sulfamethoxazole 80 mg per 1 ml Co-trimoxazole 80mg/400mg/5ml oral suspension | 100 ml | £10.95–£10.96 DT + £10.96

**Tablet**

- CAUTIONARY AND ADVISORY LABELS
- **Co-trimoxazole (Non-proprietary)**
  - Trimethoprim 80 mg, Sulfamethoxazole 400 mg Co-trimoxazole 80mg/400mg tablets | 28 tablet | £15.50 DT + £2.01 | 100 tablet [Pip] £7.18–£10.91
  - Trimethoprim 160 mg, Sulfamethoxazole 800 mg Co-trimoxazole 160mg/800mg tablets | 100 tablet [Pip] £23.40–£23.46 DT + £23.46

**Sulfadiazine**

(Sulfaphidazine)

- **DRUG ACTION** Sulfadiazine is a short-acting sulphonamide with bacteriostatic activity against a broad spectrum of organisms. The importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

- **INDICATIONS AND DOSE**
  - Prevention of rheumatic fever recurrence
  - **By mouth**
  - Adult (body-weight up to 30 kg): 500 mg daily
  - Adult (body-weight 30 kg and above): 1 g daily

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**

Sulfadiazine has been confused with sulfasalazine; care must be taken to ensure the correct drug is prescribed and dispensed.

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058
- **CAUTIONS** Asthma - avoid in blood disorders (unless under specialist supervision) - avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus - elderly - G6PD deficiency (risk of haemolytic anaemia) - maintain adequate fluid intake - predisposition to folate deficiency - predisposition to hyperkaemia
- **INTERACTIONS**
  - Appendix 1: sulfonamides
- **SIDE-EFFECTS**
  - Rare or very rare: Haemolytic anaemia

- **SIDE-EFFECTS, FURTHER INFORMATION** Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens-Johnson syndrome, toxic epidermal necrolysis) develop.

- **PREGNANCY** Risk of neonatal haemolyis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.
- **BREAST FEEDING** Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment or jaundice.
- **RENAL IMPAIRMENT** Use with caution in mild to moderate impairment; avoid in severe impairment; high risk of crystalluria.
- **MONITORING REQUIREMENTS** Monitor blood counts on prolonged treatment.
**Tetracyclines**

**Overview**

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. They remain, however, the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline below with either streptomycin or rifampicin p. 582), and the spirochaete, *Borrelia burgdorferi* (See Lyme disease). They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin p. 539).

Tetracyclines have a role in the management of meticillin-resistant *Staphylococcus aureus* (MRSA) infection. Microbiologically, there is little to choose between the various tetracyclines, the only exception being minocycline (including Q-fever), brucella (doxycycline below with either streptomycin or rifampicin p. 582), and the spirochaete, *Borrelia burgdorferi* (See Lyme disease). They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin p. 539).

Tetracyclines sometimes cause irreversible pigmentation.

**Tetracyclines**

- **CAUTIONS** Myasthenia gravis (muscle weakness may be increased) · systemic lupus erythematosus (may be exacerbated)
- **SIDE-EFFECTS**
  - Common or very common Angioedema, diarrhoea, headache, Hoench-Schönlein purpura, hypersensitivity, nausea, pericarditis, photosensitivity reaction, skin reactions · systemic lupus erythematosus exacerbated · vomiting
  - Rare or very rare Appetite decreased, discoloration of thyroid gland, dysphagia, eosinophilia, fontanelle bulging (in infants), gastrointestinal disorders, haemolytic anaemia, hepatic disorders, idiopathic intracranial hypertension · increased risk of infection · neutropenia · oral disorders · pancreatitis · pseudodemembranous enterocolitis · Stevens-Johnson syndrome · thrombocytopenia
  - Frequency not known Dizziness · tooth discolouration
- **SIDE-EFFECTS, FURTHER INFORMATION** Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment if raised intracranial pressure develops).
- **PREGNANCY** Should not be given to pregnant women; effects on skeletal development have been documented in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth, and maternal hepatotoxicity has been reported with large parenteral doses.
- **BREAST FEEDING** Should not be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).
- **HEPATIC IMPAIRMENT** Should be avoided or used with caution in patients with hepatic impairment.

**INDICATIONS AND DOSE**

**Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)**

- **BY MOUTH**
  - Adult: 150 mg 4 times a day, alternatively 300 mg twice daily

**Treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable**

- **BY MOUTH**
  - Adult: Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily

**CAUTIONS** Photosensitivity more common than with other tetracyclines

**INTERACTIONS** → Appendix 1: tetracyclines

**SIDE-EFFECTS**

- Rare or very rare: Agranulocytosis · aplastic anaemia · hearing impairment · nephritis · severe cutaneous adverse reactions (SCARs)
- Frequency not known: Intracranial pressure increased · muscle weakness · nephrogenic diabetes insipidus · vision disorders
- **HEPATIC IMPAIRMENT** Dose adjustments: Max. 1 g daily in divided doses.

**RENAI IMPAIRMENT** May exacerbate renal failure and should not be given to patients with renal impairment.

**PATIENT AND CARER ADVICE** Patients should be advised to avoid exposure to sunlight or sun lamps.

**MEDICINAL FORMS**

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**Demeclocycline hydrochloride**

**Indications and Dose**

**Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)**

- **BY MOUTH**
  - Adult: 150 mg 4 times a day, alternatively 300 mg twice daily

**Treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable**

- **BY MOUTH**
  - Adult: Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily

**CAUTIONS** Photosensitivity more common than with other tetracyclines

**INTERACTIONS** → Appendix 1: tetracyclines

**SIDE-EFFECTS**

- Rare or very rare: Agranulocytosis · aplastic anaemia · hearing impairment · nephritis · severe cutaneous adverse reactions (SCARs)
- Frequency not known: Intracranial pressure increased · muscle weakness · nephrogenic diabetes insipidus · vision disorders
- **HEPATIC IMPAIRMENT** Dose adjustments: Max. 1 g daily in divided doses.

**RENAI IMPAIRMENT** May exacerbate renal failure and should not be given to patients with renal impairment.

**PATIENT AND CARER ADVICE** Patients should be advised to avoid exposure to sunlight or sun lamps.

**MEDICINAL FORMS**

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<td>Oral solution</td>
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**Doxycycline**

**Indications and Dose**

**Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)**

- **BY MOUTH**
  - Adult: 150 mg 4 times a day, alternatively 300 mg twice daily

**Treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable**

- **BY MOUTH**
  - Adult: Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily

**CAUTIONS** Photosensitivity more common than with other tetracyclines

**INTERACTIONS** → Appendix 1: tetracyclines

**SIDE-EFFECTS**

- Rare or very rare: Agranulocytosis · aplastic anaemia · hearing impairment · nephritis · severe cutaneous adverse reactions (SCARs)
- Frequency not known: Intracranial pressure increased · muscle weakness · nephrogenic diabetes insipidus · vision disorders
- **HEPATIC IMPAIRMENT** Dose adjustments: Max. 1 g daily in divided doses.

**RENAI IMPAIRMENT** May exacerbate renal failure and should not be given to patients with renal impairment.

**PATIENT AND CARER ADVICE** Patients should be advised to avoid exposure to sunlight or sun lamps.

**MEDICINAL FORMS**

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Acute sinusitis | Acute cough [if systemically very unwell or at higher risk of complications]
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 14 days
Adult: 100 mg twice daily for 7 days

Acute exacerbation of bronchiectasis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 14 days
Adult: 100 mg twice daily for 7 days

Acute exacerbation of chronic obstructive pulmonary disease
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 100 mg twice daily for 14 days

Severe infections (including refractory urinary-tract infections)
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 200 mg daily
Adult: 200 mg daily

Acne
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg once daily
Adult: 100 mg once daily

Rosacea
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 100 mg once daily

Papulopustular facial rosacea (without ocular involvement)
▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: 40 mg once daily for 16 weeks, dose to be taken in the morning, consider discontinuing treatment if no response after 6 weeks

Early syphilis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 14 days
Adult: 100 mg twice daily for 14 days

Late latent syphilis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 28 days
Adult: 100 mg twice daily for 28 days

Neurosyphilis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 200 mg twice daily for 28 days

Uncomplicated genital chlamydia | Non-gonococcal urethritis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 7 days
Adult: 100 mg twice daily for 7 days

Pelvic inflammatory disease
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily for 14 days
Adult: 100 mg twice daily for 14 days

Lyme disease [erythema migrans and/or non-focal symptoms] | Lyme disease [affecting cranial nerves or peripheral nervous system] | Lyme carditis
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 200 mg daily in 1–2 divided doses for 21 days

Lyme disease [affecting central nervous system]
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 400 mg daily in 1–2 divided doses for 21 days

Lyme arthritis | Acrodermatitis chronica atrophicans
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 200 mg daily in 1–2 divided doses for 28 days

Anthrax (treatment or post-exposure prophylaxis)
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg twice daily
Adult: 100 mg twice daily

Prophylaxis of malaria
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years
Adult: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years

Adjuct to quinine in treatment of Plasmodium falciparum malaria
▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Child 12-17 years: 200 mg daily for 7 days
Adult: 200 mg daily for 7 days

Periodontitis (as an adjunct to gingival scaling and root planing)
▶ BY MOUTH USING DISPERSIBLE TABLETS
Adult: 100 mg twice daily, continue treatment for at least 3 days after fever subsides, minimum treatment duration is 5–7 days

Unlicensed use
Doxycycline may be used as detailed below, although these situations are considered outside the scope of its licence:

† IV/IM Duration of treatment for acute sinusitis (d), see Sinusitis (acute) p. 1203 for further information;
† IV/IM Lyme disease (d);
† treatment or post-exposure prophylaxis of anthrax;
† malaria prophylaxis during pregnancy;
† recurrent aphthous ulceration.
In adults Immediate-release doxycycline may be used for the treatment of rosacea, but it is not licensed for this indication.

Caution
Alcohol dependence

Interactions
Appendix 1: tetracyclines

Side-effects
Common or very common
Dyspnoea • hypotension • peripheral oedema • tachycardia
Uncommon
Gastrointestinal discomfort
Rare or very rare
Antibiotic associated colitis • anxiety • arthralgia • flushing • intracranial pressure increased with papilloedema • Jarisch–Herxheimer reaction • myalgia • photosensitisation • severe cutaneous adverse reactions (SCARs) • skin hyperpigmentation (long term use) • tinnitus • vision disorders

Pregnancy
When travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks' gestation.

Renal impairment
Use with caution (avoid excessive doses).

Monitoring requirements
When used for periodontitis, monitor for superficial fungal infection, particularly if predisposition to oral candidiasis.

Directions for administration
Capsules and Tablets should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals.

Prescribing and dispensing information
See Lyme disease p. 577 for place in therapy and further information on treatment.

Patient and carer advice
Counselling on administration advised.
**Minocycline**

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily
  - Adult: 100 mg twice daily

Acne

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg once daily, alternatively 50 mg twice daily
  - Adult: 100 mg once daily, alternatively 50 mg twice daily

Prophylaxis of asymptomatic meningococcal carrier state (but no longer recommended)

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 100 mg twice daily for 5 days, minocycline treatment is usually followed by administration of rifampicin

**CAUTIONS** Systemic lupus erythematosus

**INTERACTIONS** → Appendix 1: tetracyclines

**SIDE-EFFECTS**

- Rare or very rare Acute kidney injury - hearing impairment - respiratory disorders - tinnitus

- Frequency not known Alopecia - antibiotic associated colitis - arthralgia - ataxia - breast secretion - conjunctival discoloration - drug reaction with eosinophilia and systemic symptoms (DRESS) - dyspepsia - hyperbilirubinaemia - hyperhidrosis - polyarteritis nodosa - sensation abnormal - tear discolouration - tongue discolouration - vertigo

**RENAL IMPAIRMENT** Use with caution (avoid excessive doses).

**MONITORING REQUIREMENTS** If treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens.

**DIRECTIONS FOR ADMINISTRATION** Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing.

**PATIENT AND CARER ADVICE** Counselling on administration advised (posture).

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing (compared with other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome; it sometimes causes irreversible pigmentation).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

| Capsule |
|——|
| **CAUTIONARY AND ADVISORY LABELS** 6, 9 |
| **Minocycline (Non-proprietary)** |
| Minocycline (as Minocycline hydrochloride) 50 mg | Minocycline 50 mg tablets | 28 tablet (PO) £8.50 DT = £6.19 |
| Minocycline (as Minocycline hydrochloride) 100 mg | Minocycline 100 mg tablets | 28 tablet (PO) £14.50 DT = £14.16 |

**Modified-release capsule**

| CAUTIONARY AND ADVISORY LABELS 6, 25 |
| **Minocycline (Non-proprietary)** |
| Minocycline (as Minocycline hydrochloride) 100 mg | Minocycline 100 mg modified-release capsules | 56 capsule (PO) £20.08 DT = £20.08 |
Oxytetracycline

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
- **BY MOUTH**
  - Child 12-17 years: 250–500 mg 4 times a day
  - Adult: 250–500 mg 4 times a day

Rosacea
- **BY MOUTH**
  - Adult: 500 mg twice daily usually for 6–12 weeks (course may be repeated intermittently)

Acne
- **BY MOUTH**
  - Adult: 500 mg twice daily for at least 3 months, if there is no improvement after the first 3 months another oral antibacterial should be used, maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer

- **BY MOUTH**
  - Adult: 500 mg twice daily for at least 3 months, if there is no improvement after the first 3 months another oral antibacterial should be used, maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer

- **BY MOUTH**
  - Adult: 500 mg twice daily for at least 3 months, if there is no improvement after the first 3 months another oral antibacterial should be used, maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer

- **BY MOUTH**
  - Adult: 500 mg twice daily for at least 3 months, if there is no improvement after the first 3 months another oral antibacterial should be used, maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer

- **BY MOUTH**
  - Adult: 500 mg twice daily for at least 3 months, if there is no improvement after the first 3 months another oral antibacterial should be used, maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer

**INTERACTIONS**
- Appendix 1: tetracyclines

**SIDE-EFFECTS**
- Gastrointestinal discomfort - renal impairment
- Renal impairment. May exacerbate renal failure and should not be given to patients with renal impairment.

**PROFESSIONAL INFORMATION**
- Dental practitioners' formulary
- Oxytetracycline Tablets may be prescribed.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

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<td><strong>Tablet</strong></td>
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<tr>
<td>CAUTIONARY AND ADVISORY LABELS</td>
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<td><strong>Oxytetracycline (as Oxytetracycline dihydrate)</strong></td>
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<td>250 mg</td>
<td>Oxytetracycline 250mg tablets</td>
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**Tetracycline**

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia, mycoplasma)
- **BY MOUTH**
  - Child 12-17 years: 250 mg 4 times a day, increased if necessary to 500 mg 3–4 times a day, increased dose used in severe infections
Tigecycline

**DRUG ACTION** Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, but *Pseudomonas aeruginosa* and many strains of *Proteus spp* are resistant to tigecycline.

**INDICATIONS AND DOSE**

Complicated skin and soft tissue infections (when other antibiotics are not suitable).

Complicated intra-abdominal infections (when other antibiotics are not suitable).

**Caution:** Abscess, appetite decreased, diarrhoea, dizziness, gastrointestinal discomfort, headache, healing impaired, hyperbilirubinaemia, hypoglycaemia, hypoproteinaemia, increased risk of infection, nausea, sepsis, skin reactions, vomiting.

**Uncommon** Hepatic disorders, pancreatitis, thrombocytopenia, thrombophlebitis.

**Frequency not known** Acidosis, azotaemia, hyperphosphataemia, hypofibrinogenaemia, idiopathic intracranial hypertension, photosensitivity reaction, pseudomembranous enterocolitis, severe cutaneous adverse reactions (SCARs), tooth discoloration.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Side-effects similar to those of the tetracyclines can potentially occur.
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients hypersensitive to tetracyclines.
- **PREGNANCY** Tetracyclines should not be given to pregnant women; effects on skeletal development have been documented in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth, and maternal hepatotoxity has been reported with large parenteral doses.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.
- **Dose adjustments** Manufacturer advises dose reduction to 25 mg every 12 hours following the loading dose in severe impairment.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Tygacil®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute each vial with 5.3 mL infusion fluid to produce a 10 mg/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 30–60 minutes.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks: Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness.
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tigecycline (Non-proprietary)**
    - Tigecycline 50 mg Tigecycline 50mg powder for solution for infusion vials | 10 vial | £290.79 (Hospital only)

**ANTIBACTERIALS**

**Chloramphenicol**

**DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

Life threatening infections particularly those caused by *Haemophilus influenzae* Typhoid fever.

- **By mouth, or by intravenous injection, or by intravenous infusion**
  - Adult: 12.5 mg/kg every 6 hours, in exceptional cases dose can be doubled for severe infections such as sepsicaemia and meningitis, providing high doses reduced as soon as clinically indicated.

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058
- Associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections.

**PREGNANCY** Manufacturer advises avoid; neonatal ‘grey baby syndrome’ if used in third trimester.

**BREAST FEEDING** Manufacturer advises avoid; use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause ‘grey syndrome’.

**HEPATIC IMPAIRMENT** Avoid if possible—increased risk of bone–marrow depression.

**Dose adjustments** Reduce dose.

**MONITORING REQUIREMENTS**

- Plasma concentration monitoring preferred in the elderly.
- Recommended peak plasma concentration (approx. 2 hours after administration by mouth, intravenous injection or infusion) 10–25 mg/litre; pre-dose (‘trough’*) concentration should not exceed 15 mg/litre.
- Blood counts required before and periodically during treatment.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion, give intermittently or via drip tubing in Glucose 5% or Sodium Chloride 0.9%.

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**Daptomycin**

**DRUG ACTION** Daptomycin is a lipopeptide antibacterial with a spectrum of activity similar to vancomycin but its efficacy against enterococci has not been established. It needs to be given with other antibacterials for mixed infections involving Gram-negative bacteria and some anaerobes.

**INDICATIONS AND DOSE**

**Complicated skin and soft-tissue infections caused by Gram-positive bacteria**

- **BY INTRAVENOUS INFUSION**
  - **Child 12-23 months:** 10 mg/kg once daily for up to 14 days, alternatively 12 mg/kg once daily, higher dose only if associated with *Staphylococcus aureus* bacteremia—duration of treatment in accordance with risk of complications in individual patients
  - **Child 2-6 years:** 9 mg/kg once daily for up to 14 days, alternatively 12 mg/kg once daily, higher dose only if associated with *Staphylococcus aureus* bacteremia—duration of treatment in accordance with risk of complications in individual patients
  - **Child 7-11 years:** 7 mg/kg once daily for up to 14 days, alternatively 9 mg/kg once daily, higher dose only if associated with *Staphylococcus aureus* bacteremia—duration of treatment in accordance with risk of complications in individual patients
  - **Child 12-17 years:** 5 mg/kg once daily for up to 14 days, alternatively 7 mg/kg once daily, higher dose only if associated with *Staphylococcus aureus* bacteremia—duration of treatment in accordance with risk of complications in individual patients

**Complicated skin and soft-tissue infections caused by Gram-positive bacteria**

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - **Adult:** 4 mg/kg once daily for 7–14 days or longer if necessary, alternatively 6 mg/kg once daily, higher dose only if associated with *Staphylococcus aureus* bacteremia—duration of treatment may need to be longer than 14 days in accordance with risk of complications in individual patients

**Right-sided infective endocarditis caused by *Staphylococcus aureus* (administered on expert advice)**

- **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - **Adult:** 6 mg/kg once daily, duration of treatment in accordance with official recommendations

**CAUTIONS** Obesity (limited information on safety and efficacy)

**INTERACTIONS** → Appendix 1: daptomycin

**SIDE-EFFECTS**

- **Common or very common** Anaemia · anxiety · asthenia · constipation · diarrhoea · dizziness · fever · flatulence · gastrointestinal discomfort · headache · hypertension · hypotension · increased risk of infection · insomnia · nausea · pain · skin reactions · vomiting
- **Uncommon** Appetite decreased · arrhythmias · arthralgia · electrolyte imbalance · eosinophilia · flushing · glossitis · hyperglycaemia · muscle weakness · myalgia · myopathy · paraesthesia · renal impairment · taste altered · thrombocytosis · tremor · vertigo
- **Rare or very rare** Jaundice
- **Frequency not known** Acute generalised exanthematous pustulosis (AGEP) · antibiotic associated colitis · chills · cough · infusion related reaction · peripheral neuropathy · respiratory disorders · syncope

**SIDE-EFFECTS, FURTHER INFORMATION** If unexplained muscle pain, tenderness, weakness, or cramps develop during treatment, measure creatine kinase every 2 days; discontinue if unexplained muscular symptoms and creatine elevated markedly.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Present in milk in small amounts, but absorption from gastrointestinal tract negligible.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

**RENAL IMPAIRMENT**

- **In children** Manufacturer advises the dosage regimen has not been established—use with caution and monitor renal function regularly.
- **In adults** Manufacturer advises use only when potential benefit outweighs risk—higher risk of developing myopathy; monitor renal function regularly.

**Dose adjustments**

- **In adults** Use normal dose every 48 hours if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- **Manufacturer advises monitor plasma creatine phosphokinase (CPK) before treatment and then at least weekly during treatment; monitor CPK more frequently in patients at higher risk of developing myopathy, including those with renal impairment, taking other drugs associated with myopathy, or if CPK elevated more than 5 times upper limit of normal before treatment.**

**DIRECTIONS FOR ADMINISTRATION**

- **In children** For intravenous infusion, manufacturer advises give intermittently in Sodium Chloride 0.9%; reconstitute with Sodium Chloride 0.9% (350 mg in 7 mL, 500 mg in 10 mL); gently rotate vial without shaking; allow to stand for at least 10 minutes then rotate gently to dissolve; dilute requisite dose in 50 mL infusion fluid and give over 60 minutes for children aged 1–6 years and over 30 minutes for children aged 7–17 years.
- **In adults** For intravenous infusion, manufacturer advises give intermittently in Sodium Chloride 0.9%; reconstitute with Sodium Chloride 0.9% (350 mg in 7 mL, 500 mg in 10 mL); gently rotate vial without shaking; allow to stand for at least 10 minutes then rotate gently to dissolve; dilute requisite dose in 50 mL infusion fluid and give over 30 minutes. For intravenous injection, give over 2 minutes.

**HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for further information regarding storage after reconstitution and dilution.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

- **SMC No. 248/06**
  - In adults The *Scottish Medicines Consortium* has advised (April 2006) that daptomycin (Cubicin®) is accepted for restricted use within NHS Scotland for treatment of...
complicated skin and soft tissue infections in patients with known or suspected methicillin resistant *Staphylococcus aureus* infection and on the advice of local microbiologists or specialists in infectious disease.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

- **Daptomycin (Non-proprietary)**
  - Daptomycin 350 mg: Daptomycin 350mg powder for solution for infusion vials | 1 vial (£00) £60.00-£62.00 (Hospital only)
  - Daptomycin 500 mg: Daptomycin 500mg powder for solution for infusion vials | 1 vial (£00) £88.00-£88.57 (Hospital only)
- **Cubicin** (Merck Sharp & Dohme Ltd)
  - Cubicin 350 mg: Cubicin 350mg powder for concentrate for solution for infusion vials | 1 vial (£00) £62.00
  - Cubicin 500 mg: Cubicin 500mg powder for concentrate for solution for infusion vials | 1 vial (£00) £88.57 (Hospital only)

**Fidaxomicin**  **08-Feb-2019**

- **DRUG ACTION**  Fidaxomicin is a macrocyclic antibacterial that is poorly absorbed from the gastro-intestinal tract, and, therefore, it should not be used to treat systemic infections.

- **INDICATIONS AND DOSE**
  - **Clostridium difficile infection**
    - **BY MOUTH**
    - Adult: 200 mg every 12 hours for 10 days, limited clinical data is available on the use of fidaxomicin in severe or life-threatening *C. difficile* infection

- **CAUTIONS**  Inflammatory bowel disease - severe or life-threatening *C. difficile* infection

- **INTERACTIONS**  → Appendix 1: fidaxomicin

- **SIDE-EFFECTS**
  - **Common or very common**  Constipation - nausea - vomiting
  - **Uncommon**  Abdominal distension - appetite decreased - dizziness - dry mouth - flatulence - headache - skin reactions - taste altered
  - **Frequency not known**  Angioedema - dyspnoea - hypersensitivity

- **ALLERGY AND CROSS-SENSITIVITY**  Use with caution in macrolide hypersensitivity.

- **PREGNANCY**  Manufacturer advises avoid—no information available.

- **BREAST FEEDING**  Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**  Manufacturer advises caution in moderate to severe impairment—limited information available.

- **RENAI IMPAIRMENT**  Manufacturer advises caution in severe impairment—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - SMC No. 791/12
      - The Scottish Medicines Consortium has advised (July 2012) that fidaxomicin (Dificlir®) is accepted for restricted use within NHS Scotland to treat the first recurrence of *C. difficile* infection, on the advice of a microbiologist or specialist in infectious diseases.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Dificlir** (Astellas Pharma Ltd)
      - Fidaxomicin 200 mg  Dificlir 200mg tablets | 20 tablet (£00) £1,350.00

**Fosfomycin**  **25-Apr-2019**

- **DRUG ACTION**  Fosfomycin, a phosphonic acid antibacterial, is active against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* and *Enterobacteriaceae.*

- **INDICATIONS AND DOSE**
  - **Acute uncomplicated lower urinary-tract infections**
    - **BY MOUTH USING GRANULES**
      - Adult: 3 g for 1 dose
  - **Prophylaxis of urinary-tract infections in transurethral surgical procedures**
    - **BY MOUTH USING GRANULES**
      - Adult: 3 g, to be given 3 hours before surgery. Dose may be repeated once, 24 hours after surgery
  - **Osteomyelitis when first-line treatments are inappropriate or ineffective**
    - **Hospital-acquired lower respiratory-tract infections when first-line treatments are inappropriate or ineffective**
      - **BY INTRAVENOUS INFUSION**
        - Adult: 12–24 g daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms
  - **Complicated urinary-tract infections when first-line treatment ineffective or inappropriate**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 12–16 g daily in 2–3 divided doses (max. per dose 8 g)
  - **Bacterial meningitis when first-line treatment ineffective or inappropriate**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 16–24 g daily in 3–4 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

- **CAUTIONS**  With intravenous use: Cardiac insufficiency - elderly (high doses) - hyperaldosteronism - hypernatraemia - hypertension - pulmonary oedema

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Common or very common**  Abdominal pain - diarrhoea - headache - nausea - vomiting
  - **Uncommon**  Skin reactions
  - **Frequency not known**  Antibiotic associated colitis

- **SPECIFIC SIDE-EFFECTS**
  - **Common or very common**  With oral use: Dizziness - vulvovaginal infection
  - **Uncommon**  With parenteral use: Appetite decreased - dyspnoea - electrolyte imbalance - fatigue - oedema - taste altered - vertigo
  - **Rare or very rare**  With parenteral use: Asthmatic attack - anaphylaxis - anaphylactoid reaction - angioedema - angioneurotic oedema - anaphylactic shock - urticaria - vasculitis
  - **Frequency not known**  With parenteral use: Bone marrow disorders - eosinophilia - hepatic disorders - visual impairment

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**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—present in milk.

**RENAL IMPAIRMENT**
- With oral use Avoid oral treatment if eGFR less than 10 mL/minute/1.73 m².
- With intravenous use Use intravenous treatment with caution if eGFR 40–80 mL/minute/1.73 m² and consult product literature for dose if eGFR less than 40 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**
- With intravenous use Monitor electrolytes and fluid balance.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous infusion (Fomicyt®), give intermittently in Glucose 5% or 10% or Water for Injections; reconstitute each 2-g vial with 50 mL infusion fluid; give 2 g over 15 minutes.
- With oral use Manufacturer advises granules should be taken on an empty stomach (about 2–3 hours before or after a meal), preferably before bedtime and after emptying the bladder. The granules should be dissolved into a glass of water and taken immediately.

**PRESCRIBING AND DISPENSING INFORMATION**
- Doses expressed as Fusidic acid base.

**NATIONAL FUNDING/ACCESS DECISIONS**
- Scottish Medicines Consortium (SMC) decisions
  - SMC No. 1033/15
    - The Scottish Medicines Consortium has advised (March 2015) that Fosfomycin (Fomicyt®) is accepted for restricted use within NHS Scotland; initiation should be restricted to microbiologists or infectious disease specialists.
  - SMC No. 1163/16
    - The Scottish Medicines Consortium has advised (September 2016) that Fosfomycin trometamol (Monuril®) is accepted for use within NHS Scotland for the treatment of acute lower uncomplicated urinary tract infections, caused by pathogens sensitive to Fosfomycin in adult and adolescent females and for prophylaxis in diagnostic and surgical transurethral procedures.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

**ELECTROLYTES:** May contain Sodium

- Fomicyt (Nordic Pharma Ltd)
  - Fosfomycin (as Fosfomycin sodium) 2 gram Fomicyt 2g powder for solution for infusion vials | 10 vial (BOL) £150.00
  - Fosfomycin (as Fosfomycin sodium) 4 gram Fomicyt 4g powder for solution for infusion vials | 10 vial (BOL) £300.00

**Granules**

**CAUTIONARY AND ADVISORY LABELS**: May contain Sucrose

- Fosfomycin (Non-proprietary)
  - Fosfomycin (as Fosfomycin trometamol) 3 gram Fosfomycin 3g granules sachets | 1 sachet (BOL) £75.45 DT + £4.86
- Monuril (Profile Pharma Ltd)
  - Fosfomycin (as Fosfomycin trometamol) 3 gram Monuril 3g granules sachets | 1 sachet (BOL) £4.86 DT + £4.86

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**Fusidic acid**

**DRUG ACTION** Fusidic acid and its salts are narrow-spectrum antibiotics used for staphylococcal infections.

**INDICATIONS AND DOSE**

**Staphylococcal skin infection**
- **BY MOUTH USING TABLETS**
  - Child 12–17 years: 250 mg every 12 hours for 5–10 days, dose expressed as sodium fusidate
  - Adult: 250 mg every 12 hours for 5–10 days, dose expressed as sodium fusidate

**SIDE-EFFECTS**

- **GENERAL SIDE-EFFECTS**
  - **Uncommon** Skin reactions
  - **Common or very common**
    - With intravenous use Dizziness, drowsiness, hepatic disorders, hyperbilirubinaemia, thrombophlebitis, vascular pain (reduced if given via central vein)
    - With oral use Diarrhoea, dizziness, drowsiness, gastrointestinal discomfort, nausea, vomiting
  - **Rare**
    - With topical use Angioedema, conjunctivitis
  - **Frequency not known**
    - With intravenous use Agranulocytosis, anaemia, leucopenia, neutropenia, pancytopenia, renal failure, rhabdomyolysis, thrombocytopenia
    - With oral use Agranulocytosis, anaemia, hepatic disorders, hyperbilirubinaemia, leucopenia, neutropenia

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**DOSAGE AND ADMINISTRATION**

- **BY MOUTH USING TABLETS**
  - Child: Apply 3–4 times a day usually for 7 days
  - Adult: Apply 3–4 times a day

**Penicillin-resistant staphylococcal infection including osteomyelitis**

- **Staphylococcal endocarditis in combination with other antibacterials**
  - **BY MOUTH USING ORAL SUSPENSION**
    - Child 1–11 months: 15 mg/kg 3 times a day
    - Child 1–4 years: 250 mg 3 times a day
    - Child 5–11 years: 500 mg 3 times a day
    - Child 12–17 years: 750 mg 3 times a day
  - Adult: 750 mg 3 times a day

**Staphylococcal infections due to susceptible organisms**

- **BY INTRAVENOUS INFUSION**
  - Child (body-weight up to 50 kg): 6–7 mg/kg 3 times a day, dose expressed as sodium fusidate
  - Child (body-weight 50 kg and above): 500 mg 3 times a day, dose expressed as sodium fusidate
  - Adult (body-weight up to 50 kg): 6–7 mg/kg 3 times a day, dose expressed as sodium fusidate
  - Adult (body-weight 50 kg and above): 500 mg 3 times a day, dose expressed as sodium fusidate

**DOSE EQUIVALENCE AND CONVERSION**

- With oral use
  - Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets.
Linezolid

**Drug Action** Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including metillin-resistant Staphylococcus aureus (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.

**Indications and Dose**

Pneumonia (when other antibacterials e.g. a glycopeptide, such as vancomycin, cannot be used) (initiated under specialist supervision) / Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)

- **By Mouth**
  - Adult: 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days)

- **By Intravenous Infusion**
  - Adult: 600 mg every 12 hours

**Important Safety Information**

CHM Advice (Optic Neuropathy)

Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:

- patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
- patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;
- visual function should be monitored regularly if treatment is required for longer than 28 days.

**Blood Disorders**

Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

**Caution**

Acute confusional states - bipolar depression - carcinoid tumour - elderly (increased risk of blood disorders) - history of seizures - phaeochromocytoma - schizophrenia - thyrotoxicosis - uncontrolled hypertension

**Caution, Further Information**

Close observation. Unless close observation and blood pressure monitoring possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states.

**Interactions** Appendix 1: linezolid

**Side-Effects**

- Common or very common Anaemia - constipation - diarrhoea - dizziness - gastrointestinal discomfort -
Tedizolid

07-Feb-2019

**DRUG ACTION** Tedizolid is an oxazolidinone antibacterial, which inhibits bacterial protein synthesis.

**INDICATIONS AND DOSE**

Treatment of acute bacterial skin and skin structure infections

- **By intravenous infusion, or by mouth**
- **Adult:** 200 mg once daily for 6 days, patients should be switched from the intravenous to the oral route when clinically appropriate

**CAUTIONS** Neutropenia—limited clinical experience; patients aged 75 years and over—limited clinical experience

**INTERACTIONS** → Appendix 1: tedizolid

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Diarrhoea, dizziness, fatigue, headache, nausea, skin reactions, vomiting
- **Uncommon** Abcess, alopecia, antibiotic associated colitis, anxiety, arthralgia, bradycardia, chills, constipation, cough, dehydration, diabetic control impaired, drowsiness, dry mouth, fever, gastrointestinal discomfort, gastrointestinal disorders, haematochezia, hyperhidrosis, hyperkalaemia, increased risk of infection, irritability, limb discomfort, lymphadenopathy, muscle spasms, nasal dryness, pain, peripheral oedema, pulmonary congestion, sensation abnormal, sleep disorders, taste altered, tremor, urine odour abnormal, vasodilation, vision blurred, vitreous floater, vulvovaginal pruritus

**SPECIFIC SIDE-EFFECTS**

- **Uncommon**
  - With intravenous use: Infusion related reaction
  - **CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception in women of childbearing potential; an additional method of contraception is advised in women taking hormonal contraceptives—effectiveness may be reduced
  - **PREGNANCY** Manufacturer advises avoid—fetal developmental toxicity in animal studies
  - **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies
  - **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Sivextro®) give intermittently in Sodium Chloride 0.9%; reconstitute each 200 mg vial with 4 mL Water for Injections, then dilute reconstituted solution in 250 mL sodium chloride 0.9%; give over approx. 1 hour
  - **POTENTIAL AND CARER ADVICE** Optic neuropathy. Although neuropathy (peripheral and optic) has not been reported in patients treated with tedizolid, manufacturer advises patients and carers are warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately; patients should be evaluated promptly, and referred to an ophthalmologist if necessary
  - **Missed doses** Manufacturer advises that if a dose is more than 16 hours late, the missed dose should not be taken and the next dose should be taken at the normal time
  - **DRIVING AND SKILLED TASKS** Patients and carers should be counselled on the effects on driving and skilled tasks—increased risk of dizziness and fatigue
  - **NATIONAL FUNDING/ACCESS DECISIONS** Scottish Medicines Consortium (SMC) decisions SMC No. 1080/15
  - The Scottish Medicines Consortium has advised (August 2015) that tedizolid (Sivextro®) is accepted for restricted use within NHS Scotland as an alternative oxazolidinone antibacterial for the treatment of acute bacterial skin and skin structure infections caused by Gram-positive *Staphylococcus aureus* (specifically methicillin-resistant *Staphylococcus aureus* [MRSA]) isolates, on the specific advice of local microbiologists or specialists in infectious disease

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

**EXCIPIENTS:** May contain Glucose ELECTROLYTES: May contain Sodium

- **Linezolid (Non-proprietary)**
  - Linezolid 2 mg per 1 ml Linezolid 600mg/300ml infusion bags 10 bag £445.00–£515.20 | (Hospital only)

- **Zyvox (Pfizer Ltd)**
  - Linezolid 2 mg per 1 ml Zyvox 600mg/300ml infusion bags 10 bag £445.00

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 9, 10

**EXCIPIENTS:** May contain Aspartame

- **Zyvox (Pfizer Ltd)**
  - Linezolid 20 mg per 1 ml Zyvox 100mg/5ml granules for oral suspension 150 ml £222.50 DT £222.50

**Tablet**

CAUTIONARY AND ADVISORY LABELS 9, 10

- **Linezolid (Non-proprietary)**
  - Linezolid 600 mg Linezolid 600mg tablets 10 tablet £82.12–£445.00 DT £327.22

- **Zyvox (Pfizer Ltd)**
  - Linezolid 600 mg Zyvox 600mg tablets 10 tablet £445.00 DT £327.22
**Tablet**
- **Sivextro (Merck Sharp & Dohme Ltd)**

**Tedizolid phosphate 200 mg**
- Sivextro 200mg tablets | 6 tablet **PO** £8.62.00

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**Trimethoprim**

- **INDICATIONS AND DOSE**
  - **Urinary-tract infections** | **Respiratory-tract infections**
    - **BY MOUTH**
      - Child 4-5 weeks: 4 mg/kg twice daily (max. per dose 200 mg)
      - Child 6 weeks–5 months: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 25 mg twice daily
      - Child 6 months–5 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 50 mg twice daily
      - Child 6–11 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 100 mg twice daily
      - Child 12–17 years: 200 mg twice daily
      - Adult: 200 mg twice daily

  - **Prophylaxis of urinary-tract infection (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)**
    - **BY MOUTH**
      - Child 4–5 weeks: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night
      - Child 6 weeks–5 months: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 12.5 mg once daily, dose to be taken at night
      - Child 6 months–5 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 25 mg once daily, dose to be taken at night
      - Child 6–11 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 50 mg once daily, dose to be taken at night
      - Child 12–17 years: 100 mg once daily, dose to be taken at night
      - Adult: 100 mg once daily, dose to be taken at night

  - **Treatment of mild to moderate Pneumocystis jirovecii (Pneumocystis carinii) pneumonia in patients who cannot tolerate co-trimoxazole (in combination with dapsone)**
    - **BY MOUTH**
      - Child: 5 mg/kg every 6–8 hours
      - Adult: 5 mg/kg every 6–8 hours

- **Acne resistant to other antibacterials**
  - **BY MOUTH**
  - Adult: 300 mg twice daily

- **Prostatitis**
  - Adult: (consult product literature)

- **Shigellosis | Invasive salmonella infection**
  - **BY MOUTH**
  - Adult: (consult product literature)

- **UNLICENSED USE**
  - Not licensed for treatment of pneumocystis pneumonia.
  - In children Not licensed for use in children under 6 weeks.
  - In adults Not licensed for treatment of acne resistant to other antibacterials.

- **CONTRA-INDICATIONS**
  - Blood dyscrasias

- **CAUTIONS**
  - Elderly: Acute porphyrias p. 1058 • predisposition to folate deficiency

- **INTERACTIONS**
  - Appendix 1: trimethoprim

- **SIDE-EFFECTS**
  - Common or very common: Diarrhoea • electrolyte imbalance • fungal overgrowth • headache • nausea • skin reactions • vomiting
  - Rare or very rare: Agranulocytosis • angioedema • anxiety • appetite decreased • arthralgia • behaviour abnormal • bone marrow disorders • confusion • constipation • cough • depression • dizziness • dyspnoea • eosinophilia • erythema nodosum • fever • haemolysins • haemolytic anaemia • haemorrhage • hallucination • hepatic disorders • hypoglycaemia • lethargy • leucopenia • meningitis aseptic • movement disorders • myalgia • neutropenia • oral disorders • pancreatitis • paraesthesia • peripheral neuritis • photosensitivity reaction • pseudomembranous enterocolitis • renal impairment • seizure • severe cutaneous adverse reactions (SCARs) • sleep disorders • syncope • systemic lupus erythematosus (SLE) • thrombocytopenia • tinnitus • tremor • uveitis • vasculitis • vertigo • wheezing

- **Frequency not known**
  - Gastrointestinal disorder • megaloblastic anaemia • methaemoglobinemia

- **PREGNANCY**
  - Teratogenic risk in first trimester (folate antagonist). Manufacturers advise avoid during pregnancy.

- **BREAST FEEDING**
  - Present in milk—short-term use not known to be harmful.

- **RENAL IMPAIRMENT**
  - **Dose adjustments**
    - In adults
      - Use half normal dose after 3 days if eGFR 15–30 mL/minute/1.73 m². Use half normal dose if eGFR less than 15 mL/minute/1.73 m².
    - In children
      - Use normal dose after 3 days if estimated glomerular filtration rate 15–30 mL/minute/1.73 m². Use half normal dose if estimated glomerular filtration rate less than 15 mL/minute/1.73 m².

  - **Monitoring**
    - Monitor plasma-trimethoprim concentration if eGFR less than 10 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Manufacturer recommends blood counts on long-term therapy (but evidence of practical value unsatisfactory).

- **PATIENT AND CARER ADVICE**
  - Blood disorders
    - On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

- **Medicines for Children leaflet: Trimethoprim for bacterial infections**
  - www.medicinesforchildren.org.uk/trimethoprim-bacterial-infections

- **MEDIcINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Oral suspension**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Trimethoprim (Non-proprietary)**
      - **Trimethoprim 10 mg per 1 ml**
        - Trimethoprim 50mg/5ml oral suspension sugar free
        - 100 ml **PO** £5.70 DT = £5.70
      - **Monotrim (Chemidex Pharma Ltd)**
        - **Trimethoprim 10 mg per 1 ml**
          - Monotrim 50mg/5ml oral suspension sugar-free
          - 100 ml **PO** £1.77 DT = £5.70

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Trimethoprim (Non-proprietary)**
      - **Trimethoprim 100 mg**
        - Trimethoprim 100mg tablets | 28 tablet **PO** £3.99 DT = £3.83
      - **Trimethoprim 200 mg**
        - Trimethoprim 200mg tablets | 6 tablet **PO** £2.15 DT = £0.38 | 14 tablet **PO** £9.99 DT = £0.89

  - Combinations available: **Co-trimoxazole**, p. 562

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ANTIMYCOBACTERIALS > RIFAMYCINS

Rifabutin

● INDICATIONS AND DOSE
Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count
- BY MOUTH
  - Adult: 300 mg once daily, also consult product literature

Treatment of non-tuberculous mycobacterial disease, in combination with other drugs
- BY MOUTH
  - Adult: 450–600 mg once daily for up to 6 months after cultures negative

Treatment of pulmonary tuberculosis, in combination with other drugs
- BY MOUTH
  - Adult: 150–450 mg once daily for at least 6 months

● CAUTIONS
Acute porphyrias p. 1058 - discoulours soft contact lenses

● INTERACTIONS
  - Appendix 1: rifabutin

● SIDE-EFFECTS
Agranulocytosis - anaemia - arthralgia - bronchospasm - chest pain - coarcal deposits - decreased leucocytes - dyspnoea - eosinophilia - fever - haemolysis - hepatic disorders - influenza like illness - myalgia - nausea - neutropenia - pancreatitis - skin reactions - thrombocytopenia - urine discolouration - uveitis (more common following high doses or concomitant use with drugs that increase plasma concentration) - vomiting

● ALLERGY AND CROSS-SENSITIVITY
Contra-indicated in patients with rifamycin hypersensitivity.

● CONCEPTION AND CONTRACEPTION
Important Rifabutin induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced; alternative family planning advice should be offered.

● PREGNANCY
Manufacturer advises avoid — no information available.

● BREAST FEEDING
Manufacturer advises avoid — no information available.

● HEPATIC IMPAIRMENT
Dose adjustments Reduce dose in severe impairment.

Monitoring In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months; blood counts should also be monitored in these patients.

● RENAL IMPAIRMENT
Dose adjustments Use half normal dose if eGFR less than 30 ml/minute/1.73 m².

● MONITORING REQUIREMENTS
  - Renal function should be checked before treatment.
  - Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However hepatic function should be monitored on prolonged therapy.
  - Blood counts should be monitored on prolonged therapy.
  - Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months. Blood counts should also be monitored in these patients.

● PRESCRIBING AND DISPENSING INFORMATION
If treatment interruption occurs, re-introduce with low dosage and increase gradually.

PATIENT AND CARER ADVICE
Soft contact lenses Patients or their carers should be advised that rifabutin discoulours soft contact lenses.

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise, jaundice develop.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule
CAUTIONARY AND ADVISORY LABELS 8, 14
- Mycobutin (Pfizer Ltd)
  - Rifabutin 150 mg Mycobutin 150mg capsules | 30 capsule £9.38

Rifaximin

● DRUG ACTION
Rifaximin is a rifamycin that is poorly absorbed from the gastro-intestinal tract, and, therefore, should not be used to treat systemic infections.

● INDICATIONS AND DOSE
Travellers’ diarrhoea that is not associated with fever, bloody diarrhoea, blood or leucocytes in the stool, or 8 or more unformed stools in the previous 24 hours
- BY MOUTH
  - Adult: 200 mg every 8 hours for 3 days

Reduction in recurrence of hepatic encephalopathy
- BY MOUTH
  - Adult: 550 mg twice daily

● CONTRA-INDICATIONS
Intestinal obstruction

● INTERACTIONS
  - Appendix 1: rifaximin

● SIDE-EFFECTS
  - Common or very common Arthralgia - ascites - constipation - depression - dizziness - dyspnoea - gastrointestinal discomfort - gastrointestinal disorders - headaches - muscle complaints - nausea - oedema - skin reactions - vomiting
  - Rare or very rare Hypertension - hypotension
  - Frequency not known Angioedema - syncope - thrombocytopenia - urine discolouration

● ALLERGY AND CROSS-SENSITIVITY
Contra-indicated if history of rifamycin hypersensitivity.

● PREGNANCY
Manufacturer advises avoid — toxicity in animal studies.

● BREAST FEEDING
Unlikely to be present in milk in significant amounts, but manufacturer advises avoid.

● HEPATIC IMPAIRMENT
  - When used for Hepatic encephalopathy Manufacturer advises caution in severe impairment (risk of increased exposure).

● PRESCRIBING AND DISPENSING INFORMATION
Not recommended for diarrhoea associated with invasive organisms such as Campylobacter and Shigella.

www.getintopharma.com
Prophylaxis should continue for [unlicensed indication] for exposure prophylaxis extensive oedema, or lesions of the head or neck. Amoxicillin p.

Diseases, London (telephone (020) 3456 7890).

The World Health Organization has made recommendations to overcome the problem of dapsone p. 577 resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are dapsone, rifampicin p. 582, and clofazimine below. Other drugs with significant activity against Mycobacterium leprae include ofloxacin p. 561, minocycline p. 566 and clarithromycin p. 538, but none of these are as active as rifampicin; at present they should be reserved as second-line drugs for leprosy.

A three-drug regimen is recommended for multibacillary leprosy (lepromatous, borderline-lepromatous, and borderline leprosy) and a two-drug regimen for paucibacillary leprosy (borderline-tuberculoid, tuberculoid, and indeterminate).

Multibacillary leprosy should be treated with a combination of rifampicin, dapsone and clofazimine for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum lepromatous) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone p. 578 should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide p. 962 [unlicensed] is also useful in patients who have become corticosteroid dependent, but it should be used only under specialist supervision. Thalidomide is teratogenic and, therefore, contra-indicated in pregnancy; it must not be given to women of child-bearing potential unless they comply with a pregnancy prevention programme. Increased doses of clofazimine are also useful.

Paucibacillary leprosy should be treated with rifampicin and dapsone for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

Neither the multibacillary nor the paucibacillary antileprosy regimen is sufficient to treat tuberculosis.

**ANTI-MYCOBACTERIALS**

**Clofazimine**

- **INDICATIONS AND DOSE**
  - Multibacillary leprosy in combination with rifampicin and dapsone (3-drug regimen) (administered on expert advice)
    - **BY MOUTH**
      - Adult: 300 mg once a month, to be administered under supervision and 50 mg daily, to be self-administered, alternatively 300 mg once a month, to be administered under supervision and 100 mg once daily on alternate days, to be self-administered
  - Lepromatous lepra reactions (administered on expert advice)
    - **BY MOUTH**
      - Adult: 300 mg daily for max. 3 months
  - Severe type II (erythema nodosum lepromatous) reactions (administered on expert advice)
    - **BY MOUTH**
      - Adult: 100 mg 3 times a day for one month, subsequent dose reductions are required, may take 4–6 weeks to attain full effect

- **CAUTIONS** Avoid if persistent abdominal pain and diarrhoea; may discolour soft contact lenses
- **INTERACTIONS** Appendix 1: clofazimine
- **SIDE-EFFECTS** Abdominal pain; appetite decreased; dry eye; eye discolouration; fatigue; gastrointestinal disorders; hair colour changes (reversible); headache; lymphadenopathy; nausea; photosensitivity reaction; red discoloration of body fluids; skin discoloration (including areas exposed to light); skin reactions; splenic infarction; urinary red; visual impairment; vomiting (hospitalise if persistent); weight decreased
- **PREGNANCY** Use with caution.

**2.1 Anthrax**

**Anthrax**

Treatment and post-exposure prophylaxis

Inhalation or gastro-intestinal anthrax should be treated initially with either ciprofloxacin p. 558 or, in patients over 12 years, doxycycline p. 564 [unlicensed indication] combined with one or two other antibacterials (such as amoxicillin p. 548, benzylpenicillin sodium p. 547, chloramphenicol p. 568, clarithromycin p. 538, clindamycin p. 535, imipenem with cilastatin p. 522, rifampicin p. 582 [unlicensed indication], and vancomycin p. 534). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed.

Cutaneous anthrax should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] for 7 days. Treatment may be switched to amoxicillin if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for post-exposure prophylaxis. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of *B. anthracis* is susceptible. Vaccination against anthrax may allow the duration of antibacterial prophylaxis to be shortened.

**2.2 Leprosy**

**Leprosy**

Management

Advice from a member of the Panel of Leprosy Opinion is essential for the treatment of leprosy (Hansen’s disease). Details can be obtained from the Hospital for Tropical Diseases, London (telephone (020) 3456 7890).

The World Health Organization has made recommendations to overcome the problem of dapsone p. 577 resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are rifampicin p. 582, and clofazimine below. Other drugs with significant activity against Mycobacterium leprae include ofloxacin p. 561, minocycline p. 566 and clarithromycin p. 538, but none of these are as active as rifampicin; at present they should be reserved as second-line drugs for leprosy.

A three-drug regimen is recommended for multibacillary leprosy (lepromatous, borderline-lepromatous, and borderline leprosy) and a two-drug regimen for paucibacillary leprosy (borderline-tuberculoid, tuberculoid, and indeterminate).

Multibacillary leprosy should be treated with a combination of rifampicin, dapsone and clofazimine for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum lepromatous) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone p. 578 should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide p. 962 [unlicensed] is also useful in patients who have become corticosteroid dependent, but it should be used only under specialist supervision. Thalidomide is teratogenic and, therefore, contra-indicated in pregnancy; it must not be given to women of child-bearing potential unless they comply with a pregnancy prevention programme. Increased doses of clofazimine are also useful.

Paucibacillary leprosy should be treated with rifampicin and dapsone for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

Neither the multibacillary nor the paucibacillary antileprosy regimen is sufficient to treat tuberculosis.

**ANTI-MYCOBACTERIALS**

**Clofazimine**

- **INDICATIONS AND DOSE**
  - Multibacillary leprosy in combination with rifampicin and dapsone (3-drug regimen) (administered on expert advice)
    - **BY MOUTH**
      - Adult: 300 mg once a month, to be administered under supervision and 50 mg daily, to be self-administered, alternatively 300 mg once a month, to be administered under supervision and 100 mg once daily on alternate days, to be self-administered
  - Lepromatous lepra reactions (administered on expert advice)
    - **BY MOUTH**
      - Adult: 300 mg daily for max. 3 months
  - Severe type II (erythema nodosum lepromatous) reactions (administered on expert advice)
    - **BY MOUTH**
      - Adult: 100 mg 3 times a day for one month, subsequent dose reductions are required, may take 4–6 weeks to attain full effect

- **CAUTIONS** Avoid if persistent abdominal pain and diarrhoea; may discolour soft contact lenses
- **INTERACTIONS** Appendix 1: clofazimine
- **SIDE-EFFECTS** Abdominal pain; appetite decreased; dry eye; eye discolouration; fatigue; gastrointestinal disorders; hair colour changes (reversible); headache; lymphadenopathy; nausea; photosensitivity reaction; red discoloration of body fluids; skin discoloration (including areas exposed to light); skin reactions; splenic infarction; urinary red; visual impairment; vomiting (hospitalise if persistent); weight decreased
- **PREGNANCY** Use with caution.
**BREAST FEEDING** May alter colour of milk; skin discoloration of infant.
**HEPATIC IMPAIRMENT** Use with caution.
**RENAL IMPAIRMENT** Use with caution.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

<table>
<thead>
<tr>
<th>Form</th>
<th>Details</th>
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<tr>
<td><strong>Tablet</strong></td>
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<tr>
<td><strong>Dapsone (Non-proprietary)</strong></td>
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<tr>
<td>Dapsone 50 mg</td>
<td>Dapsone 50mg tablets</td>
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<td>Dapsone 100 mg</td>
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### 2.3 Lyme disease

#### Description of condition

Lyme disease, also known as Lyme borreliosis, is an infection caused by bacteria called *Borrelia burgdorferi*. It is transmitted to humans by the bite of an infected tick. Ticks are mainly found in grassy and wooded areas including urban gardens and parks. Most tick bites do not cause Lyme disease, and the prompt and correct removal of the tick reduces the risk of infection.

Lyme disease usually presents with a characteristic erythema migrans rash. This usually becomes visible 1–4 weeks after a tick bite, but can appear from 3 days to 3 months, and last for several weeks. It may be accompanied by non-focal (non-organ-related) symptoms, such as fever, swollen glands, malaise, fatigue, neck pain or stiffness, joint or muscle pain, headache, cognitive impairment, or paraesthesia.

Other signs and symptoms of Lyme disease may also appear months or years after the initial infection and are typically characterised by focal symptoms (relating to at least 1 organ system). These include neurological (affecting cranial nerves, peripheral and central nervous systems), joint (Lyme arthritis, cardiac (Lyme carditis), or skin (acrodermatitis chronica atrophicans) manifestations.

#### Drug treatment

**ECG** Patients diagnosed with Lyme disease should be given treatment with an antibacterial drug; the choice of drug should be based on presenting symptoms. In patients who present with focal symptoms, a discussion with, or referral to, a specialist should be considered but should not delay treatment.

In patients presenting with *erythema migrans* rash with or without non-focal symptoms, oral doxycycline p. 564 [unlicensed indication] is recommended as first-line treatment. If doxycycline cannot be given, oral amoxicillin p. 548 should be used as an alternative. Oral azithromycin p. 536 [unlicensed indication] should be given if both doxycycline and amoxicillin p. 548 are unsuitable.

In patients presenting with focal symptoms of *cranial nerve or peripheral nervous system* involvement, oral doxycycline p. 564 [unlicensed indication] is recommended as first-line treatment. If doxycycline cannot be given, oral amoxicillin p. 548 should be used as an alternative.

In patients presenting with symptoms of *central nervous system* involvement, intravenous ceftriaxone p. 528 is recommended as first-line treatment. Oral doxycycline [unlicensed indication] should be used as an alternative if ceftriaxone p. 528 cannot be given, or when switching to oral antibacterial treatment.

In patients with symptoms of *Lyme arthritis* or *acrodermatitis chronica atrophicans*, oral doxycycline [unlicensed indication] is recommended as first-line treatment. If doxycycline cannot be given, oral amoxicillin p. 548 should be used as an alternative. Intravenous
In patients with symptoms of *Lyme carditis who are haemodynamically stable*, oral doxycycline [unlicensed indication] is recommended as first-line treatment. If doxycycline cannot be given, intravenous ceftriaxone p. 528 should be used as an alternative.

In patients with symptoms of *Lyme carditis who are haemodynamically unstable*, intravenous ceftriaxone p. 528 is recommended. Oral doxycycline [unlicensed indication] should be given when switching to oral antibacterial treatment. A

### Ongoing symptom management

If symptoms continue to persist or worsen after antibacterial treatment, patients should be assessed for possible alternative causes, re-infection with *Lyme disease*, treatment failure or non-adherence to previous antibacterial treatment, or progression to organ damage caused by *Lyme disease* (such as nerve palsy).

A second course of antibacterial treatment should be given to patients presenting with signs and symptoms of re-infection. In patients presenting with ongoing symptoms due to possible treatment failure, treatment with an alternative antibacterial drug should be considered. A third course of antibacterial treatment is not recommended, and further management should be discussed with a national reference laboratory or suitable specialist depending on symptoms (for example, a rheumatologist or neurologist).

### Useful Resources


## 2.4 Methicillin-resistant staphylococcus aureus

### MRSA

#### Management

Infection from *Staphylococcus aureus* strains resistant to meticillin [now discontinued] (meticillin-resistant *Staph. aureus*; MRSA) and to fluoroquinolone p. 554 can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin p. 582 or fusidic acid p. 571 should not be used alone because resistance may develop rapidly. A *tetracycline* alone or a combination of rifampicin and fusidic acid can be used for *skin and soft-tissue infections* caused by MRSA; clindamycin p. 535 alone is an alternative. A *glycopeptide* (e.g. vancomycin p. 534) can be used for severe skin and soft-tissue infections associated with MRSA; if a glycopeptide is unsuitable, linezolid p. 572 can be used on expert advice. As linezolid is not active against Gram-negative organisms, it can be used for mixed skin and soft-tissue infections only when other treatments are not available; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A combination of a glycopeptide and fusidic acid or a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial.

Tigecycline p. 568 and daptomycin p. 569 are licensed for the treatment of complicated skin and soft-tissue infections involving MRSA.

A *tetracycline* or clindamycin can be used for *bronchectasis* caused by MRSA. A *glycopeptide* can be used for *pneumonia* associated with MRSA; if a glycopeptide is unsuitable, linezolid can be used on expert advice. Linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms.

A *tetracycline* can be used for *urinary-tract infections* caused by MRSA; trimethoprim p. 574 or nitrofurantoin p. 590 are alternatives. A *glycopeptide* can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A *glycopeptide* can be used for *septicaemia* associated with MRSA.

See the management of *endocarditis, osteomyelitis, or septic arthritis* associated with MRSA.

Prophylaxis with vancomycin or teicoplanin p. 532 (alone or in combination with another antibacterial active against other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient’s MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

See eradication of nasal carriage of MRSA in Nose p. 1201.

## 2.5 Tuberculosis

### Treatment phases, overview

Active tuberculosis is treated in two phases—an *initial phase* using four drugs and a *continuation phase* using two drugs in fully sensitive cases. Treatment requires specialised knowledge and supervision, particularly where the disease involves resistant organisms or non-respiratory organs.

There are two regimens recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen should be used; the two regimens should not be used concurrently. Compliance with therapy is a major determinant of its success.

#### Initial phase

The concurrent use of four drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as fixed-dose, combination preparations unless one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of rifampicin p. 582, ethambutol hydrochloride p. 586, pyrazinamide p. 588 and isoniazid p. 587 (with pyridoxine hydrochloride p. 1080 for prophylaxis of isoniazid-induced neuropathy); modified according to drug susceptibility testing. Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for two months. Where a positive culture for *M. tuberculosis* has been obtained, but susceptibility results are not available after two months, treatment with rifampicin, ethambutol hydrochloride, isoniazid and pyrazinamide (with pyridoxine hydrochloride) should be continued until full susceptibility is confirmed, even if this is for longer than two months.
Streptomycin p. 520 is rarely used in the UK but it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced, or when patients cannot tolerate standard treatment.

**Continuation phase**

After the initial phase, daily treatment is continued for a further four months with rifampicin and isoniazid (preferably given as a combination preparation) with pyridoxine hydrochloride. Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

**Unsupervised treatment**

The unsupervised treatment regimen should be used for patients who are likely to take antituberculosis drugs reliably **without supervision**. Patients who are unable or unlikely to comply with daily administration of therapy should be treated with the regimen described under **Supervised Treatment**.

**Pregnancy and breast-feeding**

The standard unsupervised six month treatment regimen may be used during pregnancy. Streptomycin should not be given in pregnancy.

The standard unsupervised six month treatment regimen may be used during breast-feeding.

**Supervised treatment**

Drug administration should be **fully supervised** (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. If daily directly observed therapy is not possible, a supervised dosing schedule of three times a week should be considered. Regimens with a dosing schedule of fewer than three times a week should not be used.

Directly observed therapy should be offered to patients who:
- have a history of non-adherence;
- have previously been treated for tuberculosis;
- are in denial of the tuberculosis diagnosis;
- have multidrug-resistant tuberculosis;
- have a major psychiatric or cognitive disorder;
- have a history of homelessness, drug or alcohol misuse;
- are in prison, or have been in the past 5 years;
- are too ill to self-administer treatment;
- request directly observed therapy.

**Immunocompromised patients**

Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity.

Confirmed *M. tuberculosis* infection sensitive to first-line drugs should be treated with a standard six month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.

Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis for patients who are HIV-positive (see also **Latent tuberculosis** below); care is required in choosing the regimen and in avoiding potentially serious interactions. Starting antiretroviral treatment in the first two months of antituberculosis treatment increases the risk of immune reconstitution syndrome. Treatment for tuberculosis should not routinely exceed six months in patients who are HIV-positive, unless the tuberculosis has central nervous system involvement (in which case treatment should not routinely extend beyond twelve months).

Infection may also be caused by other mycobacteria e.g. *M. avium* complex, in which case specialist advice on management is needed.

**Extrapulmonary tuberculosis**

**Central nervous system tuberculosis**

Patients with active central nervous system tuberculosis should be offered treatment with rifampicin, ethambutol hydrochloride, isoniazid and pyrazinamide (with pyridoxine hydrochloride for prophylaxis of isoniazid-induced neuropathy) for two months. After completion of the initial treatment phase, rifampicin and isoniazid (with pyridoxine hydrochloride) should be continued for a further ten months. Treatment for tuberculosis meningitis should be offered if clinical signs and laboratory findings are consistent with the diagnosis, even if a rapid diagnostic test is negative.

An initial high dose of dexamethasone p. 675 or prednisolone p. 678 should be started at the same time as antituberculosis therapy, and then slowly withdrawn over 4–8 weeks.

Referral for surgery should be considered only in patients who have raised intracranial pressure.

**Pericardial tuberculosis**

An initial high dose of oral prednisolone should be offered to patients with active pericardial tuberculosis at the same time as initiation of antituberculosis therapy; it should then be slowly withdrawn over 2–3 weeks.

**Latent tuberculosis**

Clinicians should be aware that some patients with latent tuberculosis are at increased risk of developing active tuberculosis (such as patients who are HIV-positive, diabetic or receiving treatment with a tumour necrosis factor alpha inhibitor). These patients should be advised of the risks and symptoms of active tuberculosis.

**Note:** the risk of adverse events to chemoprophylaxis in patients aged over 35 years with a risk of hepatotoxicity is likely to be greater than the potential benefit of treating latent disease. **When indicated,** drug treatment should only be offered to patients aged 35–65 years if hepatotoxicity is not a concern. Treatment for latent tuberculosis is not usually indicated in patients over 65 years.

**Close contacts**

Anyone aged under 65 years who is a close contact (prolonged, frequent or intense contact, e.g. household contacts or partners) of a person with pulmonary or laryngeal drug-sensitive tuberculosis should be assessed for active disease, and if negative, offered chemoprophylaxis.

**Immunocompromised**

Patients who are immunocompromised, such as those with HIV or who have had a solid organ or allogeneic stem cell transplant, should be tested for latent tuberculosis using an appropriate method. Patients who test positive should then be assessed for active disease, and if negative, offered treatment for latent tuberculosis.

**Healthcare workers**

New NHS employees who are new entrants from a high incidence country should be offered appropriate testing for latent tuberculosis; those who are not new entrants from a high incidence country, but who will be in contact with patients or clinical materials should be offered appropriate testing for latent tuberculosis if prior BCG vaccination cannot be verified (see also BCG vaccine p. 1297).

Those who test positive should then be assessed for active disease, and if negative, offered treatment for latent tuberculosis.
### Recommended dosage for standard unsupervised 6-month treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin with isoniazid and pyrazinamide</td>
<td><strong>Adult:</strong>&lt;br&gt;body-weight up to 40 kg: 3 tablets daily for 2 months (initial phase), use <em>Rifater</em> tablets, preferably taken before breakfast;&lt;br&gt;body-weight 40-49 kg: 4 tablets daily for 2 months (initial phase), use <em>Rifater</em> tablets, preferably taken before breakfast;&lt;br&gt;body-weight 50-64 kg: 5 tablets daily for 2 months (initial phase), use <em>Rifater</em> tablets, preferably taken before breakfast;&lt;br&gt;body-weight 65 kg and above: 6 tablets daily for 2 months (initial phase), use <em>Rifater</em> tablets, preferably taken before breakfast.</td>
</tr>
<tr>
<td>Ethambutol hydrochloride</td>
<td><strong>Adult:</strong> 15 mg/kg once daily for 2 months (initial phase)</td>
</tr>
<tr>
<td>Rifampicin with isoniazid</td>
<td><strong>Adult:</strong>&lt;br&gt;body-weight up to 50 kg: 450/300 mg daily for 4 months (continuation phase after 2-month initial phase), use <em>Rifina®</em> 150/100 tablets, preferably taken before breakfast;&lt;br&gt;body-weight 50 kg and above: 600/300 mg daily for 4 months (continuation phase after 2-month initial phase), use <em>Rifina®</em> 300/150 tablets, preferably taken before breakfast.</td>
</tr>
</tbody>
</table>

or (if combination preparations not appropriate):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td><strong>Child:</strong> 10 mg/kg once daily (max. per dose 300 mg) for 6 months (initial and continuation phases)&lt;br&gt;<strong>Adult:</strong> 300 mg daily for 6 months (initial and continuation phases)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td><strong>Child:</strong>&lt;br&gt;body-weight up to 50 kg: 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 450 mg per day;&lt;br&gt;body-weight 50 kg and above: 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 600 mg per day&lt;br&gt;<strong>Adult:</strong>&lt;br&gt;body-weight up to 50 kg: 450 mg once daily for 6 months (initial and continuation phases);&lt;br&gt;body-weight 50 kg and above: 600 mg once daily for 6 months (initial and continuation phases)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td><strong>Child:</strong>&lt;br&gt;body-weight up to 50 kg: 35 mg/kg once daily for 2 months (initial phase); maximum 1.5 g per day;&lt;br&gt;body-weight 50 kg and above: 35 mg/kg once daily for 2 months (initial phase); maximum 2 g per day&lt;br&gt;<strong>Adult:</strong>&lt;br&gt;body-weight up to 50 kg: 1.5 g once daily for 2 months (initial phase);&lt;br&gt;body-weight 50 kg and above: 2 g once daily for 2 months (initial phase)</td>
</tr>
<tr>
<td>Ethambutol hydrochloride</td>
<td><strong>Child:</strong> 20 mg/kg once daily for 2 months (initial phase)&lt;br&gt;<strong>Adult:</strong> 15 mg/kg once daily for 2 months (initial phase)</td>
</tr>
</tbody>
</table>

### Recommended dosage for intermittent supervised 6-month treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td><strong>Child:</strong> 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)&lt;br&gt;<strong>Adult:</strong> 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td><strong>Child:</strong> 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)&lt;br&gt;<strong>Adult:</strong> 600-900 mg 3 times a week for 6 months (initial and continuation phases)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td><strong>Child:</strong>&lt;br&gt;body-weight up to 50 kg: 50 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase);&lt;br&gt;body-weight 50 kg and above: 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)&lt;br&gt;<strong>Adult:</strong>&lt;br&gt;body-weight up to 50 kg: 2 g 3 times a week for 2 months (initial phase);&lt;br&gt;body-weight 50 kg and above: 2.5 g 3 times a week for 2 months (initial phase)</td>
</tr>
<tr>
<td>Ethambutol hydrochloride</td>
<td><strong>Child:</strong> 30 mg/kg 3 times a week for 2 months (initial phase)&lt;br&gt;<strong>Adult:</strong> 30 mg/kg 3 times a week for 2 months (initial phase)</td>
</tr>
</tbody>
</table>
For healthcare workers who are immunocompromised, follow standard advice for testing and treatment (see *Immunocompromised above*).

**Chemoprophylaxis for latent tuberculosis**
Chemoprophylaxis involves use of either isoniazid p. 587 (with pyridoxine hydrochloride p. 1080) alone for six months (recommended if interactions with rifampicins are a concern) or rifampicin p. 582 and isoniazid (with pyridoxine hydrochloride) for three months (recommended when hepatotoxicity is a concern).

Choice of regimen is dependent on clinical factors, including age, risk of hepatotoxicity and possible drug interactions. Testing for HIV, hepatitis B and hepatitis C should be offered before starting antituberculosis treatment as this may affect choice of therapy.

Patients with severe liver disease should be treated under the care of a specialist team; careful monitoring of liver function is necessary in patients with non-severe liver disease, abnormal liver function, or who misuse alcohol or drugs.

See advice on immunisation against tuberculosis in BCG vaccine p. 1297.

**Treatment failure**
Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the patient. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist physician.

**Treatment interruptions**
A break in antituberculosis treatment of at least two weeks (during the initial phase) or missing more than 20% of prescribed doses is classified as treatment interruption. Re-establishing treatment appropriately following interruptions is key to ensuring treatment success without relapse, drug resistance or further adverse events. If an adverse reaction recurs upon re-introducing a particular drug, do not give that drug in future regimens and consider extending the total regimen accordingly.

**Treatment interruptions due to drug-induced hepatotoxicity**
Following treatment interruption due to drug-induced hepatotoxicity, all potential causes of hepatotoxicity should be investigated. Once hepatic function has recovered, antituberculosis therapy should be sequentially re-introduced at previous full doses over a period of no more than ten days, initially with ethambutol hydrochloride p. 586 and either isoniazid (with pyridoxine hydrochloride) or rifampicin.

In patients with severe or highly infectious tuberculosis who need to interrupt the standard regimen, consider continuing treatment with at least two drugs with low risk of hepatotoxicity, such as ethambutol hydrochloride and streptomycin p. 520 (with or without a quinoline, such as levofloxacin p. 559 or moxifloxacin p. 560), with ongoing monitoring by a liver specialist.

**Treatment interruptions due to cutaneous reactions**
If a patient with severe or highly infectious tuberculosis has a cutaneous reaction, consider continuing treatment with a combination of at least two drugs with low risk for causing cutaneous reactions, such as ethambutol hydrochloride and streptomycin, with monitoring by a dermatologist.

**Antituberculosis drugs**
Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculosis regimen unless there is a specific contra-indication.

Rifampicin, a rifamycin, is a key component of any antituberculosis regimen. Like isoniazid it should always be included unless there is a specific contra-indication.

During the first two months (‘initial phase’) of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease.

On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20–30% of patients.

Rifabutin p. 575, another rifamycin, is indicated for *prophylaxis* against *M. avium* complex infections in patients with a low CD4 count; it is also licensed for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis.

Pyrazinamide p. 588 is a bactericidal drug only active against intracellular dividing forms of *Mycobacterium tuberculosis*; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against *M. bovis*.

Ethambutol hydrochloride is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.

Streptomycin [unlicensed] is now rarely used in the UK except for resistant organisms.

**Drug-resistant tuberculosis**
Drug-resistant tuberculosis should be treated by a specialist physician with experience in such cases, and where appropriate facilities for infection-control exist. Multidrug-resistant tuberculosis (*resistance to isoniazid and rifampicin*, with or without any other resistance) requires treatment with at least six antituberculosis drugs to which the mycobacterium is likely to be sensitive. Testing for resistance to second-line drugs is recommended and treatment should be modified according to susceptibility. The risk of resistance is minimised by ensuring therapy is administered in the correct dose and combination for the prescribed duration.

Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include aminosalicylic acid p. 584, amikacin p. 518, capreomycin p. 585, cycloserine p. 585, newer macrolides (e.g. azithromycin p. 536 and clarithromycin p. 538), moxifloxacin and protonamide (prothionamide; no longer on UK market). Bedaquiline p. 585 and delamanid p. 586 are licensed for the treatment of multiple-drug resistant pulmonary tuberculosis. Bedaquiline has a long half-life.

**Single drug-resistant tuberculosis**
For single drug-resistance the following treatment regimens are recommended:

**Resistance to isoniazid:**
- First two months (initial phase): rifampicin, pyrazinamide and ethambutol hydrochloride
- Continue with (continuation phase): rifampicin and ethambutol hydrochloride for seven months (up to ten months for extensive disease)

**Resistance to pyrazinamide:**
- First two months (initial phase): rifampicin, ethambutol hydrochloride and isoniazid (with pyridoxine hydrochloride)
- Continue with (continuation phase): rifampicin and isoniazid (with pyridoxine hydrochloride) for seven months
** Resistance to ethambutol hydrochloride: **
- First two months (initial phase): rifampicin, pyrazinamide and isoniazid (with pyridoxine hydrochloride)
- Continue with (continuation phase): rifampicin and isoniazid (with pyridoxine hydrochloride) for four months

** Resistance to rifampicin below: **
- Offer treatment with at least six antituberculosis drugs to which the mycobacterium is likely to be sensitive.

** Management of tuberculosis in children **
Children are given isoniazid p.o. for 3–6 months followed by isoniazid and rifampicin during the next four months. However, care is needed in young children receiving ethambutol hydrochloride because of the difficulty in testing eyesight and in obtaining reports of visual symptoms.

** Antimycobacterials > Rifamycins **

** Rifampicin **

- Indications and dose
  - Brucellosis in combination with other antibiotics
  - Legionnaires disease in combination with other antibiotics
  - Serious staphylococcal infections in combination with other antibiotics
  - **By mouth, or by intravenous infusion**
  - Child 1–11 months: 5–10 mg/kg twice daily
  - Child 1–17 years: 10 mg/kg twice daily (max. per dose 600 mg)
  - Adult: 0.6–1.2 g daily in 2–4 divided doses

- Endocarditis in combination with other drugs
  - **By mouth, or by intravenous infusion**
  - Adult: 0.6–1.2 g daily in 2–4 divided doses

- Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment)(under expert supervision)
  - **By mouth**
  - Child: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)
  - Adult: 600–900 mg 3 times a week for 6 months (initial and continuation phases)

- Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)
  - **By mouth**
  - Child (body-weight up to 50 kg): 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 450 mg per day
  - Child (body-weight 50 kg and above): 15 mg/kg once daily for 6 months (initial and continuation phases); maximum 600 mg per day
  - Adult (body-weight up to 50 kg): 450 mg once daily for 6 months (initial and continuation phases)
  - Adult (body-weight 50 kg and above): 600 mg once daily for 6 months (initial and continuation phases)

** Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, in combination with isoniazid **
- **By mouth**
  - Child 1–11 years (body-weight up to 50 kg): 15 mg/kg daily for 3 months; maximum 450 mg per day
  - Child 1–11 years (body-weight 50 kg and above): 15 mg/kg daily for 3 months; maximum 600 mg per day
  - Child 12–17 years (body-weight up to 50 kg): 450 mg daily for 3 months
  - Child 12–17 years (body-weight 50 kg and above): 600 mg daily for 3 months
  - Adult (body-weight up to 50 kg): 450 mg daily for 3 months
  - Adult (body-weight 50 kg and above): 600 mg daily for 3 months

** Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, who are isoniazid-resistant **
- **By mouth**
  - Child 1 month–11 years (body-weight up to 50 kg): 15 mg/kg daily for 6 months; maximum 450 mg per day
  - Child 1 month–11 years (body-weight 50 kg and above): 15 mg/kg daily for 6 months; maximum 600 mg per day
  - Child 12–17 years (body-weight up to 50 kg): 450 mg daily for 6 months
  - Child 12–17 years (body-weight 50 kg and above): 600 mg daily for 6 months

** Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, who are isoniazid-resistant and under 35 years **
- **By mouth**
  - Adult 18–34 years (body-weight up to 50 kg): 450 mg daily for 6 months
  - Adult 18–34 years (body-weight 50 kg and above): 600 mg daily for 6 months

** Prevention of secondary case of Haemophilus influenzae type b disease **
- **By mouth**
  - Child 1–2 months: 10 mg/kg once daily for 4 days
  - Child 3 months–11 years: 20 mg/kg once daily (max. per dose 600 mg) for 4 days
  - Child 12–17 years: 600 mg once daily for 4 days
  - Adult: 600 mg once daily for 4 days

** Prevention of secondary case of meningococcal meningitis **
- **By mouth**
  - Child 1–11 months: 5 mg/kg every 12 hours for 2 days
  - Child 1–11 years: 10 mg/kg every 12 hours (max. per dose 600 mg), for 2 days
  - Child 12–17 years: 600 mg every 12 hours for 2 days
  - Adult: 600 mg every 12 hours for 2 days

** Multibacillary leprosy in combination with dapsone and clofazimine (3-drug regimen) > Paucibacillary leprosy in combination with dapsone (2-drug regimen) **
- **By mouth**
  - Adult (body-weight up to 35 kg): 450 mg once a month, supervised administration
  - Adult (body-weight 35 kg and above): 600 mg once a month, supervised administration

** Contra-indications **
- Acute porphyrias p. 1058: jaundice

** Precautions **
- Discourages soft contact lenses

** Interactions **
- Appendix 1: rifampicin

** Side-effects **
- Common or very common: Nausea, thrombocytopenia, vomiting
- Uncommon: Diarrhoea, leucopenia
- Frequency not known: Abdominal discomfort, acute kidney injury, adrenal insufficiency, agranulocytosis, appetite decreased, disseminated intravascular coagulation, dysphoria, eosinophilia, flushing, haemolytic anaemia, hepatitis, hypersensitivity, influenza, intracranial haemorrhage, menstrual disorder, muscle weakness, myopathy, oedema, pseudomembranous enterocolitis, severe cutaneous adverse reactions (SCARs), shock, skin reactions, sputum discolouration, sweat discolouration, teardiscolouration, urine discolouration, vasculitis, wheezing

** Specific Side-effects **
- With intravenous use: Bone pain, gastrointestinal disorder, hyperbilirubinaemia, psychotic disorder
- With oral use: Psychosis

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SIDENOTES, FURTHER INFORMATION

Side-effects that mainly occur with intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, thrombocytopenic purpura, and acute renal failure. Discontinue if serious side-effects develop.

- ALLERGY AND CROSS-SENSITIVITY
  Contra-indicated in patients with rifamycin hypersensitivity.

- CONCEPTION AND CONTRACEPTION
  Important - effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered.

- PREGNANCY
  Manufacturers advise very high doses teratogenic in animal studies in first trimester; risk of increase gradually.

- BREAST FEEDING
  Guideline advice - breast feeding is not contraindicated; manufacturers advise caution.

- HEPATIC IMPAIRMENT
  Monitor liver function weekly for two weeks, then every two weeks for the next six weeks.

- MONITORING REQUIREMENTS
  - Renal function should be checked before treatment.
  - Hepatic function should be checked before treatment. If there is no evidence of liver disease (pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, liver function should be monitored on prolonged therapy.
  - Blood counts should be monitored in patients on prolonged therapy.
  - In adults with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 weeks. Blood counts should also be monitored in these patients.

- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use in adults. For intravenous infusion (Rifadin®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute with solvent provided then dilute with 500 mL infusion fluid; give over 2–3 hours.
  - With intravenous use in children. Displacement value may be significant, consult local reconstitution guidelines; reconstitute with solvent provided. May be further diluted with Glucose 5% or Sodium chloride 0.9% to a final concentration of 1.2 mg/mL. Infuse over 2–3 hours.

- PRESCRIBING AND DISPENSING INFORMATION
  If treatment interruption occurs, re-introduce with low dosage and increase gradually.
  - Flavours of syrup may include raspberry.
  - With oral use in children. In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may also need to be recalculated to allow for weight gain in younger children.

- PATIENT AND CARER ADVICE
  - Soft contact lenses. Patients or their carers should be advised that rifampicin discolours soft contact lenses.
  - Hepatic disorders. Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

- Oral suspension
  - CAUTIONARY AND ADVISORY LABELS 8, 14, 23
  - Excipients: May contain Sucrose.
  - Rifadin® (Sanofi)
  - Rifampicin 20 mg per 1 mL. Rifadin 100mg/5mL syrup | 120 mL [PO] £4.27 DT + £4.27
  - Capsule
  - CAUTIONARY AND ADVISORY LABELS 8, 14, 23
  - Rifampicin (Non-proprietary)
  - Rifampicin 150 mg Rifampicin 150mg capsules | 100 capsule [PO] £50.49 DT + £50.49
  - Rifampicin 300 mg Rifampicin 300mg capsules | 100 capsule [PO] £123.89 DT + £123.89
  - Rifadin® (Sanofi)
  - Rifampicin 150 mg Rifadin 150mg capsules | 100 capsule [PO] £18.32 DT + £50.49
  - Rifampicin 300 mg Rifadin 300mg capsules | 100 capsule [PO] £36.63 DT + £123.89
  - Rimactane (Sandoz Ltd)
  - Rifampicin 300 mg Rimactane 300mg capsules | 60 capsule [PO] £21.98

- Powder and solvent for solution for infusion
  - Electrolytes: May contain Sodium.
  - Rifadin® (Sanofi)
  - Rifampicin 600 mg Rifadin 600mg powder and solvent for solution for infusion vials | 1 vial [PO] £3.20

Rifampicin with ethambutol, isoniazid and pyrazinamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, rifampicin p. 582, ethambutol hydrochloride p. 586, isoniazid p. 587, pyrazinamide p. 588.

- INDICATIONS AND DOSE
  - Initial treatment of tuberculosis
  - By mouth
  - Adult (body-weight 30–39 kg): 2 tablets daily for 2 months (initial phase).
  - Adult (body-weight 40–54 kg): 3 tablets daily for 2 months (initial phase).
  - Adult (body-weight 55–69 kg): 4 tablets daily for 2 months (initial phase).
  - Adult (body-weight 70 kg and above): 5 tablets daily for 2 months (initial phase).

- DOSE EQUIVALENCE AND CONVERSION
  - Tablet quantities refer to the number of Voractiv® Tablets which should be taken. Each Voractiv® Tablet contains ethambutol hydrochloride 275 mg, isoniazid 75 mg, pyrazinamide 400 mg and rifampicin 150 mg.

- CAUTIONS
  - Peripheral neuropathy. The risk of peripheral neuropathy may be increased by high doses of isoniazid; pyridoxine should, therefore, be considered for those receiving Voractiv® 5 tablets daily.

- INTERACTIONS
  + Appendix 1: ethambutol - isoniazid - pyrazinamide - rifampicin
**Rifampicin with isoniazid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, rifampicin p. 582, isoniazid p. 587.

**INDICATIONS AND DOSE**

**Treatment of tuberculosis (continuation phase)**

- **BY MOUTH**
  - Adult (body-weight up to 50 kg): 450/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifinah® 150/100 Tablets, preferably taken before breakfast.
  - Adult (body-weight 50 kg and above): 600/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifinah® 300/150 Tablets, preferably taken before breakfast.

**DOSE EQUIVALENCE AND CONVERSION**

- Rifinah® Tablets contain rifampicin and isoniazid; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of rifampicin and isoniazid respectively.
  - Each Rifinah® 150/100 Tablet contains rifampicin 150 mg and isoniazid 100 mg.
  - Each Rifinah® 300/150 Tablet contains rifampicin 300 mg and isoniazid 150 mg.

**INTERACTIONS** → Appendix 1: isoniazid · rifampicin

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

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**Rifampicin with isoniazid and pyrazinamide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, rifampicin p. 582, isoniazid p. 587, pyrazinamide p. 588.

**INDICATIONS AND DOSE**

**Initial unsupervised treatment of tuberculosis (in combination with ethambutol)**

- **BY MOUTH**
  - Adult (body-weight up to 40 kg): 3 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.
  - Adult (body-weight 40–49 kg): 4 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.
  - Adult (body-weight 50–64 kg): 5 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.

**ADULT (body-weight 65 kg and above):** 6 tablets daily for 2 months (initial phase), use Rifater® Tablets, preferably taken before breakfast.

**DOSE EQUIVALENCE AND CONVERSION**

- Tablet quantities refer to the number of Rifater® Tablets which should be taken. Each Rifater® Tablet contains isoniazid 50 mg, pyrazinamide 300 mg and rifampicin 120 mg.

**INTERACTIONS** → Appendix 1: isoniazid · pyrazinamide · rifampicin

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

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**Aminosalicylic acid**

**INDICATIONS AND DOSE**

**Multiple-drug resistant tuberculosis, in combination with other drugs**

- **BY MOUTH**
  - Adult: 4 g every 8 hours for a usual treatment duration of 24 months; maximum 12 g per day

**Desensitisation regimen**

- **BY MOUTH**
  - Adult: (consult product literature)

**CAUTIONS** Peptic ulcer

**INTERACTIONS** → Appendix 1: aminosalicylic acid

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea · gastrointestinal discomfort · nausea · skin reactions · vestibular syndrome · vomiting
- **Uncommon** Appetite decreased
- **Rare or very rare** Agranulocytosis · anaemia · crystalluria · dizziness · gastrointestinal disorders · gastrointestinal haemorrhage · headache · hepatic disorders · hypoglycaemia · hypothyroidism · leucopenia · methaemoglobinemia · peripheral neuropathy · taste metallic · tendon pain · thrombocytopenia · visual impairment · weight decreased
- **Frequency not known** Hypersensitivity

**PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies (highest risk during first trimester).

**BREAST FEEDING** Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Manufacturer advises use with caution.

**RENAI IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment due to accumulation of inactive metabolites.

**MONITORING REQUIREMENTS**

- Monitor for hypersensitivity reaction during the first 3 months of treatment—for desensitisation dosing regimen consult product literature.
- Monitor liver function—discontinue immediately if signs or symptoms of hepatic toxicity (including rash, fever and gastrointestinal disturbance).

**DIRECTIONS FOR ADMINISTRATION** Disperse granules in orange or tomato juice and take immediately (granules will not dissolve, ensure all granules are swallowed). Granules can be sprinkled on apple sauce or yoghurt for administration.
**Bedaquiline**

**INDICATIONS AND DOSE**

Multiple-drug resistant pulmonary tuberculosis, in combination with other drugs

- **BY MOUTH**
  - Adult: Initially 400 mg once daily for 2 weeks, then 200 mg 3 times a week for 22 weeks, intervals of at least 48 hours between each dose, continue appropriate combination therapy after bedaquiline

**MONITORING REQUIREMENTS**

- **GASTRO-INTESTINAL**
  - Nausea, vomiting, diarrhea, abdominal pain

- **HEPATIC IMPAIRMENT**
  - If severe abnormalities in liver function tests.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

**CONTRA-INDICATIONS**

- QTc interval more than 500 milliseconds (derived using Fridericia’s formula) - ventricular arrhythmia
- Hypothyroidism - QTc interval more than 500 milliseconds - risk factors for QT interval prolongation (e.g. electrolyte disturbances, heart failure with reduced left ventricular ejection fraction, history of symptomatic arrhythmias (avoid if ventricular arrhythmia present), bradycardia, congenital long QT syndrome).

**INTERACTIONS**

- Common or very common: Arthralgia - diarrhoea - dizziness - headache - hepatic function abnormal - myalgia - nausea - QT interval prolongation - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

If syncope occurs, obtain ECG.

**PREGNANCY**

Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

**RENAK IMPAIRMENT**

Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Determine serum potassium, calcium, and magnesium before starting treatment (correct if necessary) - remeasure if QT prolongation occurs during treatment.
- Obtain ECG before starting treatment, and then at least monthly during treatment or more frequently if concomitant use with other drugs known to prolong the QT interval.
- Monitor liver function before starting treatment and then at least monthly during treatment - discontinue treatment if severe abnormalities in liver function tests.

**PATIENT AND CARER ADVICE**

- **Missed doses**
  - If a dose is missed during the first two weeks of treatment, the missed dose should not be taken and the next dose should be taken at the usual time; if a dose is missed during weeks 3–24 of treatment, the missed dose should be taken as soon as possible and then the usual regimen resumed.

- **Driving and skilled tasks**
  - Dizziness may affect performance of skilled tasks (e.g. driving)

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS**
  - 4, 8, 21
  - Sirturo (Janssen-Cilag Ltd)

- **Bedaquiline (as Bedaquiline fumarate) 100 mg**
  - Sirturo 100mg tablets | 188 tablet | £18,700.00

**Capreomycin**

**INDICATIONS AND DOSE**

Tuberculosis resistant to first-line drugs, in combination with other drugs

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 g daily (max. per dose 20 mg/kg) for 2–4 months, then reduced to 1 g 2–3 times a week

**CAUTIONS**

Auditory impairment

**INTERACTIONS**

- Appendix 1: capreomycin

**SIDE-EFFECTS**

Auditory, vestibular, and peripheral nervous system disorders (e.g. vertigo), visual disorders (e.g. blurred vision), and skin disorders (e.g. urticaria, rash)

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk - teratogenic in animal studies.

**RENAK IMPAIRMENT**

Nephrotic, ototoxic. Dose adjustments: Reduce dose - consult product literature.

**MONITORING REQUIREMENTS**

Monitor renal, hepatic, auditory, and vestibular function and electrolytes.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Capreomycin (Non-proprietary)**
  - Capreomycin (as Capreomycin sulphate) 1 gram
  - Capreomycin 1g powder for solution for injection | 1 vial | £11.47

**Cycloserine**

**INDICATIONS AND DOSE**

Tuberculosis resistant to first-line drugs, in combination with other drugs

- **BY MOUTH**
  - Adult: Initially 250 mg every 12 hours for 2 weeks, then increased if necessary up to 500 mg every 12 hours, dose to be increased according to blood concentration and response

**PHARMACOKINETICS**

- Cycloserine penetrates the CNS.

**CONTRA-INDICATIONS**

- Alcohol dependence - depression - epilepsy - psychotic states - severe anxiety

**INTERACTIONS**

- Appendix 1: cycloserine

**SIDE-EFFECTS**


**SIDE-EFFECTS, FURTHER INFORMATION**

- CNS toxicity
  - Discontinue or reduce dose if symptoms of CNS toxicity occur.

- Rash or allergic dermatitis
  - Discontinue or reduce dose if rashes or allergic dermatitis develop.

- **PREGNANCY**
  - Manufacturer advises use only if potential benefit outweighs risk - crosses the placenta.
**Delamanid**

**INDICATIONS AND DOSE**

Multiple-drug resistant pulmonary tuberculosis, in combination with other drugs

**BY MOUTH**

Adult: 100 mg twice daily for 2 weeks, continue appropriate combination therapy after delamanid

**CONTRA-INDICATIONS**

QTc interval more than 500 milliseconds (derived using Fridericia’s formula).

**CAUTIONS**

Risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, severe hypertension, left ventricular hypertrophy, bradycardia, congenital long QT syndrome, history of symptomatic arrhythmias)

**INTERACTIONS**

Appendix 1: delamanid

**SIDE-EFFECTS**

Common or very common: Anxiety, appetite decreased, asthenia, chest pain, cough, depression, dyslipidaemia, dyspnoea, ear pain, electrolyte imbalance, gastrointestinal discomfort, haemoptysis, headache, hyperhidrosis, hypertension, hypotension, malaise, muscle weakness, nausea, oropharyngeal pain, osteoarthritis, pain, palpitations, peripheral neuropathy, photophobia, psychotic disorder, QT interval prolongation, reticulocytosis, sensation abnormal, skin reactions, sleep disorders, throat irritation, tinnitus, tremor, vomiting

Uncommon: Aggression, atrioventricular block, balance impaired, dehydration, delusional disorder, persecutory type, dysphagia, extrasystole, hepatic function abnormal, increased risk of infection, lethargy, leucopenia, oral paraesthesia, psychiatric disorders, thrombocytopenia, urinary disorders

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in moderate to severe impairment.

**RENAL IMPAIRMENT**

Manufacturer advises avoid in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor serum albumin and electrolytes before starting treatment and then during treatment—discontinue treatment if serum albumin less than 28 g/litre.
- Obtain ECG before starting treatment and then monthly during treatment (more frequently if serum albumin 28–34 g/litre, or if concomitant use of potent CYP3A4 inhibitors, or if risk factors for QT interval prolongation, or if QTc interval 450–500 milliseconds in men or 470–500 milliseconds in women)—discontinue treatment if QTc interval more than 500 milliseconds (derived using Fridericia’s formula).

**HANDLING AND STORAGE**

Dispense in original container (contains desiccant).

**Ethambutol hydrochloride**

**INDICATIONS AND DOSE**

Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)

**BY MOUTH**

- Child: 20 mg/kg once daily for 2 months (initial phase)
- Adult: 15 mg/kg once daily for 2 months (initial phase)

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)

**BY MOUTH**

- Child: 30 mg/kg 3 times a week for 2 months (initial phase)
- Adult: 30 mg/kg 3 times a week for 2 months (initial phase)

**CONTRA-INDICATIONS**

Optic neuritis - poor vision

**CAUTIONS**

Elderly, young children

**CAUTIONS, FURTHER INFORMATION**

Understanding warnings: Patients who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

**INTERACTIONS**

Appendix 1: ethambutol

**SIDE-EFFECTS**

Common or very common: Hyperuricaemia, nerve disorders, visual impairment

Rare or very rare: Nephritis tubulointerstitial

Frequency not known: Alveolitis allergic, appetite decreased, asthenia, confusion, dizziness, eosinophilia, fever, flatulence, gastrointestinal discomfort, gout, hallucination, headache, jaundice, leucopenia, nausea, nephrotoxicity, neutropenia, photosensitive lichenoid eruption, sensation abnormal, severe cutaneous adverse reactions (SCARs), skin reactions, taste metallic, thrombocytopenia, tremor, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Ocular toxicity is more common where excessive dosage is used or if the patient’s renal function is impaired. Early discontinuation of the drug is almost always followed by recovery of eyesight.

**PREGNANCY**

Not known to be harmful.

**BREAST FEEDING**

Amount too small to be harmful.

**RENAL IMPAIRMENT**

Risk of optic nerve damage. Should preferably be avoided in patients with renal impairment.
Dose adjustments ▶ In adults If creatinine clearance less than 30 mL/minute, use 15–25 mg/kg (max. 2.5 g) 3 times a week.
▶ In children If creatinine clearance less than 30 mL/minute/1.73 m², use 15–25 mg/kg (max. 2.5 g) 3 times a week.
Monitoring If creatinine clearance less than 30 mL/minute, monitor plasma-ethambutol concentration.

MONITORING REQUIREMENTS
▶ 'Peak' concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); 'trough' (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre).
▶ Renal function should be checked before treatment.
▶ Visual acuity should be tested by Snellen chart before treatment with ethambutol.

PATIENT AND CARER ADVICE
▶ Renal function should be checked before treatment.

PRESCRIBING AND DISPENSING INFORMATION The RCPCH and NPPG recommend that, when a liquid special is required, the following strength is used: 400 mg/5 mL.

PATIENT AND CARER ADVICE
ocular toxicity The earliest features of ocular toxicity are subjective and patients should be advised to discontinue therapy immediately if they develop deterioration in vision and promptly seek further advice. Medicines for Children leaflet: Ethambutol for the treatment of tuberculosis www.medicinesforchildren.org.uk/ethambutol-treatment-tuberculosis

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
Tablet
CAUTIONARY AND ADVISORY LABELS 8
Ethambutol hydrochloride (Non-proprietary)
Ethambutol hydrochloride 100 mg Ethambutol 100mg tablets | 56 tablet ▶ £17.00 DT + £11.51
Ethambutol hydrochloride 400 mg Ethambutol 400mg tablets | 56 tablet ▶ £42.74 DT + £42.74
Combinations available: Rifampicin with ethambutol, isoniazid and pyrazinamide, p. 583

Isoniazid

INDICATIONS AND DOSE
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)
▶ By mouth, or by intramuscular injection, or by intravenous injection
Child: 10 mg/kg once daily (max. per dose 300 mg) for 6 months (initial and continuation phases)
Adult: 300 mg daily for 6 months (initial and continuation phases)
Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)
▶ By mouth, or by intramuscular injection, or by intravenous injection
Child: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)
Adult: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)

PREVENTION OF TUBERCULOSIS IN SUSCEPTIBLE CLOSE CONTACTS OR THOSE WHO HAVE BECOME TUBERCULIN POSITIVE
▶ Initially by mouth, or by intramuscular injection, or by intravenous injection
Child 1 month–11 years: 10 mg/kg daily (max. per dose 300 mg) for 6 months, alternatively (by mouth) 10 mg/kg daily (max. per dose 300 mg) for 3 months, to be taken in combination with rifampicin
Child 12–17 years: 300 mg daily for 6 months, alternatively (by mouth) 300 mg daily for 3 months, to be taken in combination with rifampicin
Adult: 300 mg daily for 6 months, alternatively (by mouth) 300 mg daily for 3 months, to be taken in combination with rifampicin

CONTRA-INDICATIONS Drug-induced liver disease

CAUTIONS Acute porphyrias p. 1058 · alcohol dependence · diabetes mellitus · epilepsy · history of psychosis · HIV infection · malnutrition · slow acetylator status (increased risk of side-effects)

SAFETY IN PREGNANCY Peripheral neuropathy In pregnant women peripheral neuropathy is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, pregnancy, malnutrition and HIV infection. In patients at increased risk of peripheral neuropathy, pyridoxine hydrochloride p. 1080 should be given prophylactically from the start of treatment.

INTERACTIONS → Appendix 1: isoniazid

SIDE-EFFECTS
▶ Uncommon Hepatic disorders
▶ Rare or very rare Severe cutaneous adverse reactions (SCARs)
▶ Frequency not known Agranulocytosis · alopecia · anaemia · aplastic anaemia · eosinophilia · fever · gynaecomastia · haemolytic anaemia · hyperglycaemia · lupus-like syndrome · nerve disorders · optic atrophy · pancreatitis · pellagra · psychosis · seizure · skin reactions · thrombocytopenia · vasculitis

SIDE-EFFECTS, FURTHER INFORMATION Hepatitis more common in those aged over 35 years and those with a daily alcohol intake.

PREGNANCY Not known to be harmful; prophylactic pyridoxine recommended.

BREAST FEEDING Theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother.

MONITORING In breast-feeding, monitor infant for possible toxicity.

HEPATIC IMPAIRMENT Use with caution.

MONITORING In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months.

RENAL IMPAIRMENT Risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine hydrochloride p. 1080 recommended.

MONITORING REQUIREMENTS
▶ Renal function should be checked before treatment.
▶ Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.
▶ In adults Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.

PRESCRIBING AND DISPENSING INFORMATION
▶ With oral use in children In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. The RCPCH and NPPG

www.getintopharma.com
recommend that, when a liquid special of isoniazid is required, the following strength is used: 50 mg/5 mL.

- In children Doses may need to be recalculated to allow for weight gain in younger children.

**PATIENT AND CARER ADVICE**

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to continue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Medicines for Children leaflet: Isoniazid for latent tuberculosis
www.medicinesforchildren.org.uk/isoniazid-latent-tuberculosis

Medicines for Children leaflet: Isoniazid for the treatment of tuberculosis
www.medicinesforchildren.org.uk/isoniazid-treatment-tuberculosis

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Solution for injection**

- **Isoniazid (Non-proprietary)**
  - Isoniazid 25 mg per 1 mL Isoniazid 50mg/2ml solution for injection ampoules | 10 ampoule [POM] £161.98

- **Cemidon (Imported (Spain))**
  - Isoniazid 60 mg per 1 mL Cemidon Intravenousso 300mg/5ml solution for injection ampoules | 5 ampoule [POM] £

**Tablet**

CAUTIONARY AND ADVISORY LABELS 8, 22

- **Isoniazid (Non-proprietary)**
  - Isoniazid 50 mg Isoniazid 50mg tablets | 56 tablet [POM] £19.25 DT + £
  - Isoniazid 100 mg Isoniazid 100mg tablets | 28 tablet [POM] £19.24 DT + £
  - Isoniazid 300 mg Isoniazid 300mg tablets | 30 tablet [POM]

**Combinations available:** Rifampicin with ethambutol, isoniazid and pyrazinamide, p. 583 - Rifampicin with isoniazid and pyrazinamide, p. 584

**Pyrazinamide**

**INDICATIONS AND DOSE**

**Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)**

- **BY MOUTH**
  - Child (body-weight up to 50 kg): 35 mg/kg once daily for 2 months (initial phase); maximum 1.5 g per day
  - Child (body-weight 50 kg and above): 35 mg/kg once daily for 2 months (initial phase); maximum 2 g per day
  - Adult (body-weight up to 50 kg): 1.5 g once daily for 2 months (initial phase)
  - Adult (body-weight 50 kg and above): 2 g once daily for 2 months (initial phase)

**Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)**

- **BY MOUTH**
  - Child (body-weight up to 50 kg): 50 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase)
  - Child (body-weight 50 kg and above): 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)
  - Adult (body-weight up to 50 kg): 2 g 3 times a week for 2 months (initial phase)
  - Adult (body-weight 50 kg and above): 2.5 g 3 times a week for 2 months (initial phase)

**CONTRA-INDICATIONS**

Acute attack of gout (in adults)

**CAUTIONS**

Diabetes - gout (in adults)

**INTERACTIONS**

→ Appendix 1: pyrazinamide

**SIDE-EFFECTS**

Appetite decreased, arthralgia, dysuria, flushing, gout aggravated, hepatic disorders, malaise, nausea, peptic ulcer aggravated, photosensitivity reaction, sideroblastic anaemia, skin reactions, splenomegaly, vomiting

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in severe impairment, acute hepatic disease and for up to 6 months after occurrence of hepatitis (risk of increased exposure).

**RENAL IMPAIRMENT**

Dose adjustments

- In adults 25–30 mg/kg 3 times a week if eGFR less than 30 mL/minute/1.73 m².
- In children If estimated glomerular filtration rate less than 30 mL/minute/1.73 m², use 25–30 mg/kg 3 times a week.

**Monitoring**

Monitor for gout in renal impairment.

**MONITORING REQUIREMENTS**

- **Renal function** should be checked before treatment.
- **Hepatic function** should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.
- In adults Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.

**PRESCRIBING AND DISPENSING INFORMATION**

- In children In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may also need to be recalculated to allow for weight gain in younger children. The RCPCH and NPPG recommend that, when a liquid special of pyrazinamide is required, the following strength is used: 500 mg/5 mL.

**PATIENT AND CARER ADVICE**

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to continue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Medicines for Children leaflet: Pyrazinamide for treatment of tuberculosis
www.medicinesforchildren.org.uk/pyrazinamide-treatment-tuberculosis

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 8, 22

- **Pyrazinamide (Non-proprietary)**
  - Pyrazinamide 500 mg Pyrazinamide 500mg tablets | 30 tablet [POM] £36.12 DT + £36.12
  - Zinamid (Genus Pharmaceuticals Ltd) Pyrazinamide 500 mg Zinamide 500mg tablets | 30 tablet [POM] £31.35 DT + £36.12

**Combinations available:** Rifampicin with ethambutol, isoniazid and pyrazinamide, p. 583 - Rifampicin with isoniazid and pyrazinamide, p. 584
2.6 Urinary tract infections

Urinary-tract infections

Overview

Urinary-tract infection is more common in women than in men; when it occurs in men there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage. *Escherichia coli* is the most common cause of urinary-tract infection; *Staphylococcus saprophyticus* is also common in sexually active young women. Less common causes include *Proteus* and *Klebsiella* spp. *Pseudomonas aeruginosa* infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. *Staphylococcus epidermidis* and *Enterococcus faecalis* infection may complicate catheterisation or instrumentation.

A specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy;

- in men;
- in pregnant women;
- in children under 3 years of age;
- in patients with suspected upper urinary-tract infection;
- complicated infection, or recurrent infection;
- if resistant organisms are suspected;
- if urine dipstick testing gives a single positive result for leucocyte esterase or nitrite;
- if clinical symptoms are not consistent with results of dipstick testing.

Treatment should not be delayed while waiting for results. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.

Antibacterial therapy for lower urinary-tract infections

Uncomplicated lower urinary-tract infections often respond to trimethoprim p. 574 or nitrofurantoin p. 590, or alternatively, amoxicillin p. 548, ampicillin p. 550 or oral cephalosporin.

Suggested duration of treatment is 7 days, but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women.

Infections caused by fully sensitive bacteria respond to amoxicillin.

Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav p. 551 (amoxicillin with clavulanic acid), an oral cephalosporin, nitrofurantoin, pivmecillinam hydrochloride p. 554, or a quinolone.

Fosfomycin p. 570 can be used, on the advice of a microbiologist, for the treatment of acute uncomplicated lower urinary-tract infections caused by organisms sensitive to fosfomycin.

Long-term low dose therapy may be required in selected patients to prevent recurrence of infection; indications include frequent relapses and significant kidney damage. Trimethoprim, nitrofurantoin and cefalexin p. 524 have been recommended for long-term therapy.

Methenamine hippurate below (hexamine hippurate) should not generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections.

Antibacterial therapy for upper urinary-tract infections

Acute pyelonephritis can lead to sepsicaemia and is treated initially by injection of a broad-spectrum antibacterial such as a cephalosporin (e.g. cefuroxime p. 526) or a quinolone if the patient is severely ill; gentamicin p. 519 can also be used. Suggested duration of treatment is 10–14 days (longer treatment may be necessary in complicated pyelonephritis). Prostatitis can be difficult to cure and requires treatment for several weeks with an antibacterial which penetrates prostatic tissue such as one of the quinolones (ciprofloxacin p. 558 or ofloxacin p. 561), or alternatively, trimethoprim.

Suggested duration of treatment is 28 days.

Where infection is localised and associated with an indwelling catheter, a bladder instillation is often effective.

Pregnancy

Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulfonamides and quinolones should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

Renal impairment

In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methenamine hippurate, and nitrofurantoin should be avoided altogether.

ANTIBACTERIALS

Methenamine hippurate

(Hexamine hippurate)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections</strong></td>
</tr>
<tr>
<td><em>BY MOUTH</em></td>
</tr>
<tr>
<td>Adult: 1 g every 12 hours</td>
</tr>
</tbody>
</table>

**Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections in patients with catheters**

*BY MOUTH*  
Adult: 1 g every 8–12 hours

**CONTRA-INDICATIONS**  
Gout - metabolic acidosis - severe dehydration

**INTERACTIONS**  
Appendix 1: methenamine

**SIDE-EFFECTS**

- Uncommon  
  Epigastric discomfort - skin reactions

**PREGNANCY**  
There is inadequate evidence of safety, but it has been in wide use for many years without apparent ill consequence, however, manufacturer advises it is preferable to avoid.

**BREAST FEEDING**  
Amount too small to be harmful.

**HEPATIC IMPAIRMENT**  
Manufacturer advises avoid.

**RENAL IMPAIRMENT**  
Avoid if eGFR less than 10 mL/minute/1.73 m²—risk of hippurate crystalluria.

**EFFECT ON LABORATORY TESTS**  
False results for urinary steroids, catecholamines and 5-hydroxyindole acetic acid can occur.

**LESS SUITABLE FOR PRESCRIBING**  
Methenamine (hexamine) hippurate should not generally be used.
Nitrofurantoin

**INDICATIONS AND DOSE**

**Acute uncomplicated urinary-tract infections**
- By mouth using immediate-release medicines
  - Child 3 months–11 years: 750 micrograms/kg 4 times a day for 3–7 days
  - Child 12–17 years: 50 mg 4 times a day for 3–7 days
  - Adult: 50 mg 4 times a day for 3–7 days, dose to be taken with food
- By mouth using modified-release medicines
  - Child 12–17 years: 100 mg twice daily, dose to be taken with food
  - Adult: 100 mg twice daily, dose to be taken with food

**Severe chronic recurrent urinary-tract infections**
- By mouth using immediate-release medicines
  - Child 12–17 years: 100 mg 4 times a day for 3–7 days
  - Adult: 100 mg 4 times a day for 7 days, dose to be taken with food, reduce dose or discontinue treatment if severe nausea occurs

**Prophylaxis of urinary-tract infection (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)**
- By mouth using immediate-release medicines
  - Child 3 months–11 years: 1 mg/kg once daily, dose to be taken at night
  - Child 12–17 years: 50–100 mg once daily, dose to be taken at night
  - Adult: 50–100 mg once daily, dose to be taken at night

**Genito-urinary surgical prophylaxis**
- By mouth using modified-release medicines
  - Adult: 100 mg twice daily on day of procedure and for 3 days after

**CONTRA-INDICATIONS**
- Acute porphyrias p. 1058
- G6PD deficiency
- Infants less than 3 months old

**CAUTIONS**
- Anaemia
- Diabetes mellitus
- Electrolyte imbalance
- Folate deficiency
- Pulmonary disease
- Susceptibility to peripheral neuropathy
- Urine may be coloured yellow or brown
- Vitamin B deficiency

**INTERACTIONS**
- Appendix 1: nitrofurantoin

**SIDE-EFFECTS**
- Agranulocytosis
- Alopexia
- Anaemia
- Angioedema
- Aplastic anaemia
- Appetite decreased
- Arthralgia
- Asthenia
- Chest pain
- Chills
- Circulatory collapse
- Confusion
- Cynosis
- Depression
- Diarrhoea
- Dizziness
- Drowsiness
- Dyspnoea
- Eosinophilia
- Euphoric mood
- Fever
- Granulocytopenia
- Haemolytic anaemia
- Headache
- Hepatic disorders
- Idiopathic intracranial hypertension
- Increased risk of infection
- Leucopenia
- Lupus-like syndrome
- Nausea
- Nerve disorders
- Nystagmus
- Pancreatitis
- Psychotic disorder
- Pulmonary hypersensitivity
- Pulmonary reaction (possible association with lupus erythematosus-like syndrome)
- Respiratory disorders
- Skin reactions
- Stevens-Johnson syndrome
- Thrombocytopenia
- Urine discolouration
- Vertigo
- Vomiting

**PREGNANCY**
- Avoid at term—may produce neonatal haemolysis

**BREAST FEEDING**
- Avoid; only small amounts in milk but enough to produce haemolysis in G6PD-deficient infants

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution

**RENAL IMPAIRMENT**
- Risk of peripheral neuropathy; antibacterial efficacy depends on renal secretion of the drug into urinary tract
- In adults: Avoid if eGFR less than 45 mL/minute/1.73 m²; may be used with caution if eGFR 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk
- In children: Avoid if estimated glomerular filtration rate less than 45 mL/minute/1.73 m²; may be used with caution if estimated glomerular filtration rate 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk

**MONITORING REQUIREMENTS**
- On long-term therapy, monitor liver function and monitor for pulmonary symptoms, especially in the elderly (discontinue if deterioration in lung function)

**EFFECT ON LABORATORY TESTS**
- False positive urinary glucose (if tested for reducing substances)

**PATIENT AND CARER ADVICE**
- Medicines for Children leaflet: Nitrofurantoin for urinary tract infections
  - www.medicinesforchildren.org.uk/nitrofurantoin-urinary-tract-infections

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 9, 14, 21
  - Nitrofurantoin (Non-proprietary)
    - Nitrofurantoin 50 mg Nitrofurantoin 50mg tablets | 28 tablet £35.00 DT = £8.34 | 100 tablet £52.79–£111.89
    - Nitrofurantoin 100 mg Nitrofurantoin 100mg tablets | 28 tablet £12.99 DT = £70.4 | 100 tablet £21.07–£30.00
    - Genfura (Genesis Pharmaceuticals Ltd)
      - Nitrofurantoin 50 mg Genfura 50mg tablets | 28 tablet £8.00 DT = £8.34 | 100 tablet £28.57
      - Nitrofurantoin 100 mg Genfura 100mg tablets | 100 tablet £30.36

**Oral suspension**
- CAUTIONARY AND ADVISORY LABELS 9, 14, 21
  - Nitrofurantoin (Non-proprietary)
    - Nitrofurantoin 5 mg per 1 ml Nitrofurantoin 25mg/5ml oral suspension sugar free sugar-free | 300 ml £46.95 DT = £0.95

**Modified-release capsule**
- CAUTIONARY AND ADVISORY LABELS 9, 14, 21
  - Macrolid (Advanz Pharma)
    - Nitrofurantoin 100 mg Macrolid 100mg modified-release capsules | 14 capsule £9.90 DT = £0.95
Fungal infection

3 Fungal infection

Antifungals, systemic use

Fungal infections

The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. Local treatment is suitable for a number of fungal infections (genital, bladder, eye, ear, oropharynx, and skin).

Aspergillosis

Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the heart, brain, and skin. Voriconazole p. 599 is the treatment of choice for aspergillosis; liposomal amphotericin p. 593 is an alternative first-line treatment when voriconazole cannot be used. Caspofungin p. 592, or itraconazole p. 597, can be used in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis or as an adjunct in the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication]. Posaconazole p. 598 is licensed for use in patients with invasive aspergillosis who are refractory to, or intolerant of itraconazole or amphotericin.

Candidiasis

Many superficial candidal infections including infections of the skin are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis may be treated with locally acting antifungals or with fluconazole p. 595 given by mouth; for resistant organisms in adults, itraconazole can be given by mouth.

Oral thrush is effectively treated with topical therapy; fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for infections that do not respond to fluconazole. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

For invasive or disseminated candidiasis, an echinocandin can be used. Fluconazole is an alternative for Candida albicans infection in clinically stable patients who have not received an azole antifungal recently. Amphotericin is an alternative when an echinocandin or fluconazole cannot be used, however, amphotericin should be considered for the initial treatment of CNS candidiasis. Voriconazole can be used for infections caused by fluconazole-resistant Candida spp. when oral therapy is required, or in patients intolerant of amphotericin or an echinocandin. In refractory cases, fluocytosine p. 601 can be used with intravenous amphotericin.

Cryptococcosis

Cryptococcosis is uncommon but infection in the immunocompromised, especially in HIV-positive patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is amphotericin by intravenous infusion and fluocytosine by intravenous infusion for 2 weeks, followed by fluconazole by mouth for 8 weeks or until cultures are negative. In cryptococcosis, fluconazole is sometimes given alone as an alternative in HIV-positive patients with mild, localised infections or in those who cannot tolerate amphotericin. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

Histoplasmosis

Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons.

Itraconazole can be used for the treatment of immunocompetent patients with indolent non-meningeal infection, including chronic pulmonary histoplasmosis. Amphotericin by intravenous infusion is used for the initial treatment of fulminant or severe infections, followed by a course of itraconazole by mouth. Following successful treatment, itraconazole can be used for prophylaxis against relapse until immunity recovers.

Skin and nail infections

Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy. Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Oral imidazole or triazole antifungals (particularly itraconazole) and terbinafine p. 1234 are used more frequently than griseofulvin p. 601 because they have a broader spectrum of activity and require a shorter duration of treatment. Tinea capitis is treated systemically; additional topical application of an antifungal may reduce transmission. Griseofulvin is used for tinea capitis in adults and children; it is effective against infections caused by Trichophyton tonsurans and Microsporum spp. Terbinafine is used for tinea capitis caused by T. tonsurans [unlicensed indication]. The role of terbinafine in the management of Microsporum infections is uncertain.

Pityriasis versicolor may be treated with itraconazole by mouth if topical therapy is ineffective; fluconazole by mouth is an alternative. Oral terbinafine is not effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. Terbinafine and itraconazole have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; terbinafine is considered to be the drug of choice. Itraconazole can be administered as intermittent “pulse” therapy. Topical antifungals also have a role in the treatment of onychomycosis.

Immunocompromised patients

Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral triazole antifungals are the drugs of choice for prophylaxis. Fluconazole is more reliably absorbed than itraconazole, but fluconazole is not effective against Aspergillus spp. Itraconazole is preferred in patients at risk of invasive aspergillosis. Posaconazole can be used for prophylaxis in patients who are undergoing haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome. Micafungin p. 593 can be used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation when fluconazole, itraconazole or posaconazole cannot be used.

Amphotericin by intravenous infusion or caspofungin is used for the empirical treatment of serious fungal infections; caspofungin is not effective against fungal infections of the CNS.

Triazole antifungals

Triazole antifungal drugs have a role in the prevention and systemic treatment of fungal infections. Fluconazole is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Fluconazole is excreted largely unchanged in the urine and can be used to treat candiduria.

Itraconazole is active against a wide range of dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption.
Itraconazole has been associated with liver damage and should be avoided or used with caution in patients with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Posaconazole is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment. Voriconazole is a broad-spectrum antifungal drug which is licensed for use in life-threatening infections.

**Imidazole antifungals**
The imidazole antifungals include clotrimazole p. 829, econazole nitrate p. 830, ketoconazole p. 830, and tioconazole p. 1233. They are used for the local treatment of vaginal candidiasis and for dermatophyte infections. Miconazole p. 1219 can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.

**Polyene antifungals**
The polyene antifungals include amphoterin p. 593 and nystatin p. 1219; neither drug is absorbed when given by mouth. Nystatin is used for oral, oropharyngeal, and perioral infections by local application in the mouth. Nystatin is also used for *Candida albicans* infection of the skin.

Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (Abelcet® and AmBisome®) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; lipid formulations are more expensive.

**Echinocandin antifungals**
The echinocandin antifungals include anidulafungin below, caspofungin below and micafungin p. 593. They are only active against *Aspergillus* spp. and *Candida* spp.; however, anidulafungin and micafungin are not used for the treatment of aspergillosis. Echinocandins are not effective against fungal infections of the CNS.

**Other antifungals**
Flucytosine p. 601 is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in HIV-positive patients; weekly blood counts are necessary during prolonged therapy.

Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment. Flucytosine has a role in the treatment of systemic candidiasis and cryptococcal meningitis. Griseofulvin p. 601 is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophytosis infections in children. Duration of therapy is dependent on the site of the infection and may extend to a number of months.

Terbinafine p. 1234 is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

**ANTIFUNGALS > ECHINOCANDIN ANTIFUNGALS**

### Anidulafungin

**INDICATIONS AND DOSE**

**Invasive candidiasis**
- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 200 mg once daily for 1 day, then 100 mg once daily

**SIDE-EFFECTS**
- **Common or very common** Bronchospasm · cholestasis · diarrhoea · dyspnoea · headache · hyperglycaemia · hypertension · hypokalaemia · hypotension · nausea · seizure · skin reactions · vomiting
- **Uncommon** Abdominal pain upper · coagulation disorder · vasodilation

**PREGNANCY**
Manufacturer advises avoid unless potential benefit outweighs risk—*toxicity in animal studies.*

**BREAST FEEDING**
Manufacturer advises avoid unless potential benefit outweighs risk—*present in milk in animal studies.*

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (*Ecalta®*), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 100 mg with 30 mL water for injections and allow up to 5 minutes for reconstitution; dilute dose in infusion fluid to a concentration of 770 micrograms/mL, give at a rate not exceeding 1.1 mg/minute. Follow product information if using stock supplied with ethanol solvent.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

** Powder for solution for infusion**
- **Anidulafungin (Non-proprietary)**
  - Anidulafungin 100 mg Anidulafungin 100mg powder for concentrate for solution for infusion vials | 1 vial (£84.99) (£84.99 (Hospital only))
- **Ecalta (Pfizer Ltd)**
  - Anidulafungin 100 mg Ecalta 100mg powder for concentrate for solution for infusion vials | 1 vial (£99.99 (Hospital only))

**Caspofungin**

**INDICATIONS AND DOSE**

**Invasive aspergillosis**| **Invasive candidiasis**| **Empirical treatment of systemic fungal infections in patients with neutropenia**
- **BY INTRAVENOUS INFUSION**
  - Adult (body-weight up to 81 kg): 70 mg once daily for 1 day, then 50 mg once daily
  - Adult (body-weight 81 kg and above): 70 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Manufacturer advises increase dose to 70 mg daily with concurrent use of some enzyme inducers (such as carbamazepine, dexamethasone, phenytoin, and rifampicin); no dose adjustment required for patients already on 70 mg daily.

**INTERACTIONS**
Appendix 1: caspofungin

**SIDE-EFFECTS**
- **Common or very common** Arthralgia · diarrhoea · dyspnoea · electrolyte imbalance · fever · headache · hyperhidrosis · nausea · skin reactions · vomiting
- **Uncommon** Anaemia · anxiety · appetite decreased · arthralgias · ascites · chest discomfort · coagulation disorder · congestive heart failure · constipation · cough · disorientation · dizziness · drowsiness · dry mouth · dysphagia · excessive tearing · eyelid oedema · fatigue · flatulence · fluid overload · flushing · gastrointestinal discomfort · haematuria · hepatic disorders ·

www.getintopharma.com
hyperbilirubinaemia · hyperglycaemia · hypertension · hypoten-sion · hypoxia · induration · insomnia · laryngeal pain · leucopenia · malaise · metabolic acidosis · muscle weakness · myalgia · nasal congestion · oedema · pain · palpitations · renal impairment · respiratory disorders · sensation abnormal · taste altered · thrombocyto-penia · thrombophlebitis · tremor · vision blurred

- **Frequency not known** Severe cutaneous adverse reactions (SCARs)
- **PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies.
- **BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** No information available for severe impairment.
- **DIRECTIONS FOR ADMINISTRATION**
  - **HEPATIC IMPAIRMENT**
  - **BREAST FEEDING**
  - **PREGNANCY**

- **Adult (body-weight 40 kg and above):**
  - **BY INTRAVENOUS INFUSION**
  - **Adult (body-weight up to 40 kg):**
  - **BY INTRAVENOUS INFUSION**

- **Severe systemic fungal infections in patients not responding to conventional amphotericin B or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin B, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptoco-ccosis in HIV patients**
  - **BY INTRAVENOUS INFUSION**
  - **Adult:** Test dose 1 mg, to be given over 15 minutes, then 5 mg/kg once daily for at least 14 days

- **AmBisome**
  - **Severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin B**
  - **Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials**
  - **BY INTRAVENOUS INFUSION**
  - **Adult:** Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day
Fungal infection

Aspergillosis
- **BY INTRAVENOUS INFUSION**
- **Adult:** Test dose 1 mg, to be given over 10–20 minutes, then 3 mg/kg daily; maximum 5 mg/kg per day

Viral encephalitis (unresponsive to the antimonial alone)
- **BY INTRAVENOUS INFUSION**
- **Adult:** 1–2 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg, alternatively 3 mg/kg for 5 consecutive days, followed by 3 mg/kg after 6 days for 1 dose

**FUNGIZONE®**

Systemic fungal infections
- **BY INTRAVENOUS INFUSION**
- **Adult:** Test dose 1 mg, to be given over 20–30 minutes, then 250 micrograms/kg daily, gradually increased over 2–4 days, increased if tolerated to 1 mg/kg daily, max. (severe infection) 1.5 mg/kg daily or on alternate days. Prolonged treatment usually necessary; if interrupted for longer than 7 days recommence at 250 micrograms/kg daily and increase gradually

**UNLICENSED USE**

**AMBISOME®** Use at the maximum dose of 5 mg/kg once daily is an unlicensed dose.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: PARENTERAL AMPHOTERICIN B: REMINDER OF RISK OF POTENTIALLY FATAL ADVERSE REACTION IF FORMULATIONS CONFUSED (JULY 2018)**

The MHRA is aware of three fatal overdoses which were caused by medication error in which Fungizone® was administered (a non-lipid-based formulation of amphotericin B) instead of a lipid-based formulation. Healthcare professionals are advised:
- when prescribing and dispensing amphotericin products, both the complete generic name and the proprietary name should be used;
- the product name and dose should be verified before administration, especially if the dose prescribed exceeds the maximum recommended dose for Fungizone®.

**CAUTIONS** Avoid rapid infusion (risk of arrhythmias) - when given parenterally, toxicity common (close supervision necessary and close observation required for at least 30 minutes after test dose)

**CAUTIONS, FURTHER INFORMATION**
- Anaphylaxis Anaphylaxis can occur with any intravenous amphotericin product and a test dose is advisable before the first infusion; the patient should be carefully observed for at least 30 minutes after the test dose. Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential).

**INTERACTIONS** Appendix 1: amphotericin

**SIDE-EFFECTS**
- Common or very common Anaemia · appetite decreased · azotaemia · chills · diarrhoea · dyspnoea · electrolyte imbalance · fever · headache · hepatic function abnormal (discontinue) · hypotension · hypotension · nausea · nephrocalcinosis · renal impairment · renal tubular acidosis · skin reactions · vomiting
- Uncommon Agranulocytosis · arthralgias · flushing · gastrointestinal discomfort · hepatic disorders · leucopenia · myalgia · peripheral neuropathy · respiratory disorders · thrombocytopenia
- Rare or very rare Arthralgia · cardiac arrest · coagulation disorder · deafness · encephalopathy · eosinophilia · haemorrhage · heart failure · hypersensitivity · hypertension · malaise · nephrogenic diabetes insipidus · pain · pulmonary oedema non-cardiogenic · seizure · severe cutaneous adverse reactions (SCARs) · shock · tinnitus · vertigo · vision disorders · weight decreased

**PREGNANCY** Not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk.

**BREAST FEEDING** No information available.

**RENAI IMPAIRMENT** Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation.

**MONITORING REQUIREMENTS** Hepatic and renal function tests, blood counts, and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required.

**DIRECTIONS FOR ADMINISTRATION**

**ABELCET® Amphotericin (lipid complex)**

For intravenous infusion, give intermittently in Glucose 5%. Allow suspension to reach room temperature, shake gently to ensure no yellow settlement, withdraw requisite dose (using 17–19 gauge needle) into one or more 20–25 mL syringes; replace needle on syringe with a 5-micron filter needle provided (fresh needle for each syringe) and dilute to a concentration of 1 mg/mL (2 mg/mL can be used in fluid restriction and in children); preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose of 1 mg over 15 minutes); an in-line filter (pore size no less than 15 micron) may be used; do not use sodium chloride or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line.

**AMBISOME® Amphotericin (liposomal)**

For intravenous infusion (Ambisome®), give intermittently in Glucose 5% or 10%. Reconstitute each vial with 12 mL water for injections and shake vigorously to produce a preparation containing 4 mg/mL; withdraw requisite dose from vial and introduce into infusion fluid through the 5 micron filter provided to produce a final concentration of 0.2–2 mg/mL; infuse over 30–60 minutes, or if non-anaphylactic infusion-related reactions occur infuse over 2 hours (initial test dose of 1 mg over 10 minutes); an in-line filter (pore size no less than 1 micron) may be used; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or 10%, or use separate line.

**FUNGIZONE® Amphotericin (as sodium deoxycholate complex)**

For intravenous infusion (Fungizone®), give intermittently in Glucose 5%. Reconstitute each vial with 10 mL water of injections and shake immediately to produce a 5 mg/mL colloidal solution; dilute further in infusion fluid to a concentration of 100 micrograms/mL; pH of the glucose must not be below 4.2 (check each container—consult product literature for details of the buffer); infuse over 2–4 hours, or longer if not tolerated (initial test dose of 1 mg over 20–30 minutes); begin infusion immediately after dilution; protect from light; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or use separate line; an in-line filter (pore size no less than 1 micron) may be used.

**PRESCRIBING AND DISPENSING INFORMATION** Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should not be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.
Fungal infection

**Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis)**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Child: 6–12 mg/kg daily (max. per dose 800 mg), treatment continued according to response (at least 8 weeks for cryptococcal meningitis)
  - Adult: 400 mg, dose to be given on first day, then 200–400 mg daily (max. per dose 800 mg once daily), treatment continued according to response (at least 8 weeks for cryptococcal meningitis), maximum dose for use in severe infections

**Prevention of fungal infections in immunocompromised patients**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Child: 3–12 mg/kg daily (max. per dose 400 mg), commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose given according to extent and duration of neutropenia
  - Adult: 50–400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose adjusted according to risk

**Prevention of fungal infections in immunocompromised patients (for patients with high risk of systemic infections e.g. following bone-marrow transplantation)**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Adult: 400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range

**Prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Adult: 200 mg daily

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**Indications and dose**

**Candidal balanitis**

**BY MOUTH**

- Child 16-17 years: 150 mg for 1 dose
- Adult: 150 mg for 1 dose

**Vaginal candidiasis**

**BY MOUTH**

- Adult: 150 mg for 1 dose

**Vulvovaginal candidiasis (recurrent)**

**BY MOUTH**

- Adult: Initially 150 mg every 72 hours for 3 doses, then 150 mg once weekly for 6 months

**Mucosal candidiasis (except genital)**

**BY MOUTH, OR BY INTRAVENOUS INFUSION**

- Child 1 month-11 years: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg daily (max. per dose 100 mg) for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)
- Child 12-17 years: 50 mg daily for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections
- **BY MOUTH**
  - Adult: 50 mg daily for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections

**Tinea pedis, corporis, cruris, pityriasis versicolor**

**DERMAL CANDIDIASIS**

**BY MOUTH**

- Adult: 50 mg daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks

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**Contra-indications**

Acute porphyrias p. 1058

**Caution**

Susceptibility to QT interval prolongation

**Interactions**

Appendix 1: antifungals, azoles

**Side-effects**

**General side-effects**

- **Common or very common** Diarrhoea; gastrointestinal discomfort; headache; nausea; skin reactions; vomiting
- **Uncommon** Dizziness; flatulence; hepatic disorders; oesophagitis; oedema; neutropenia; QT interval prolongation; severe cutaneous adverse reactions (SCARs); thrombocytopenia; taste altered
- **Rare or very rare** Agranulocytosis; alopecia; dyslipidaemia; hypokalaemia; leucopenia; neutropenia; QT interval prolongation; severe cutaneous adverse reactions (SCARs); thrombocytopenia; torsade de pointes

**Specific side-effects**

**Uncommon**

- With parenteral use Anaemia; appetite decreased; asthenia; constipation; drowsiness; dry mouth; fever; hyperhidrosis; insomnia; malaise; myalgia; paraesthesia; vertigo
- **Rare or very rare**
  - With parenteral use Angioedema; face oedema; tremor
  - Frequency not known
  - With oral use Cardio-respiratory distress; oedema

**Side-effects, further information**

If rash occurs, discontinue treatment (or monitor closely if infection invasive or systemic); severe cutaneous reactions are more likely in patients with AIDS.

**Pregnancy**

Manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses.

**Breast feeding**

Present in milk but amount probably too small to be harmful.

**Hepatic impairment**

Manufacturer advises caution—limited information available.
Fluconazole Capsules

- **CAUTIONARY AND ADVISORY LABELS**
  - Flavours of Fluconazole may contain sodium.
  - Electrolytes: May contain sodium.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Fluconazole capsules can be sold to the public for vaginal candidiasis and associated candidal balanitis in those aged 16–60 years, in a container or packaging containing not more than 150 mg and labelled to show a max. dose of 150 mg.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Infusion**
    - Fluconazole (Non-proprietary) 2 mg per 1 ml: Fluconazole 200mg/100ml infusion solution for infusion bags | 5 bag [POT] £19.45 (Hospital only)
    - Fluconazole 400mg/200ml infusion solution | 5 bag [POT] £72.50 (Hospital only)

  - **Solution for infusion**
    - Fluconazole (Non-proprietary) 2 mg per 1 ml: Fluconazole 200mg/100ml infusion solution for infusion vials | 1 vial [POT] £15.00–£29.28
    - Fluconazole 400mg/250ml infusion solution for infusion vials | 1 vial [POT] £12.00 (Hospital only)
    - Fluconazole 200mg/100ml solution for infusion vials | 10 vial [POT] £373.60 | 20 bottle [POT] £603.17

  - **Diflucan** (Pfizer Ltd)
    - Fluconazole 2 mg per 1 ml: Diflucan 200mg/100ml solution for infusion vials | 1 vial [POT] £29.28 (Hospital only)

  - **Oral suspension**
    - Fluconazole (Non-proprietary)
      - Fluconazole 10 mg per 1 ml: Fluconazole 200mg/5ml oral suspension solution | 35 ml [POT] £26.52 DT = £20.51
      - Fluconazole 50 mg capsules | 7 capsule [POT] £6.00 DT = £0.72
      - Fluconazole 150 mg capsules | 1 capsule [POT] £16.00 DT = £0.72

  - **Capsule**
    - Fluconazole (Non-proprietary)
      - Fluconazole 50 mg: Fluconazole 50mg capsules | 7 capsule [POT] £6.00 DT = £0.60
      - Fluconazole 150 mg: Fluconazole 150mg capsules | 1 capsule [POT] £16.00 DT = £0.60
      - Fluconazole 200 mg: Fluconazole 200mg capsules | 7 capsule [POT] £6.02 DT = £0.60

  - **Canesten (Fluconazole)** (Bayer Plc)
    - Fluconazole 150 mg: Canesten Thrush Oral 150mg capsules | 1 capsule [POT] £6.33 DT = £0.69

  - **Diflucan (Pfizer Ltd)**
    - Fluconazole 50 mg: Diflucan 50mg capsules | 7 capsule [POT] £16.61 DT = £0.72
    - Fluconazole 150 mg: Diflucan 150mg capsules | 1 capsule [POT] £7.12 DT = £0.69
    - Fluconazole 200 mg: Diflucan 200mg capsules | 7 capsule [POT] £6.42 DT = £3.94

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**Isavuconazole**

- **DRUG ACTION** Isavuconazole is a triazole antifungal that blocks the synthesis of ergosterol, a key component of the fungal cell membrane.

- **INDICATIONS AND DOSE**

  - Invasive aspergillosis: | *Mucormycosis in patients for whom amphotericin B is inappropriate* |
    - By mouth, or by intravenous infusion
    - Adult: Loading dose 200 mg every 8 hours for 48 hours (6 administrations in total), then maintenance 200 mg once daily, maintenance dose to be started at least 12 hours after the last loading dose; long-term treatment should be reviewed after 6–months

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 1058 - short QT syndrome

- **CAUTIONS**
  - Elderly—limited information

- **INTERACTIONS**
  - Appendix 1: antifungals, azoles

- **SIDE-EFFECTS**

  - **GENERAL SIDE-EFFECTS**
    - Common or very common:
      - Appetite decreased - asthenia - chest pain - delirium - diarrhoea - drowsiness - electrolyte imbalance - gastrointestinal discomfort - headache - hepatic disorders - nausea - skin reactions - thrombophlebitis
    - Uncommon:

  - **SPECIFIC SIDE-EFFECTS**
    - Common or very common:
      - With intravenous use: Hyperbilirubinaemia
    - Uncommon:
      - With intravenous use: Peripheral oedema

  - **SIDE-EFFECTS, FURTHER INFORMATION**

  - Infusion-related reactions have been reported, including hypotension, dysphagia, dizziness, paraesthesia, nausea, and headache—manufacturer advises discontinue treatment if these reactions occur.

- **PREGNANCY**
  - Manufacturer advises avoid unless severe or life-threatening infection—toxicity in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment (no information available)—monitor for drug toxicity.

- **DIRECTIONS FOR ADMINISTRATION**

  - With intravenous use: For intravenous infusion, reconstitute each 200 mg with 5 mL water for injection; dilute dose to concentration of 0.8 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give via a 0.2–1.2 micron filter over at least 1 hour.

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- **RENAI IMPAIRMENT**
  - **Dose adjustments**
    - In adults: Usual initial dose then halve subsequent doses if eGFR less than 50 mL/minute/1.73 m².
    - In children: Usual initial dose then halve subsequent doses if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor liver function with high doses or extended courses—discontinue if signs or symptoms of hepatic necrosis.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children: For intravenous infusion, give over 10–30 minutes; do not exceed an infusion rate of 5–10 mL/minute.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral liquid formulations may include orange.

- **PRACTICE SPECIFIC INFORMATION**
  - Dental practitioners’ formula.
  - Fluconazole Capsules 50 mg may be prescribed.
  - Fluconazole Oral Suspension 50 mg; 5 mL may be prescribed.

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Uncommon:
**HANDLING AND STORAGE**
- With intravenous use Manufacturer advises store in a refrigerator (2–8°C)—consult product literature for storage after reconstitution or dilution.

**PATIENT AND CARER ADVICE**
- **Driving and skilled tasks** Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—an increased risk of confusion, syncope and dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**All Wales Medicines Strategy Group (AWMSG) decisions**

**AWMSG No. 2433**

The All Wales Medicines Strategy Group has advised (January 2017) that isavuconazole (Cresemba<sup>®</sup>) is recommended as an option for use in adults within NHS Wales for the treatment of invasive aspergillosis, and the treatment of mucormycosis in patients for whom amphotericin B is inappropriate, only if the approved Wales Patient Access Scheme (WPAS) is used or where the list/contract price is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- Cresemba (Pfizer Ltd)  
  - Isavuconazole (as isavuconazolium sulfate) 200 mg Cresemba 200mg powder for concentrate for solution for infusion vials | £297.84 (Hospital only)

**Capsule**
- Cresemba (Pfizer Ltd)  
  - Isavuconazole (as isavuconazolium sulfate) 100 mg Cresemba 100mg capsules | 14 capsule pack £599.28 (Hospital only)

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**Itraconazole**

**INDICATIONS AND DOSE**

**Vulvovaginal candidiasis**
- **BY MOUTH**
  - Adult: 200 mg twice daily for 1 day

**Vulvovaginal candidiasis (recurrent)**
- **BY MOUTH**
  - Adult: 50–100 mg daily for 6 months

**Oral or oesophageal candidiasis that has not responded to fluconazole**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 100–200 mg twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)

**Oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 200 mg daily in 1–2 divided doses for 1 week (continue for another week if no response)

**Systemic candidiasis where other antifungal drugs inappropriate or ineffective**
- **BY MOUTH**
  - Adult: 100–200 mg once daily

**Systemic candidiasis (invasive or disseminated) where other antifungal drugs inappropriate or ineffective**
- **BY MOUTH**
  - Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Tinea pedis | Tinea manuum**
- **BY MOUTH**
  - Adult: 100 mg once daily for 30 days, alternatively 200 mg twice daily for 7 days

**Tinea corporis | Tinea cruris**
- **BY MOUTH**
  - Adult: 100 mg once daily for 15 days, alternatively 200 mg once daily for 7 days

**Onychomycosis**
- **BY MOUTH**
  - Adult: 200 mg once daily for 3 months, alternatively 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals; fingernails 2 courses, toenails 3 courses

**Aspergillosis**
- **BY MOUTH**
  - Adult: 200 mg twice daily

**Systemic aspergillosis where other antifungal drugs inappropriate or ineffective**
- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Histoplasmosis**
- **BY MOUTH**
  - Adult: 200 mg 3 times a day for 3 days, then 200 mg 1–2 times a day

**BY INTRAVENOUS INFUSION**
  - Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Systemic cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective**
- **BY MOUTH**
  - Adult: 200 mg once daily, dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 200 mg twice daily

**Prophylaxis of deep fungal infections (when standard therapy inappropriate)**
- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate**
- **BY MOUTH**
  - Adult: 200 mg once daily, then increased to 200 mg twice daily, dose increased only if low plasma-itraconazole concentration

**Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 5 mg/kg daily in 2 divided doses, to be started before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers, safety and efficacy not established in elderly patients

**Dose adjustments due to interactions**
- Manufacturer advises max. dose 200 mg daily with concurrent use of cobicistat.

**UNLICENSED USE** Itraconazole doses in BNF may differ from those in product literature.

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**IMPORTANT SAFETY INFORMATION**

**Heart failure**

Following reports of heart failure, caution is advised when prescribing itraconazole to patients at high risk of heart failure. Those at risk include:

- patients receiving high doses and longer treatment courses;

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Infection

- older adults and those with cardiac disease;
- patients with chronic lung disease (including chronic obstructive pulmonary disease) associated with pulmonary hypertension;
- patients receiving treatment with negative inotropic drugs, e.g. calcium channel blockers.

itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure unless the infection is serious.

CONTRA-INDICATIONS Acute porphyrias p. 1058

CAUTIONS Active liver disease • history of hepatotoxicity with other drugs • susceptibility to congestive heart failure

INTERACTIONS ➔ Appendix 1: antifungals, azoles

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Common or very common Alopecia • constipation • diarrhoea • dyspnoea • gastrointestinal discomfort • headache • heart failure • hepatic disorders • hyperbilirubinaemia • nausea • oedema • pulmonary oedema • skin reactions • vision disorders • vomiting
- Uncommon Hearing loss • taste altered
- Rare or very rare Angioedema • hypersensitivity vasculitis • hypertiglyceridaemia • pancreatitis • photosensitivity reaction • severe cutaneous adverse reactions (SCARs)
- Frequency not known Peripheral neuropathy (discontinue)

SPECIFIC SIDE-EFFECTS

- Common or very common
  - With intravenous use Chest pain • confusion • cough • dizziness • drowsiness • electrolyte imbalance • fatigue • gastrointestinal disorder • granulocytopenia • hyperglycaemia • hyperhidrosis • hypersensitivity • hypotension • hypotension • myalgia • pain • renal impairment • tachycardia • tremor • urinary incontinence
- Rare or very rare
  - With oral use Dysphoria • numbness • thrombocytopenia
  - With oral use Flatulence • increased risk of infection • menstrual disorder
- Rare or very rare
  - With oral use Erectile dysfunction • leucopenia • sensation abnormal • serum sickness • tinnitus • urinary frequency increased

SIDE-EFFECTS, FURTHER INFORMATION Potentially life-threatening hepatotoxicity reported very rarely — discontinue if signs of hepatitis develop.

CONCEPTION AND CONTRACEPTION Ensure effective contraception during treatment and until the next menstrual period following end of treatment.

PREGNANCY Manufacturer advises use only in life-threatening situations (toxicity at high doses in animal studies).

BREAST FEEDING Small amounts present in milk — may accumulate; manufacturer advises avoid.

HEPATIC IMPAIRMENT Use only if potential benefit outweighs risk of hepatotoxicity.

Dose adjustments Dose reduction may be necessary.

RENAL IMPAIRMENT Risk of congestive heart failure.

- With oral use Bioavailability of oral formulations possibly reduced.
- With intravenous use Use intravenous infusion with caution if eGFR 30–80 mL/minute/1.73 m²; avoid intravenous infusion if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS

- Absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary).
- Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment.

DIRECTIONS FOR ADMINISTRATION

- With intravenous use For intravenous infusion (Sporanox®), give intermittently in Sodium Chloride 0.9%; dilute 250 mg in 50 mL infusion fluid and infuse only 60 mL through an in-line filter (0.2 micron) over 60 minutes.
- With oral use For oral liquid, do not take with food; swish around mouth and swallow, do not rinse afterwards.

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include cherry.

PATIENT AND CARER ADVICE Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop.

- With oral use Patients or carers should be given advice on how to administer itraconazole oral liquid.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Solution for infusion

EXCIPIENTS: May contain Propylene glycol

- Sporanox (Janssen-Cilag Ltd)
  Itraconazole 10 mg per 1 ml Sporanox IV. 250mg/25ml solution for infusion amoroso and diluent • 1 ampoule (£58.34-£59.25) £59.25

Oral solution

CAUTIONARY AND ADVISORY LABELS 9, 23

- Itraconazole (Non-proprietary)
  - Itraconazole 10 mg per 1 ml Itraconazole 50mg/5ml oral solution sugar free sugar-free • 150 ml (£50) £58.34–£59.25 DT = £59.25
  - Sporanox (Janssen-Cilag Ltd)
  Itraconazole 10 mg per 1 ml Itraconazole 50mg/5ml oral solution sugar-free • 150 ml (£58.34–£59.25 DT = £59.25

Capsule

CAUTIONARY AND ADVISORY LABELS 5, 9, 21, 25

- Itraconazole (Non-proprietary)
  - Itraconazole 100 mg Itraconazole 100mg capsules • 15 capsule (£69.77 DT = £3.24) • 60 capsule (£69.77 DT = £12.96–£15.10
  - Sporanox (Janssen-Cilag Ltd)
  Itraconazole 100 mg Sporanox-Pulse 100mg capsules • 28 capsule (£25.72) £25.72
  Sporanox 100mg capsules • 4 capsule (£3.67) • 15 capsule (£69.77 DT = £3.24) • 60 capsule (£69.77 DT = £55.10

Posaconazole

INDICATIONS AND DOSE

Invasive aspergillosis either refractory to, or in patients intolerant of, itraconazole or amphotericin | Fusariosis either refractory to, or in patients intolerant of, amphotericin | Chromoblastomycosis and mycetoma either refractory to, or in patients intolerant of, itraconazole | Coccidioidomycosis either refractory to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole

- BY MOUTH USING ORAL SUSPENSION
  - Adult: 400 mg twice daily, to be taken with food, alternatively 200 mg 4 times a day, if unable to tolerate food
  - BY MOUTH USING TABLETS, OR BY INTRAVENOUS INFUSION
  - Adult: Loading dose 300 mg twice daily on first day, then 300 mg once daily, switch from intravenous to oral route when appropriate

Oral pain (severe infection or in immunocompromised patients only)

- BY MOUTH USING ORAL SUSPENSION
  - Adult: Loading dose 200 mg on first day, then 100 mg once daily for 13 days, dose to be taken with food

598 | Fungal infection

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Prophylaxis of invasive fungal infections in patients at high risk and undergoing high-dose immunosuppressive therapy for haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome and expected to develop prolonged neutropenia

▶ BY MOUTH USING ORAL SUSPENSION
> Adults: 200 mg 3 times a day, dose to be taken with food, for chemotherapy patients, start several days before the expected onset of neutropenia and continue for 7 days after neutrophil count rises above 500 cells/mm³
> Adults: Loading dose 300 mg twice daily on first day, then 300 mg once daily, for chemotherapy patients, start several days before the expected onset of neutropenia and continue for 7 days after neutrophil count rises above 500 cells/mm³, switch from intravenous to oral route when appropriate

Dose equivalence and conversion
> Posaconazole oral suspension is not interchangeable with tablets on a milligram-for-milligram basis.

Pharmacokinetics
> Posaconazole oral suspension should be taken with food (preferably a high fat meal) or nutritional supplement to ensure adequate exposure for systemic effects. Where possible, tablets should be used in preference to suspension because tablets have a higher bioavailability.

Contraindications
> Acute porphyrias p. 1058

Cautions
> Administration by intravenous infusion, particularly by peripheral catheter—increased risk of QTc interval prolongation - body-weight over 120 kg—risk of treatment failure possibly increased - body-weight under 60 kg—risk of side effects increased • bradycardia - cardiomyopathy - history of QTc interval prolongation - symptomatic arrhythmias

Interactions
> Appendix 1: antifungals, azoles

Side-effects
> Common or very common • Appetite decreased - asthenia - constipation - diarrhoea - dizziness - drowsiness - dry mouth - electrolyte imbalance - gastrointestinal discomfort - gastrointestinal disorders - headache - hypertension - nausea - neutropenia - sensation abnormal - skin reactions - taste altered - vomiting

Rare or very rare • Adrenal insufficiency - breast pain - cardiac arrest - coagulation disorder - depression - encephalopathy - haemolytic uraemic syndrome - hearing impairment - heart failure - myocardial infarction - nephritis tubulointerstitial - neuropathy - perineural disorder - pulmonary hypertension - renal tubular acidosis - Stevens-Johnson syndrome - stroke - sudden cardiac death - syncope

Conception and contraception
> Manufacturer recommends effective contraception during treatment.

Pregnancy
> Manufacturer advises avoid unless potential benefit outweighs risk; toxicity in animal studies.

Breast feeding
> Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment
> Manufacturer advises caution (risk of increased exposure, limited information available).

Renal impairment
> Manufacturer advises monitor efficacy in severe impairment—variable exposure expected.
> With intravenous use • Manufacturer advises caution if eGFR less than 50 mL/minute/1.73 m²—intravenous vehicle may accumulate.

Monitoring requirements
> Monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy.
> Monitor liver function before and during therapy.

Directions for administration
> With intravenous use • Manufacturer advises for intravenous infusion (Noxafil®), give continuously in Glucose 5% or Sodium Chloride 0.9%; dilute requisite dose in infusion fluid to produce a final concentration of 1–2 mg/mL; give via a central venous catheter or peripherally inserted central catheter over approx. 90 minutes (can give a single dose via peripheral venous catheter if central access not established—dilute to a final concentration of 2 mg/mL and give over approx. 30 minutes).

Prescribing and dispensing information
> Flavours of oral liquid formulations may include cherry.

Handling and storage
> With intravenous use • Manufacturer advises store in a refrigerator (2–8 °C).

Patient and carer advice
Driving and skilled tasks • Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and somnolence.

Medicinal forms
> There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

Electrolytes: May contain Sodium
> Noxafil® (Merck Sharp & Dohme Ltd)
> Posaconazole 18 mg per 1 ml Noxafil® 300mg/16.7ml concentrate for solution for infusion vials 1 vial £211.00 (Hospital only)

Oral suspension
> Cautionary and Advisory Labels 3, 9, 21
> Noxafil® (Merck Sharp & Dohme Ltd)
> Posaconazole 40 mg per 1 ml Noxafil® 40mg/ml oral suspension 105 ml (Hospital only) £491.20 (Hospital only)

Gastro-resistant tablet
> Cautionary and Advisory Labels 3, 9, 25
> Noxafil® (Merck Sharp & Dohme Ltd)
> Posaconazole 100 mg Noxafil® 100mg gastro-resistant tablets 24 tablet £596.96 DT + £596.96 96 tablet £2,387.85

Voriconazole

Indications and dose
Invasive aspergillosis • Serious infections caused by Scedosporium spp., Fusarium spp., or invasive fluconazole-resistant Candida spp. (including C. krusei)
> By mouth
> Adult (body-weight up to 40 kg): Initially 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours
> Adult (body-weight 40 kg and above): Initially 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours
> By intravenous infusion
> Adult: Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours; reduced if not tolerated to 3 mg/kg every 12 hours; for max. 6 months
600 Fungal infection

**Dose Adjustments due to Interactions**

- With intravenous use: Manufacturer advises increase maintenance dose to 5 mg/kg every 12 hours with concurrent use of fosphenytoin, phenytoin or rifabutin.
- With oral use: Manufacturer advises increase maintenance dose with concurrent use of fosphenytoin or phenytoin: 400 mg every 12 hours for patients of body-weight 40 kg and above; 200 mg every 12 hours for patients of body-weight less than 40 kg. Manufacturer advises if concurrent use of rifabutin is unavoidable, increase maintenance dose to 350 mg every 12 hours for patients of body-weight 40 kg and above; 200 mg every 12 hours for patients of body-weight less than 40 kg.

**Contra-Indications**
- Acute porphyrias p. 1058

**Caution**
- Avoid exposure to sunlight - bradycardia - cardiomyopathy - electrolyte disturbances - history of QT interval prolongation - patients at risk of pancreatitis - symptomatic arrhythmias

**Interactions**
- Appendix 1: antifungals, azoles

**Side-Effects**

**General Side-Effects**

- **Common**
  - Acute kidney injury
  - Agranulocytosis
  - Alopoeia
  - Anaemia
  - Anxiety
  - Arrhythmias
  - Asthenia
  - Bone marrow disorders
  - Chest pain
  - Chills
  - Confusion
  - Constipation
  - Depression
  - Diarrhoea
  - Dizziness
  - Drowsiness
  - Dyspnoea
  - Electrolyte imbalance
  - Eye disorders
  - Eye inflammation
  - Fever
  - Gastrointestinal discomfort
  - Haemorrhage
  - Hallucination
  - Headache
  - Hepatic disorders
  - Hypoglycaemia
  - Hypotension
  - Increased risk of infection
  - Insomnia
  - Leucopenia
  - Muscle tone increased
  - Nausea
  - Neutropenia
  - Oedema
  - Oral disorders
  - Pain
  - Pulmonary oedema
  - Respiratory disorders
  - Seizure
  - Sensation abnormal
  - Skin reactions
  - Syncope
  - Tetany
  - Thrombocytopenia
  - Tremor
  - Vision disorders
  - Vomiting

- **Uncommon**
  - Adrenal insufficiency
  - Arthritis
  - Brain oedema
  - Duodenitis
  - Encephalopathy
  - Eosinophilia
  - Gallbladder disorders
  - Hearing impairment
  - Hypothyroidism
  - Influenza like illness
  - Lymphadenopathy
  - Lymphangitis
  - Movement disorders
  - Nephritis
  - Nerve disorders
  - Pancreatitis
  - Parkinsonism
  - Phototoxicity
  - Proteinuria
  - Pseudomembranous enterocolitis
  - QT interval prolongation
  - Renal tubular necrosis
  - Severe cutaneous adverse reactions (SCARs)
  - Taste altered
  - Thrombophlebitis
  - Tinnitus
  - Vertigo

- **Rare or very rare**
  - Angiœdœma
  - Cardiac conduction disorders
  - Disseminated intravascular coagulation
  - Hyperthyroidism

- **Frequency not known**
  - Cutaneous lupus erythematosus
  - Periostitis (more common in transplant patients)
  - Squamous cell carcinoma (more common in presence of phototoxicity)

**Specific Side-Effects**

- With intravenous use: Infusion related reaction

**Side-Effects, Further Information**

**Hepatotoxicity**

Hepatitis, cholestasis, and acute hepatic failure have been reported; risk of hepatotoxicity increased in patients with haematological malignancy. Consider treatment discontinuation if severe abnormalities in liver function tests.

**Phototoxicity**

Phototoxicity occurs uncommonly. If phototoxicity occurs, consider treatment discontinuation; if treatment is continued, monitor for pre-malignant skin lesions and squamous cell carcinoma, and discontinue treatment if they occur.

**Conception and Contraception**

Effective contraception required during treatment.

**Pregnancy**

Toxicity in animal studies - manufacturer advises avoid unless potential benefit outweighs risk.

**Breast Feeding**

Manufacturer advises avoid - no information available.

**Hepatic Impairment**

Manufacturer advises caution, particularly in severe impairment (no information available).

**Dose Adjustments**

Manufacturer advises use initial loading dose then halve maintenance dose in mild to moderate cirrhosis.

**Renal Impairment**

Intravenous vehicle may accumulate if eGFR less than 50 mL/minute/1.73 m² — use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required).

**Monitoring Requirements**

- Monitor renal function.
- Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly during treatment.

**Directions for Administration**

- With intravenous use: For intravenous infusion, reconstitute each 200 mg with 19 mL. Water for Injections or Sodium Chloride 0.9% to produce a 10 mg/mL solution; dilute dose to concentration of 0.5 – 5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give intermittently at a rate not exceeding 3 mg/kg/hour.

**Prescribing and Dispensing Information**

- Flavours of oral liquid formulations may include orange.

**Patient and Carer Advice**

- Patients and their carers should be told how to recognise symptoms of liver disorder, and advised to seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Patients and their carers should be advised that patients should avoid intense or prolonged exposure to direct sunlight, and to avoid the use of sunbeds. In sunlight, patients should cover sun-exposed areas of skin and use a sunscreen with a high sun protection factor. Patients should seek medical attention if they experience sunburn or a severe skin reaction following exposure to light or sun.

Patients and their carers should be advised to keep the alert card with them at all times.

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Powder for Solution for Infusion**

**Excipients:** May contain Sodium Bicarbonate, Sodium Chloride, Lactose, Sorbitol, Gelatin, Sodium Hypophosphite.

**Voriconazole (Non-proprietary)**

Voriconazole 200 mg

Voriconazole 50 mg, 100 mg tablets for solution for infusion vials: 1 vial (Pfizer Ltd) £51.43 – £77.14 (Hospital only)

VFEND (Pfizer Ltd)

Voriconazole 200 mg

VFEND 200 mg powder for solution for infusion vials: 1 vial (Pfizer Ltd) £77.14 (Hospital only)

**Oral Suspension**

**Cautionary and Advisory Labels** 9, 11, 23

VFEND (Pfizer Ltd)

Voriconazole 40 mg per 1 ml

VFEND 40 mg/ml oral suspension: 75 ml (Pfizer Ltd) £55.37

**Tablet**

**Cautionary and Advisory Labels** 9, 11, 23

Voriconazole 50 mg

Voriconazole 50 mg tablets: 10 tablets (Pfizer Ltd) £275.68

Voriconazole 100 mg

Voriconazole 100 mg tablets: 10 tablets (Pfizer Ltd) £1,102.74 £680.92

VFEND (Pfizer Ltd)

Voriconazole 50 mg

VFEND 50 mg tablets: 10 tablets (Pfizer Ltd) £275.68 £1,102.74

Voriconazole 200 mg

VFEND 200 mg tablets: 10 tablets (Pfizer Ltd) £1,102.74 £680.92

www.getintopharma.com
Pneumocystis pneumonia

Overview

Pneumonia caused by *Pneumocystis jirovecii* (Pneumocystis carinii) occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

**Treatment**

Mild to moderate disease

Co-trimoxazole p. 562 in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

Atovaquone p. 602 is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole. A combination of dapsone p. 577 with trimethoprim p. 574 is given by mouth for the
treatment of mild to moderate disease [unlicensed indication]. A combination of clindamycin p. 535 and primaquine p. 618 by mouth is used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

Severe disease

Co-trimoxazole in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. Pentamidine isetionate below given by intravenous infusion is an alternative for patients who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion. Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia.

Adjunctive therapy

In moderate to severe infections associated with HIV infection, prednisolone p. 678 is given by mouth for 5 days (alternatively, hydrocortisone p. 676 may be given parenterally); the dose is then reduced to complete 21 days of treatment. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

Prophylaxis

Prophylaxis against pneumocystis pneumonia should be given to all patients with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients. Prophylaxis should continue until immunity recovers sufficiently. It should not be discontinued if the patient has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy. Co-trimoxazole by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. It is given daily or on alternate days (3 times a week); the dose may be reduced to improve tolerance. Inhaled pentamidine isetionate is better tolerated than parenteral pentamidine isetionate. Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in patients unable to tolerate co-trimoxazole. It is effective but patients may be prone to extrapulmonary infection. Alternatively, dapsone can be used. Atovaquone has also been used for prophylaxis [unlicensed indication].

ANTIPROTOZOAALs

Atovaquone

- **INDICATIONS AND DOSE**
  - **Treatment of mild to moderate Pneumocystis jirovecii (Pneumocystis carinii) pneumonia in patients intolerant of co-trimoxazole**
    - **BY MOUTH**
      - Adult: 750 mg twice daily for 21 days, dose to be taken with food, particularly high fat food
  - **Prophylaxis against pneumocystis pneumonia**
    - **BY MOUTH**
      - Adult: 750 mg twice daily
  - **UNLICENSED USE** Not licensed for prophylaxis against pneumocystis pneumonia.
  - **CAUTIONS** Other causes of pulmonary disease should be sought and treated - elderly - initial diarrhoea and difficulty in taking food may reduce absorption (and require alternative therapy)

- **INTERACTIONS** → Appendix 1: antimalarials
- **SIDE-EFFECTS**
  - Common or very common Anaemia - angioedema - bronchospasm - diarrhoea - headache - hypersensitivity - hypoglycaemia - insomnia - nausea - neutropenia - skin reactions - throat tightness - vomiting
  - Frequency not known Stevens-Johnson syndrome
  - PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—no information available.
  - BREAST FEEDING Manufacturer advises avoid.
  - HEPATIC IMPAIRMENT Manufacturer advises use with caution in significant impairment and monitor closely—no information available.
  - RENAL IMPAIRMENT Manufacturer advises caution. Monitoring Monitor more closely in renal impairment.
  - PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include tutti-frutti.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
- **Oral suspension** CAUTIONARY AND ADVISORY LABELS
  - 21 Wellvone (GlaxoSmithKline UK Ltd) Atovaquone 150 mg per 1 ml Wellvone 750mg/5ml oral suspension sugar-free | 226 ml [P] £486.37 DT + £486.37

### Pentamidine isetionate

- **INDICATIONS AND DOSE**
  - **Treatment of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 4 mg/kg once daily for at least 14 days
  - **Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia (specialist use only)**
    - **BY INHALATION OF NEBULISED SOLUTION**
      - Adult: 300 mg every 4 weeks, alternatively 150 mg every 2 weeks, using suitable equipment—consult product literature
  - **Visceral leishmaniasis (specialist use only)**
    - **BY DEEP INTRAMUSCULAR INJECTION**
      - Adult: 3–4 mg/kg once daily on alternate days, maximum total of 10 injections, course may be repeated if necessary
  - **Cutaneous leishmaniasis (specialist use only)**
    - **BY DEEP INTRAMUSCULAR INJECTION**
      - Adult: 3–4 mg/kg 1–2 times a week until condition resolves
  - **Trypanosomiasis (specialist use only)**
    - **BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 4 mg/kg once daily or on alternate days for a total of 7–10 injections

- **UNLICENSED USE** Not licensed for primary prevention of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia by inhalation of nebulised solution.
- **CAUTIONS** Anaemia - bradycardia - coronary heart disease - history of ventricular arrhythmias - hyperglycaemia - hypertension - hypoglycaemia - hypokalaemia - hypomagnesaemia - hypotension - leucopenia - risk of severe hypotension following administration - thrombocytopenia
- **INTERACTIONS** → Appendix 1: pentamidine
- **SIDE-EFFECTS**
  - Common or very common Dizziness - hypoglycaemia (can be severe and sometimes fatal) - hypotension (can be
severe and sometimes fatal) - local reaction - nausea - rash - taste altered
  ▶ Rare or very rare QT interval prolongation
  ▶ Frequency not known Pancreatitis acute (can be severe and sometimes fatal)

**SPECIFIC SIDE-EFFECTS**
  ▶ Common or very common
    - When used by inhalation Cough - dyspnoea - respiratory disorders
  ▶ Rare or very rare
    - With parenteral use Arrhythmias - perioral hypoaesthesia - sensation abnormal - Stevens-Johnson syndrome
  ▶ PREGNANCY Manufacturer advises avoid unless essential.
  ▶ BREAST FEEDING Manufacturer advises avoid unless essential—no information available.
  ▶ HEPATIC IMPAIRMENT Manufacturer advises caution.
  ▶ RENAL IMPAIRMENT
    - Dose adjustments: Reduce intravenous dose for pneumocystis pneumonia if creatinine clearance less than 10 mL/minute: in life-threatening infection, use 4 mg/kg once daily for 7–10 days, then 4 mg/kg on alternate days to complete course of at least 14 doses; in less severe infection, use 4 mg/kg on alternate days for at least 14 doses.
  ▶ MONITORING REQUIREMENTS
    - Monitor blood pressure before starting treatment, during treatment and personnel should be adequately protected during handling and administration.
    - Carry out laboratory monitoring according to product literature.
    - Directions for administration: Patient should be lying down when receiving drug parenterally. Direct intravenous injection should be avoided whenever possible and never given rapidly; intramuscular injections should be deep and preferably given into the buttck. For intravenous infusion, reconstitute 300 mg with 3–5 mL. Water for Injections (displacement value may be significant), then dilute required dose with 50–250 mL. Glucose 5% or Sodium Chloride 0.9%; give over at least 60 minutes.
    - Powder for injection (dissolved in water for injection) may be used for nebulisation.
  ▶ HANDLING AND STORAGE: Pentamidine isetionate is toxic and personnel should be adequately protected during handling and administration—consult product literature.
  ▶ MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
  ▶ Pentacamrinat (Sanofi)
    - Pentamidine isetionate 300 mg
    - Pentacamrinat 300mg powder for solution for injection vials | 5 vial (PO) £158.86

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**4 Helminth infection**

**Helminth infections**

**Specialist centres**

Advice on prophylaxis and treatment of helminth infections is available from the following specialist centres:

<table>
<thead>
<tr>
<th>Location</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
<td>(0121) 424 0357</td>
</tr>
<tr>
<td>Scotland</td>
<td>Contact local Infectious Diseases Unit</td>
</tr>
<tr>
<td>Liverpool</td>
<td>(0151) 705 3100</td>
</tr>
<tr>
<td>London</td>
<td>0845 155 5000 (treatment)</td>
</tr>
</tbody>
</table>

**Threadworms**

Anthelmintics are effective in threadworm (pinworms, *Enterobius vermicularis*) infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment.

Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Washing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole p. 605 is the drug of choice for treating threadworm infection in patients of all ages over 6 months. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

**Ascaricides (common roundworm infections)**

Mebendazole is effective against *Ascaris lumbricoides* and is generally considered to be the drug of choice. Levamisole p. 605 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is the alternative when mebendazole cannot be used. It is very well tolerated.

**Tapeworm infections**

**Taenicides**

Niclosamide [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus; it is not effective against larval worms. Fears of developing cysticercosis in *Taenia solium* infections have proved unfounded. All the same, an antimitic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel p. 605 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is as effective as niclosamide.

**Hydatid disease**

Cysts caused by *Echinococcus granulosus* grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. Albenzaule p. 604 [unlicensed] (available from 'special-order' manufacturers or specialist importing companies) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Alveolar echinococcosis due to *E. multilocularis* is usually fatal if untreated. Surgical removal with albenzaule cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albenzaule (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

**Hookworms**

Hookworms (ancylostomiasis, necatoriasis) live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection
requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole has a useful broad-spectrum activity, and is effective against hookworms. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is an alternative. Levamisole is also is also effective in children.

Schistosomiasis (bilharziasis)
Adult Schistosoma haematobium worms live in the genito-urinary veins and adult S. mansoni in those of the colon and mesentery. S. japonicum is more widely distributed in veins of the alimentary tract and portal system.

Praziquantel [unlicensed] is available from Merck Serono (Cysticide®) and is effective against all human schistosomes. No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

Filaricides
Diethylcarbamazine [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is effective against microfilariae and adults of Loa loa, Wuchereria bancrofti, and Brugia malayi. To minimise reactions, treatment in adults and children over 1 month, is commenced with a dose of diethylcarbamazine citrate on the first day and increased gradually over 3 days. Length of treatment varies according to infection type, and usually gives a radical cure for these infections. Close medical supervision is necessary particularly in the early phase of treatment.

In heavy infections there may be a febrile reaction, and in heavy Loa loa infection there is a small risk of encephalopathy. In such cases specialist advice should be sought, and treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement.

Ivermectin below [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is very effective in onchocerciasis and it is now the drug of choice; reactions are usually slight. Diethylcarbamazine or suramin should no longer be used for onchocerciasis because of their toxicity.

Cutaneous larva migrans (creeping eruption)
Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical tiabendazole (no commercial preparation available). Multiple infections respond to ivermectin, albendazole or thiabendazole (thiabendazole) by mouth [all unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies).

Strongyloidiasis
Adult Strongyloides stercoralis live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. Ivermectin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for chronic Strongyloides infection in adults and children over 5 years. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is an alternative given to adults and children over 2 years.

**ANTHELMINTICS**

### Albendazole

- **INDICATIONS AND DOSE**
  - Chronic Strongyloides infection
    - By mouth
    - Adult: 400 mg twice daily for 3 days, dose may be repeated after 3 weeks if necessary
  - Hydatid disease, in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases
    - By mouth
    - Adult: (consult product literature)

- **UNLICENSED USE** Albendazole is an unlicensed drug.
- **INTERACTIONS** → Appendix 1: albendazole

### Diethylcarbamazine

- **INDICATIONS AND DOSE**
  - Wuchereria bancrofti infections | Brugia malayi infections
    - By mouth
    - Adult: Initially 1 mg/kg daily on the first day, then increased to 6 mg/kg daily in divided doses, dose to be increased gradually over 3 days

- **UNLICENSED USE** Diethylcarbamazine is an unlicensed drug.

### Ivermectin

- **INDICATIONS AND DOSE**
  - Chronic Strongyloides infection
    - By mouth
    - Adult: 200 micrograms/kg daily for 2 days
  - Onchocerciasis
    - By mouth
    - Adult: 150 micrograms/kg for 1 dose, retreatment at intervals of 6 to 12 months, depending on symptoms, must be given until the adult worms die out
Helminth infection 605

Scabies, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone

- **BY MOUTH**
  - Adult: 200 micrograms/kg for 1 dose, further doses of 200 micrograms/kg may be required

- **UNLICENSED USE** Ivermectin is unlicensed.
- **INTERACTIONS** → Appendix 1: ivermectin
- **SIDE-EFFECTS**
  - Common or very common Skin reactions

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet
  - Tablet
    - **Stromectol (Imported (France))**
      - Ivermectin 3 mg Stromectol 3mg tablets | 4 tablet [PDF]

Levamisole

- **INDICATIONS AND DOSE**
  - **Roundworm infections**
    - **BY MOUTH**
    - Adult: 120–150 mg for 1 dose

- **UNLICENSED USE** Not licensed.
- **CONTRA-INDICATIONS** Blood disorders
- **CAUTIONS** Epilepsy - Sjögren’s syndrome
- **INTERACTIONS** → Appendix 1: levamisole
- **SIDE-EFFECTS** Arthralgia (long term use) - blood disorder (long term use) - diarroha - dizziness - headache - influenza like illness (long term use) - insomnia (long term use) - myalgia (long term use) - nausea - rash (long term use) - seizure (long term use) - taste altered (long term use) - vasculitis (long term use) - vomiting
- **PREGNANCY** Embryotoxic in animal studies, avoid if possible.
- **BREAST FEEDING** No information available.
- **HEPATIC IMPAIRMENT** Dose adjustments Use with caution—dose adjustment may be necessary.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet
  - Tablet
    - CAUTIONARY AND ADVISORY LABELS 4
      - Ergamisol (Imported (Belgium))
        - Levamisole (as Levamisole hydrochloride) 50 mg Ergamisol 50mg tablets | 20 tablet [PDF]

Mebendazole

- **INDICATIONS AND DOSE**
  - **Threadworm infections**
    - **BY MOUTH**
      - Child 6 months–17 years: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks
      - Adult: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks
  - **Whipworm infections | Hookworm infections**
    - **BY MOUTH**
      - Child 1–17 years: 100 mg twice daily for 3 days
      - Adult: 100 mg twice daily for 3 days
  - **Roundworm infections**
    - **BY MOUTH**
      - Child 1 year: 100 mg twice daily for 3 days

- **Child 2–17 years**: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose
- **Adult**: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose

- **UNLICENSED USE** Not licensed for use as a single dose of 500 mg in roundworm infections.
- **In children** Not licensed for use in children under 2 years.
- **INTERACTIONS** → Appendix 1: mebendazole
- **SIDE-EFFECTS**
  - Common or very common Gastrointestinal discomfort
  - Uncommon Diarroha - flatulence
  - Rare or very rare Alopecia - dizziness - hepatitis - neutropenia - seizure - severe cutaneous adverse reactions (SCARs) - skin reactions
- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
- **BREAST FEEDING** Amount present in milk too small to be harmful but manufacturer advises avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include banana.
- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Mebendazole for worm infections www.medicinesforchildren.org.uk/mebendazole-worm-infections

- **EXCEPTIONS TO LEGAL CATEGORY** Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Oral suspension**
    - **Vermox (Janssen-Cilag Ltd)**
      - Mebendazole 20 mg per 1 ml Vermox 100mg/5ml oral suspension | 30 ml [PDF] £1.55 DT + £1.55
  - **Chewable tablet**
    - **Vermox (Janssen-Cilag Ltd)**
      - Mebendazole 100 mg Vermox 100mg chewable tablets sugar-free | 6 tablet [PDF] £1.34 DT + £1.34

Praziquantel

- **INDICATIONS AND DOSE**
  - **Tapeworm infections (Taenia solium)**
    - **BY MOUTH**
      - Adult: 5–10 mg/kg for 1 dose, to be taken after a light breakfast
  - **Tapeworm infections (Hymenolepis nana)**
    - **BY MOUTH**
      - Adult: 25 mg/kg for 1 dose, to be taken after a light breakfast
  - **Schistosoma haematobium worm infections | Schistosoma mansoni worm infections**
    - **BY MOUTH**
      - Adult: 20 mg/kg, followed by 20 mg/kg after 4–6 hours
  - **Schistosoma japonicum worm infections**
    - **BY MOUTH**
      - Adult: 20 mg/kg 3 times a day for 1 day

- **UNLICENSED USE** Praziquantel is an unlicensed drug.
- **INTERACTIONS** → Appendix 1: praziquantel

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet
  - **Tablet**
    - **Praziquantel (Imported (Germany))**
      - Praziquantel 600 mg Biltricide 600mg tablets | 6 tablet [PDF]
Protozoal infection

5 Amoebicides

Metronidazole p. 542 is the drug of choice for acute invasive amoebic dysentery since it is very effective against vegetative forms of Entamoeba histolytica in ulcers. Tindazole p. 544 is also effective. Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver. Treatment with metronidazole (or tinidazole) is followed by a 10-day course of diloxanide furoate.

Diloxanide furoate is the drug of choice for asymptomatic patients with E. histolytica cysts in the faeces; metronidazole and tinidazole are relatively ineffective. Diloxanide furoate is relatively free from toxic effects and the usual course is of 10 days, given alone for chronic infections or following metronidazole or tinidazole treatment.

For amoebic abscesses of the liver metronidazole is effective; tinidazole is an alternative. Aspiration of the abscess is indicated where it is suspected that it may rupture or where there is no improvement after 72 hours of metronidazole; the aspiration may need to be repeated. Aspiration aids penetration of metronidazole and, for abscesses with more than 100 mL of pus, if carried out in conjunction with drug therapy, may reduce the period of disability.

Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

Trichomonacides

Metronidazole is the treatment of choice for Trichomonas vaginalis infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, tinidazole may be tried.

Antigiardial drugs

Metronidazole is the treatment of choice for Giardia lamblia infections. Alternative treatments are tinidazole or mepacrine hydrochloride p. 505.

Leishmaniacides

Cautious leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate below, an organic pentavalent antimony compound, is used for visceral leishmaniasis. The dosage varies with different geographical regions and expert advice should be obtained. Some early non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate under specialist supervision.

Amphotericin, p. 593 is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (Ambisome®). Abelcet®, a lipid formulation of amphotericin, is also likely to be effective but less information is available.

Pentamidine isethionate p. 602 has been used in antimoney-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies).

Trypanocides

The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

Toxoplasmosis

Most infections caused by Toxoplasma gondii are self-limiting, and treatment is not necessary. Exceptions are patients with eye involvement (toxoplasma chorioretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine p. 620 and sulfadiazine p. 563, given for several weeks (expert advice essential). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folic acid supplements and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin p. 535 or clari-thromycin p. 538 or azithromycin p. 536. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus; specialist advice should be sought on management. Spiramycin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) may reduce the risk of transmission of maternal infection to the fetus.

5.1 Leishmaniasis

Other drugs used for Leishmaniasis Amphotericin, p. 593 • Pentamidine isethionate, p. 602

ANTIPROTOZOALS

Sodium stibogluconate

- INDICATIONS AND DOSE

Visceral leishmaniasis (specialist use only)
- By intravenous injection, or by intramuscular injection
- Adult: 20 mg/kg daily for 28 days

Cutaneous leishmaniasis (specialist use only)
- By intravenous injection, or by intramuscular injection
- Adult: 20 mg/kg daily for 20 days

- CAUTIONS
Heart disease (withdraw if conduction disturbances occur) • mucocutaneous disease • predisposition to QT interval prolongation • treat intercurrent infection (e.g. pneumonia)

- INTERACTIONS → Appendix 1: sodium stibogluconate

- SIDE-EFFECTS
• Common or very common Abdominal pain • appetite decreased • arthralgia • diarrhoea • headache • lethargy • malaise • myalgia • nausea • vomiting
• Rare or very rare Chest pain • chills • fever • flushing • haemorrhage • hyperhidrosis • jaundice • skin reactions • vertigo
Malaria, prophylaxis against malaria

The recommendations on prophylaxis against malaria reflect guidelines agreed by UK malaria specialists, published in the Public Health England Guidelines for malaria prevention in travellers from the United Kingdom (2018) published by Public Health England state that patients already taking hydroxychloroquine or doxycycline should remain on hydroxychloroquine or doxycycline, but can be used in the treatment of falciparum malaria with (or following) quinine.

Quinine
Quinine should not be used alone, but is used with sulfadoxine.

Pyrimethamine
Pyrimethamine is not recommended for the prophylaxis of falciparum malaria with (or following) quinine.

Useful resources
All recommendations on prophylaxis against malaria reflect guidelines agreed by UK malaria specialists, published in the Public Health England Guidelines for malaria prevention in travellers from the United Kingdom, 2018. The advice is aimed at residents of the UK who travel to endemic areas.

Malaria, prophylaxis against malaria

The recommendations on prophylaxis against malaria reflect guidelines agreed by UK malaria specialists, published in the Public
Infection

malaria

If all recommended precautions against contracting the disease are not taken, even if all recommended precautions against malaria were taken. Travellers should be warned of this and told that if they develop any illness particularly within 3 months of their return they should see a doctor immediately and specifically mention their exposure to malaria.

Epilepsy

Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in individuals with a history of epilepsy. In these patients, doxycycline or atovaquone with proguanil hydrochloride may be used. However doxycycline may interact with some antiepileptics and its dose may need to be adjusted, see interactions information for doxycycline.

Asplenia

Asplenic individuals (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.

Pregnancy

Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable, effective prophylaxis must be used. Chloroquine and proguanil hydrochloride can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined. In the case of proguanil hydrochloride, folic acid p. 1025 (dosed as a pregnancy at ‘high-risk’ of neural tube defects) should be given for at least the first trimester. If travelling to high risk areas or there is resistance to other drugs, mefloquine may be considered during the second or third trimester of pregnancy. Mefloquine can be used in the first trimester with caution if the benefits outweigh the risks. Doxycycline is contra-indicated during pregnancy; however, it can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation [unlicensed]. Atovaquone with proguanil hydrochloride should be avoided during pregnancy, however, it can be considered during the second and third trimesters if there is no suitable alternative. Folic acid (dosed as a pregnancy at ‘high-risk’ of neural tube defects) should be given if atovaquone with proguanil hydrochloride is used during pregnancy.

Breast-feeding

Some antimalarials should be avoided when breast feeding, see individual drugs for details.

Prophylaxis is required in breast-fed infants; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants

Travellers taking warfarin sodium p. 140 should begin chemoprophylaxis 2–3 weeks before departure and the INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Other medical conditions

For additional information on malaria prophylaxis in patients with other medical conditions, see Public Health England Guidelines for malaria prevention in travellers from the UK.

Standby treatment

Travellers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be avoided if medical help is accessible. In order to avoid excessive self-medication, the traveller should be provided with written instructions that urgent medical attention should be sought if fever (38°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

Specialist centres offering advice on specific malaria-related problems, see Malaria, treatment p. 613. The choice of drug for a particular individual should take into account:

- risk of exposure to malaria
- extent of drug resistance
- efficacy of the recommended drugs
- side-effects of the drugs
- patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen)

For more information on choice of drug, see also Antimalarials p. 607.

Protection against bites

Prophylaxis is not absolute, and breakthrough infection can occur with any of the drugs recommended. Personal protection against being bitten is very important and is recommended even in malaria-free areas as a preventive measure against other insect vector-borne diseases. Mosquito nets impregnated with permethrin p. 1237 provide the most effective barrier protection against insects; mats and vapourised insecticides are also useful. Diethyltoluamide (DEET) 20–50% (available as sprays, and modified-release polymer formulations) is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. However, ingestion should be avoided, therefore breast-feeding mothers should wash their hands and breast tissue before handling infants. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. When sunscreen is also required, DEET should be applied after the sunscreen. DEET reduces the SPF of sunscreen, so a sunscreen of SPF 30–50 should be applied. If DEET is not tolerated or is unavailable, see Public Health England Guidelines for malaria prevention in travellers from the United Kingdom for alternative options. Long sleeves and trousers worn after dusk also provide protection against bites.

Length of prophylaxis

In order to determine tolerance and to establish habit, prophylaxis should generally be started before travel into an endemic area; 1 week before travel for chloroquine p. 616 and proguanil hydrochloride p. 618; 2–3 weeks before travel for mefloquine p. 617; and 1–2 days before travel for atovaquone with proguanil hydrochloride p. 615 or doxycycline p. 564. Prophylaxis should be continued for 4 weeks after leaving the area (except for atovaquone with proguanil hydrochloride prophylaxis which should be stopped 1 week after leaving). For extensive journeys across different regions, the traveller must be protected in all areas of risk.

In those requiring long-term prophylaxis, chloroquine and proguanil hydrochloride may be used. However there is considerable concern over the protective efficacy of the combination of chloroquine and proguanil hydrochloride in certain areas where it was previously useful. Mefloquine is licensed for use up to 1 year (although, if it is tolerated in the short term, there is no evidence of harm when it is used for up to 3 years). Doxycycline can be used for up to 2 years, and atovaquone with proguanil hydrochloride for up to 1 year. Prophylaxis with mefloquine, doxycycline, or atovaquone with proguanil hydrochloride may be considered for longer durations if it is justified by the risk of exposure to malaria.

Specialist advice should be sought for long-term prophylaxis.

Return from malarial region

It is important to consider that any illness that occurs within 1 year and especially within 3 months of return might be malaria even if all recommended precautions against malaria were taken. Travellers should be warned of this and told that if they develop any illness particularly within 3 months of their return they should see a doctor immediately and specifically mention their exposure to malaria.
### Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>No risk</td>
</tr>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
</tbody>
</table>

### Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>Low risk below 2000 m from May-November</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk below 2000 m from December-April</td>
<td>1</td>
</tr>
<tr>
<td>Algeria</td>
<td>Low risk in remote focus in Illizi department only</td>
<td>1</td>
</tr>
<tr>
<td>Andaman and Nicobar Islands (India)</td>
<td>Low risk</td>
<td>1</td>
</tr>
<tr>
<td>Angola</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Argentina</td>
<td>Very low risk in low altitude areas of Salta provinces bordering Bolivia and in Chaco, Corrientes, and Misiones provinces close to border with Paraguay and Brazil</td>
<td>1</td>
</tr>
<tr>
<td>Armenia</td>
<td>No risk in Iguazu Falls and areas other than those above</td>
<td>-</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>Low risk in Chittagong Hill Tract districts (but not Chittagong city)</td>
<td>4</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Very low risk in Chittagong city and other areas, except Chittagong Hill Tract districts</td>
<td>1</td>
</tr>
<tr>
<td>Belize</td>
<td>Low risk in rural areas</td>
<td>1</td>
</tr>
<tr>
<td>Benin</td>
<td>No risk in Belize district (including Belize city and islands)</td>
<td>-</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Low risk in southern belt districts, along border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkhar, and Shemgang</td>
<td>1</td>
</tr>
<tr>
<td>No risk in areas other than those above</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bolivia</td>
<td>Low risk in Amazon basin</td>
<td>1</td>
</tr>
<tr>
<td>Botswana</td>
<td>Low risk in rural areas below 2500 m (other than above)</td>
<td>1</td>
</tr>
<tr>
<td>No risk above 2500 m</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>Low risk in Amazon basin, including city of Manaus</td>
<td>1</td>
</tr>
<tr>
<td>No risk in areas other than those above</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Burundi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Low risk, Mefloquine resistance widespread in western provinces bordering Thailand</td>
<td>1</td>
</tr>
<tr>
<td>Very low risk in Angkor Wat and Lake Tonle Sap, including Siem Reap</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No risk in Phnom Penh</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cape Verde</td>
<td>Individuals travelling to Praia who are at increased risk of malaria (such as long-term travellers and those at risk of severe complications from malaria including pregnant women, infants and young children, the elderly, and asplenic individuals) should consider taking antimalarials, seek advice from a travel health advisor. Very low risk on island of Santiago (Sao Tiago) and Boa Vista</td>
<td>1</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Chad</td>
<td>High risk</td>
<td>4</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Low risk in Yunnan and Hainan provinces</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in southern and some central provinces, including Anhui, Ghuizhou, Hena, Hubei, and Jiangsu below 1500 m</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above and below</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Hong Kong</td>
<td>-</td>
</tr>
<tr>
<td>Colombia</td>
<td>Low risk in rural areas below 1600 m</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk above 1600 m and in Cartagena</td>
<td>1</td>
</tr>
<tr>
<td>Comoros</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Low risk in Limon province, but not city of Limon (Puerto Limon)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Cote d'Ivoire (Ivory Coast)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Djibouti</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>Low risk</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in cities of Santiago and Santo Domingo</td>
<td>-</td>
</tr>
<tr>
<td>East Timor (Timor-Leste)</td>
<td>Risk present</td>
<td>4</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Low risk in areas below 1500 m including coastal provinces and Amazon basin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Galapagos islands or city of Guayaquil</td>
<td>-</td>
</tr>
<tr>
<td>Egypt</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>El Salvador</td>
<td>Low risk in rural areas of Santa Ana, Ahuachapán, and La Unión provinces in western part of country; very low risk in other areas</td>
<td>1</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Eritrea</td>
<td>High risk below 2200 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>No risk in Asmara or in areas above 2200 m</td>
<td>-</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>High risk below 2000 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>No risk in Addis Ababa or in areas above 2000 m</td>
<td>-</td>
</tr>
<tr>
<td>French Guiana</td>
<td>Risk present (particularly in border areas) except city of Cayenne or Devil’s Island (Ile du Diable)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk in city of Cayenne or Devil’s Island (Ile du Diable)</td>
<td>1</td>
</tr>
<tr>
<td>Gabon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Gambia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Georgia</td>
<td>Very low risk in rural south east from June–October</td>
<td>1</td>
</tr>
<tr>
<td>Ghana</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Low risk below 1500 m</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Guatemala City, Antigua, or Lake Atitlan and above 1500 m</td>
<td>-</td>
</tr>
<tr>
<td>Guinea</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guyana</td>
<td>Risk present in all interior regions</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Georgetown and coastal region</td>
<td>1</td>
</tr>
<tr>
<td>Haiti</td>
<td>Risk present</td>
<td>3</td>
</tr>
<tr>
<td>Honduras</td>
<td>Low risk below 1000 m and in Roatán and other Bay Islands</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in San Pedro Sula or Tegucigalpa and areas above 1000 m</td>
<td>-</td>
</tr>
<tr>
<td>India</td>
<td>Risk present in states of Assam and Orissa, districts of East Godavari, Srikakulam, Vishakhapatnam, and Vizianagaram in the state of Andhra Pradesh, and districts of Balaghat, Dindori, Mandla, and Seoni in the state of Madhya Pradesh</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk in areas other than those above and below (including Goa, Andaman and Nicobar islands)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Exceptional circumstances in low risk areas (dependent on individual risk assessment)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No risk in Lakshadweep Islands</td>
<td>-</td>
</tr>
<tr>
<td>Indonesia</td>
<td>High risk in Irian Jaya (Papua)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk in Bali, Lombok and islands of Java and Sumatra</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Jakarta</td>
<td>-</td>
</tr>
<tr>
<td>Indonesia (Borneo)</td>
<td>Low risk</td>
<td>1</td>
</tr>
</tbody>
</table>
### Key to recommended regimens for prophylaxis against malaria

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<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iran</td>
<td>Low risk from March–November in rural south eastern provinces and in north, along Azerbaijan border in Ardabil, and near Turkmenistan border in North Khorasan</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above</td>
<td></td>
</tr>
<tr>
<td>Iraq</td>
<td>Very low risk from May–November in rural northern area below 1500 m</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in areas other than those above</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>High risk (except city of Nairobi)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in the highlands above 2500 m and in city of Nairobi</td>
<td>1</td>
</tr>
<tr>
<td>Lao People's Democratic Republic (Laos)</td>
<td>Low risk</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in city of Vientiane</td>
<td></td>
</tr>
<tr>
<td>Liberia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Libya</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Madagascar</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malawi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Low risk in mainland Malaysia</td>
<td>1</td>
</tr>
<tr>
<td>Malaysia (Borneo)</td>
<td>Low risk in inland areas of Sabah and in inland, forested areas of Sarawak</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above, including coastal areas of Sabah and Sarawak</td>
<td>1</td>
</tr>
<tr>
<td>Mali</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Mauritania</td>
<td>High risk all year in southern provinces, and from July–October in the northern provinces</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk from November–June in the northern provinces</td>
<td>1</td>
</tr>
<tr>
<td>Mauritius</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Mayotte</td>
<td>Risk present</td>
<td>4</td>
</tr>
<tr>
<td>Mexico</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Mozambique</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Myanmar</td>
<td>Low risk</td>
<td>1</td>
</tr>
<tr>
<td>Namibia</td>
<td>High risk all year in regions of Caprivi Strip, Kavango, and Kunene river, and from November–June in northern third of country</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above; low risk from July–October in northern third of country</td>
<td>1</td>
</tr>
<tr>
<td>Nepal</td>
<td>Low risk below 1500 m, including the Terai district</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Kathmandu and on typical Himalayan treks</td>
<td></td>
</tr>
<tr>
<td>Nicaragua</td>
<td>Low risk (except Managua)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Managua</td>
<td>1</td>
</tr>
<tr>
<td>Niger</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>North Korea</td>
<td>Very low risk in some southern areas</td>
<td>1</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Low risk below 2000 m</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk above 2000 m</td>
<td>1</td>
</tr>
<tr>
<td>Panama</td>
<td>Low risk east of Canal Zone</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Very low risk west of Canal Zone</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Panama City or Canal Zone itself</td>
<td>-</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>High risk below 1800 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk above 1800 m</td>
<td>1</td>
</tr>
<tr>
<td>Country</td>
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</tr>
<tr>
<td>--------------------</td>
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<td>--------------------</td>
</tr>
<tr>
<td>Paraguay</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Peru</td>
<td>Low risk in Amazon basin along border with Brazil, particularly in Loreto province and in rural areas below 2000 m including the Amazon basin bordering Bolivia No risk in city of Lima and coastal region south of Chiclayo</td>
<td>1</td>
</tr>
<tr>
<td>Philippines</td>
<td>Low risk in rural areas below 600 m and on islands of Luzon, Mindanao, Mindoro, and Palawan No risk in cities or on islands of Boracay, Bohol, Catanduanes, Cebu, or Leyte</td>
<td>-</td>
</tr>
<tr>
<td>Rwanda</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>São Tomé and Príncipe</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Low risk in south-western provinces along border with Yemen, including below 2000 m in Asir province No risk in cities of Jeddah, Makkah (Mecca), Medina, Riyadh, or Ta’if, or above 2000 m in Asir province</td>
<td>1</td>
</tr>
<tr>
<td>Senegal</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Somalia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>South Africa</td>
<td>Risk from September-May in low altitude areas of Mpumalanga and Limpopo, particularly those bordering Mozambique, Swaziland (Estwatini), and Zimbabwe (including Kruger National Park) Low risk in north-east KwaZulu-Natal and in designated areas of Mpumalanga and Limpopo Very low risk in North West Province (adjacent to Molopo river) and Northern Cape Province (adjacent to Orange river)</td>
<td>4</td>
</tr>
<tr>
<td>South Korea</td>
<td>Very low risk in northern areas, in Gangwon-do and Gyeonggi-do provinces, and Incheon city (towards Demilitarized Zone)</td>
<td>1</td>
</tr>
<tr>
<td>South Sudan</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Low risk north of Vavuniya Very low risk in areas other than those above and below No risk in Colombo or Kandy</td>
<td>1</td>
</tr>
<tr>
<td>Sudan</td>
<td>High risk in central and southern areas; risk also present in rest of country (except Khartoum) Very low risk in Khartoum</td>
<td>4</td>
</tr>
<tr>
<td>Suriname</td>
<td>Risk present on the French Guiana border Low risk in areas other than above and below No risk in city of Paramaribo</td>
<td>4</td>
</tr>
<tr>
<td>Swaziland</td>
<td>Risk in northern and eastern regions bordering Mozambique and South Africa, including all of Lubombo district and Big Bend, Mhlume, Simonye, and Tshamani regions Very low risk in the areas other than those above</td>
<td>4</td>
</tr>
<tr>
<td>Syria</td>
<td>Very low risk in small, remote foci of El Hasakah</td>
<td>1</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Tanzania</td>
<td>High risk below 1800 m; risk also in Zanzibar No risk above 2000 m</td>
<td>4</td>
</tr>
<tr>
<td>Thailand</td>
<td>Mefloquine resistance present. Low risk in rural forested borders with Cambodia, Laos, and Myanmar Very low risk in areas other than those above, including Kanchanaburi (Kwai Bridge) No risk in cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya</td>
<td>1</td>
</tr>
<tr>
<td>Togo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Turkey</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Uganda</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>Very low risk in extreme south-east</td>
<td>1</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Risk present</td>
<td>4</td>
</tr>
</tbody>
</table>
Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>No risk</td>
</tr>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
</tbody>
</table>

Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venezuela</td>
<td>Risk in all areas south of, and including, the Orinoco river and Angel Falls, rural areas of Apure, Monagas, Sucre, and Zulia states</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Caracas or on Margarita Island</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>Low risk in rural areas, and in southern provinces of Tay Ninh, Lam Dong, Bac Lac, Gia Lai, and Kon Tum</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in large cities (including Ho Chi Minh City (Saigon) and Hanoi), the Red River delta, coastal areas north of Nha Trang and Phu Quoc Island</td>
<td>1</td>
</tr>
<tr>
<td>Western Sahara</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Yemen</td>
<td>Risk below 2000 m</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Very low risk on Socora Island; no risk above 2000 m, including Sana’a city</td>
<td>1</td>
</tr>
<tr>
<td>Zambia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>High risk all year in Zambezi valley, and from November-June in areas below 1200 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk from July-October in areas below 1200 m; very low risk all year in Harare and Bulawayo</td>
<td>1</td>
</tr>
</tbody>
</table>

In view of the continuing emergence of resistant strains and of the different regimens required for different areas expert advice should be sought on the best treatment course for an individual traveller. A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Malaria prophylaxis, specific recommendations

Travellers planning journeys across continents can travel into areas that have different malaria prophylaxis recommendations. The choice of prophylaxis medication must reflect overall risk to ensure protection in all areas; it may be possible to change from one regimen to another. Those travelling to remote or little-visited areas may require expert advice. For further information see Recommended regimens for prophylaxis against malaria, and Public Health England Guidelines for malaria prevention in travellers from the United Kingdom.

Important

Settled immigrants (or long-term visitors) to the UK may be unaware that any immunity they may have acquired while living in malarious areas is lost rapidly after migration to the UK, or that any non-malarious areas where they lived previously may now be malarious.

Malaria, treatment

Advice for healthcare professionals

A number of specialist centres are able to provide advice on specific problems.

PHE (Public Health England) Malaria Reference Laboratory (020) 7637 0248 (fax) (prophylaxis only) www.malaria-reference.co.uk

National Travel Health Network and Centre 0845 602 6712

Monday and Friday: 9–11 a.m. and 1–2 p.m, Tuesday to Thursday: 9–11 a.m. and 1–3:30 p.m. travelhealthpro.org.uk/ Travel Medicine Team, Health Protection Scotland (registered users of Travax only) www.travax.nhs.uk (for registered users of the NHS Travax website only) (0141) 300 1100 (weekdays 2–4 p.m. only) Birmingham (0121) 424 2358 Liverpool (0151) 705 3100 London 0845 155 5000 (treatment) Oxford (01865) 225 430

Advice for travellers

Hospital for Tropical Diseases Travel Healthline (020) 7950 7799 www.fitfortravel.nhs.uk WHO advice on international travel and health www.who.int/ith

National Travel Health Network and Centre (NaTHNaC) www.travelhealthpro.org.uk/

Treatment of malaria

Recommendations on the treatment of malaria reflect guidelines agreed by UK malaria specialists.

If the infective species is not known, or if the infection is mixed, initial treatment should be as for falciparum malaria with quinine p. 619, Malarone® (atovaquone with proguanil hydrochloride p. 615), or Riamet® (artemether with lumefantrine p. 614). Falciparum malaria can progress rapidly in unprotected individuals and antimarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.

Falciparum malaria (treatment)

Falciparum malaria (malignant malaria) is caused by Plasmodium falciparum. In most parts of the world P. falciparum is now resistant to chloroquine p. 616 which should not therefore be given for treatment.
Quinine, Malarone® (atovaquone with proguanil hydrochloro), or Riamet® (artemether with lumezantrine) can be given by mouth if the patient can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given by intravenous infusion if the patient is seriously ill or unable to take tablets. Mefloquine p. 617 is now rarely used for treatment because of concerns about resistance.

Oral quinine is given by mouth for 5–7 days, together with or followed by either doxycycline p. 564 for 7 days or clindamycin p. 535 for 7 days [unlicensed].

If the parasite is likely to be sensitive, pyrimethamine with sulfadoxine as a single dose [unlicensed] may be given (instead of either clindamycin or doxycycline) together with, or after, a course of quinine. Alternatively, Malarone®, or Riamet® may be given instead of quinine. It is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after Malarone® or Riamet® treatment. If the patient is seriously ill or unable to take tablets, or if more than 2% of red blood cell are parasitized, quinine should be given by intravenous infusion [unlicensed] (until patient can swallow tablets to complete the 7-day course together with or followed by either doxycycline or clindamycin).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intra venous artesunate may be available for ‘named-patient’ use.

Pregnancy
Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The adult treatment doses or oral and intravenous quinine (including the loading dose) can safely be given to pregnant women. Clindamycin should be given after quinine [unlicensed indication]. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development); pyrimethamine with sulfadoxine, Malarone®, and Riamet® are also best avoided until more information is available. Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quine, infection acquired in quinine-resistant areas of south east Asia) because intra venous artesunate may be available for ‘named-patient’ use.

Non-falciparum malaria (treatment)
Non-falciparum malaria is usually caused by Plasmodium vivax and less commonly by P. ovale and P. malariae. P. knowlesi is also present in the Asia-Paciﬁc region. Chloroquine is the drug of choice for the treatment of non-falciparum malaria (but chloroquine-resistant P. vivax has been reported in the Indonesian archipelago, the Malay Peninsula, including Myanmar, and eastward to Southern Vietnam).

For the treatment of chloroquine-resistant non-falciparum malaria, Malarone® [unlicensed indication], quinine, or Riamet® [unlicensed indication] can be used; as with chloroquine, primaquine p. 618 should be given for radical cure. Chloroquine alone is adequate for P. malariae and P. knowlesi infections but in the case of P. vivax and P. ovale, a radical cure (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with primaquine [unlicensed] given after chloroquine, with the dose dependent on the infecting organism. For a radical cure, primaquine [unlicensed] is then given for 14 days, with the dose also dependent on the infecting organism.

Parenteral
Parenteral If the patient is unable to take oral therapy, quinine can be given by intravenous infusion [unlicensed], changed to oral chloroquine as soon as the patient’s condition permits.

Pregnancy
The adult treatment doses of chloroquine can be given for non-falciparum malaria. In the case of P. vivax or P. ovale, however, the radical cure with primaquine should be postponed until the pregnancy is over; instead chloroquine should be continued, given weekly during the pregnancy.

**ANTIPROTOZOALS > ANTIMALARIALS**

### Artemether with Lumezantrine

#### INDICATIONS AND DOSE

**Treatment of acute uncomplicated falciparum malaria**

- **By mouth**
  - Adult (body-weight 35 kg and above): Initially 4 tablets, followed by 4 tablets for 5 doses each given at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours)

- **Unlicensed use**
  - Use in treatment of non-falciparum malaria is an unlicensed indication.

- **Contra-Indications**
  - Family history of congenital QT interval prolongation • family history of sudden death • history of arrhythmias • history of clinically relevant bradycardia • history of congestive heart failure accompanied by reduced left ventricular ejection fraction

- **Caution**
  - Avoid in Acute porphyrias p. 1058 • electrolyte disturbances

- **Interactions**
  - Appendix 1: antimalarials

- **Side-effects**
  - Common or very common Abdominal pain • appetite decreased • arthralgia • asthenia • cough • diarrhoea • dizziness • gait abnormal • headache • movement disorders • myalgia • nausea • palpitations • QT interval prolongation • sensation abnormal • skin reactions • sleep disorders • vomiting

- **Uncommon**
  - Drowsiness

- **Frequency not known**
  - Angioedema

- **Pregnancy**
  - Toxicity in animal studies with artemether.
  - Manufacturer advises use only if potential benefit outweighs risk.

- **Breastfeeding**
  - Manufacturer advises avoid breastfeeding for at least 1 week after last dose. Present in milk in animal studies.

- **Hepatic Impairment**
  - Manufacturer advises caution in severe impairment (no information available) – monitor ECG and plasma potassium concentration.

- **Renal Impairment**
  - Manufacturer advises caution in severe impairment.

- **Monitoring**
  - In severe renal impairment monitor ECG and plasma potassium concentration.

- **Monitoring Requirements**
  - Tablets may be crushed just before administration.

- **Patient and Carer Advice**
  - Driving and skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving).

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Cautionary and Advisory Labels 21**
  - Riamet (Novartis Pharmaceuticals UK Ltd)
  - Artemether 20 mg, Lumezantrine 120 mg Riamet tablets 24 tablet £22.50
Artemisom with piperaquine phosphate

(Piperaquine tetraphosphate with dihydroartemisinin)

**INDICATIONS AND DOSE**

**Treatment of uncomplicated falciparum malaria**

- **BY MOUTH**
  - Child 6 months-17 years (body-weight 7-12 kg): 0.5 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Child 6 months-17 years (body-weight 13-23 kg): 1 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Child 6 months-17 years (body-weight 24-35 kg): 2 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Child 6 months-17 years (body-weight 36-74 kg): 3 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Child 6 months-17 years (body-weight 75-99 kg): 4 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Adult (body-weight 75-99 kg): 4 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course
  - Adult (body-weight 100 kg and above): 5 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

**SIDE-EFFECTS**

- **Common or very common** Anemia, arthralgia, asthenia, conjunctivitis (in children), cough, diarrhea, dizziness (in adults), epistaxis (in children), fever, headache, hepatitis, hypernatremia, jaundice, leucopenia (in children), malaise, myalgia (in adults), myalgia, myositis (in children), nausea, oral disorders, rash, rhinorrhoea (in children), skin disorder, skin rash, stomatitis (in children), stomatitis (in adults), vomiting (in children)

**PREGNANCY** Teratogenic in animal studies—manufacturer advises use only if other antimalarials cannot be used.

**BREAST FEEDING** Manufacturer advises use only if no suitable alternative available.

**MONITORING** Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe hepatic impairment.

**RENAI IMPAIRMENT** No information available in moderate to severe impairment.

**INTERACTIONS**

- **Antimalarials**
- **Dihydroartemisinin**
- **Piperfquine**
- **Proguanil**
- **Artemisinin**

**DOSE EQUIVALENCE AND CONVERSION**

- Atovaquone with proguanil hydrochloride

**INDICATIONS AND DOSE**

**MALARONE® 250MG/100MG**

Prophylaxis of falciparum malaria, particularly where resistance to other antimalarial drugs suspected

- **BY MOUTH**
  - Adult (body-weight 40 kg and above): 1 tablet once daily, to be started 1–2 days before entering endemic area and continued for 1 week after leaving

**TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA**

**TREATMENT OF NON-FALCIPARUM MALARIA**

- **BY MOUTH**
  - Adult: 4 tablets once daily for 3 days

**DOSE EQUIVALENCE AND CONVERSION**

- Each tablet of Malarone® contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

**DIRECTIONS FOR ADMINISTRATION**

Tablet

- Eurartesim (Logixx Pharma Solutions Ltd)
- Artesinol 40 mg, Piperaquine phosphate 320 mg Eurartesim 320mg/40mg tablets 12 tablet £4.00

Atovaquone with proguanil hydrochloride

28-May-2019

**MALARONE® 250MG/100MG**

**INDICATIONS AND DOSE**

**PROPHYLAXIS OF FALCIPARUM MALARIA, PARTICULARLY WHERE RESISTANCE TO OTHER ANTIMALARIAL DRUGS SUSPECTED**

- **BY MOUTH**
  - Adult (body-weight 40 kg and above): 1 tablet once daily, to be started 1–2 days before entering endemic area and continued for 1 week after leaving

**TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA**

**TREATMENT OF NON-FALCIPARUM MALARIA**

- **BY MOUTH**
  - Adult: 4 tablets once daily for 3 days

**DOSE EQUIVALENCE AND CONVERSION**

- Each tablet of Malarone® contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

**DIRECTIONS FOR ADMINISTRATION**

Tablet

- Eurartesim (Logixx Pharma Solutions Ltd)
- Artesinol 40 mg, Piperaquine phosphate 320 mg Eurartesim 320mg/40mg tablets 12 tablet £4.00

**UNLICENSED USE** Not licensed for treatment of non-falciparum malaria.

**CAUTIONS** Diarrhoea or vomiting (reduced absorption of atovaquone) - efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure)

**INTERACTIONS**

- Appendix 1: antimalarials

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, appetite decreased, cough, depression, diarrhea, dizziness, fever, headache, palpitations, photosensitivity reaction, rash, Stevens-Johnson syndrome, tachycardia, vasculitis

**PREGNANCY**

- Manufacturer advises use only if no suitable alternative available.

**MONITORING**

- Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe hepatic impairment.

**RENAI IMPAIRMENT**

- No information available in moderate to severe impairment.

**INTERACTIONS**

- **Antimalarials**
- **Dihydroartemisinin**
- **Piperfquine**
- **Proguanil**
- **Artemisinin**
**RENAL IMPAIRMENT**  Avoid for malaria prophylaxis (and if possible for malaria treatment) if eGFR less than 30 mL/minute/1.73m².

**PATIENT AND CARER ADVICE**  Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

**NATIONAL FUNDING/ACCESS DECISIONS**  NHS restrictions Drugs for malaria prophylaxis are not prescribable in NHS primary care; health authorities may investigate circumstances under which antimalarials are prescribed.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- Malarine (GlaxoSmithKline UK Ltd)
  - Proguanil hydrochloride 100 mg, Atovaquone 250 mg
  - Malarone 250mg/100mg tablets  12 tablet

**DOSAGE**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult: Initially 620 mg, then 310 mg after 6–8 hours, then 310 mg daily for 2 days, approximate total cumulative dose of 25 mg/kg of base</td>
<td></td>
</tr>
<tr>
<td><strong>P. vivax or P. ovale infection during pregnancy while radical cure is postponed</strong></td>
<td></td>
</tr>
<tr>
<td><strong>DOSE EQUIVALENCIES AND CONVERSION</strong></td>
<td></td>
</tr>
<tr>
<td>Each tablet contains 155 mg of chloroquine base (equivalent to 250 mg of chloroquine phosphate).</td>
<td></td>
</tr>
<tr>
<td><strong>DOSES AT EXTREMES OF BODY-WEIGHT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>UNLICENSED USE</strong> Chloroquine doses for the treatment and prophylaxis of malaria in BNF publications may differ from those in product literature.</td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANCE OF SAFETY INFORMATION**

- In adults Ocular toxicity is unlikely if the dose of chloroquine phosphate does not exceed 4 mg/kg daily (equivalent to chloroquine base approx. 2.5 mg/kg daily).

**CAUTIONS**  Acute porphyrias p. 1058 - diabetes (may lower blood glucose) - elderly - G6PD deficiency - long-term therapy (regular ophthalmic examination recommended by manufacturers) - may aggravate myasthenia gravis - may exacerbate psoriasis - neurological disorders, especially epilepsy (may lower seizure threshold) - avoid for prophylaxis of malaria if history of epilepsy - severe gastrointestinal disorders

**CAUTIONS, FURTHER INFORMATION**

- Screening for retinopathy
  - In adults A review group convened by the Royal College of Ophthalmologists has updated guidelines on screening for chloroquine and hydroxychloroquine retinopathy (Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Screening 2018). Chloroquine appears to be more retinotoxic than hydroxychloroquine.
  - Screening recommendations for chloroquine:
    - All patients planning to be on long-term treatment should receive a baseline examination (including fundus photography and spectral domain optical coherence tomography) within 6–12 months of treatment initiation;
    - Annual screening is recommended in all patients who have taken chloroquine for greater than 1 year.

**INTERACTIONS**  → Appendix 1: antimalarials

**SIDE-EFFECTS**

- Rare or very rare Cardiomyopathy - hallucination - hepatitis

SIDE-EFFECTS, FURTHER INFORMATION  Side-effects which occur at doses used in the prophylaxis or treatment of malaria are generally not serious.

Overdose Chloroquine is very toxic in overdose; overdosage is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

- PREGNANCY Benefit of use in prophylaxis and treatment in malaria outweighs risk. For rheumatoid disease, it is not necessary to withdraw an antimalarial drug during pregnancy if the disease is well controlled.

- BREAST FEEDING Present in breast milk and breast-feeding should be avoided when used to treat rheumatic disease. Amount in milk probably too small to be harmful when used for malaria.

- HEPATIC IMPAIRMENT Manufacturer advises caution, particularly in cirrhosis.

- RENAL IMPAIRMENT Manufacturers advise caution. Dose adjustments Only partially excreted by the kidneys and reduction of the dose is not required for prophylaxis of malaria except in severe impairment. For rheumatoid arthritis and lupus erythematosus, reduce dose.

MONITORING REQUIREMENTS
- In adults Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory.
- In children Ophthalmic examination with long-term therapy.

PATIENT AND CARER ADVICE Warn travellers going to malarious areas about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

- NATIONAL FUNDING/ACCESS DECISIONS NHS restrictions Drugs for malaria prophylaxis are not prescribable in NHS primary care; health authorities may investigate circumstances under which antimalarials are prescribed.

- EXCEPTIONS TO LEGAL CATEGORY Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Paludrine/Avloclor (Alliance Pharmaceuticals Ltd)
  Paludrine/Avloclor tablets anti-malarial travel pack | 112 tablet | £13.50

Mefloquine

- INDICATIONS AND DOSE
  Treatment of malaria
  - BY MOUTH
  - Adult: (consult product literature)

  Prophylaxis of malaria
  - BY MOUTH
  - Child (body-weight 5–15 kg): 62.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  - Child (body-weight 16–24 kg): 125 mg once weekly, dose to be started 2–3 weeks after entering endemic area and continued for 4 weeks after leaving
  - Child (body-weight 25–44 kg): 187.5 mg once weekly, dose to be started 2–3 weeks before establishing endemic area and continued for 4 weeks after leaving
  - Child (body-weight 45 kg and above): 250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving
  - Adult (body-weight 45 kg and above): 250 mg once weekly; dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving

- UNLICENSED USE Mefloquine doses in BNF Publications may differ from those in product literature.
- In children Not licensed for use in children under 5 kg body-weight and under 3 months.

- CONTRA-INDICATIONS Avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions.
- Avoid for standby treatment if history of convulsions.

- CAUTIONS Cardiac conduction disorders - epilepsy (avoid for prophylaxis).

CONTRA-INDICATIONS
- Neuropsychiatric reactions Mefloquine is associated with potentially serious neuropsychiatric reactions. Abnormal dreams, insomnia, anxiety, and depression occur commonly. Psychosis, suicidal ideation, and suicide have also been reported. Psychiatric symptoms such as insomnia, nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event. Adverse reactions may occur and persist up to several months after discontinuation because mefloquine has a long half-life.

For a prescribing checklist, and further information on side-effects, particularly neuropsychiatric side-effects, which may be associated with the use of mefloquine for malaria prophylaxis, see the Guide for Healthcare Professionals provided by the manufacturer.

INTERACTIONS  Appendix 1: antimalarials

- SIDE-EFFECTS
  - Common or very common Anxiety, depression, diarrhoea, dizziness, gastrointestinal discomfort, headache, nausea, skin reactions, sleep disorders, vision disorders, vomiting
  - Frequency not known Acute kidney injury, agranulocytosis, alopecia, aplastic anaemia, appetite decreased, arthralgia, asthma, behaviour abnormal -

Chloroquine with proguanil

The properties listed below are those particular to the combination only. For the properties of the components please consider, chloroquine p. 616, proguanil hydrochloride p. 618.

- INDICATIONS AND DOSE
  Prophylaxis of malaria
  - BY MOUTH
  - Adult: (consult product literature)

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with hypersensitivity to quinine.

CONCESSION AND CONTRACEPTION Manufacturer advises adequate contraception during prophylaxis and for 3 months after stopping (teratogenicity in animal studies).

PREGNANCY Manufacturer advises avoid (particularly in the first trimester) unless the potential benefit outweighs the risk; however, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas.

BREAST FEEDING Present in milk but risk to infant minimal.

HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment—elimination may be prolonged.

RENAL IMPAIRMENT Manufacturer advises caution.

DIRECTIONS FOR ADMINISTRATION Tablet may be crushed and mixed with food such as jam or honey just before administration.

PATIENT AND CARER ADVICE Manufacturer advises that patients receiving mefloquine for malaria prophylaxis should be informed to discontinue its use if neuropsychiatric symptoms occur and seek immediate medical advice so that management of the condition is initiated in a timely manner.

Driving and skilled tasks Dizziness or a disturbed sense of balance may affect performance of skilled tasks (e.g. driving); effects may occur and persist up to several months after stopping mefloquine.

NATIONAL FUNDING/ACCESS DECISIONS

NHS restrictions Drugs for malaria prophylaxis are not prescribable in NHS primary care; health authorities may investigate circumstances under which antimarials are prescribed.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 10, 21, 27

Lariam (Cheplapharm Arzneimittel GmbH)

Mefloquine (as Mefloquine hydrochloride) 250 mg Lariam 250mg tablets | 8 tablet [30] £14.53 DT + £14.53

Primaquine

INDICATIONS AND DOSE

Adjunct in the treatment of non-falciparum malaria caused by *P. vivax* infection

BY MOUTH

Adult: 15 mg daily for 14 days

Adjunct in the treatment of non-falciparum malaria caused by *P. vivax* infection in patients with mild G6PD deficiency (administered on expert advice)

BY MOUTH

Adult: 45 mg once weekly for 8 weeks

Treatment of mild to moderate pneumocystis infection (in combination with clindamycin)

BY MOUTH

Adult: 30 mg daily, this combination is associated with considerable toxicity

UNLICENSED USE Not licensed.

CAUTIONS G6PD deficiency - systemic diseases associated with granulocytopenia (e.g. juvenile idiopathic arthritis, rheumatoid arthritis, leukaemia, aplastic anaemia) - lupus erythematosus

INTERACTIONS → Appendix 1: antimalarials

SIDE-EFFECTS

Common or very common Abdominal pain - appetite decreased - nausea - vomiting

Uncommon Haemolytic anaemia (more common in G6PD deficiency) - leucopenia - methaemoglobinemia

PREGNANCY Risk of neonatal haemolysis and methaemoglobinemia in third trimester.

BREAST FEEDING No information available; theoretical risk of haemolysis in G6PD-deficient infants.

PRE-TREATMENT SCREENING Before starting primaquine, blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity since the drug can cause haemolysis in G6PD-deficient patients. Specialist advice should be obtained in G6PD deficiency.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

Primaquine (Non-proprietary)

Primaquine (as Primaquine phosphate) 7.5 mg Primaquine 7.5mg tablets | 100 tablet £19.70

Primaquine (as Primaquine phosphate) 15 mg Primaquine 15mg tablets | 100 tablet [30] £6.04

Proguanil hydrochloride

INDICATIONS AND DOSE

Prophylaxis of malaria

BY MOUTH

Child 4-11 weeks (body-weight up to 6 kg): 25 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 3-11 months (body-weight 6-9 kg): 50 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 1-3 years (body-weight 10-15 kg): 75 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 4-7 years (body-weight 16-24 kg): 100 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

Child 8-12 years (body-weight 25-44 kg): 150 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

www.getintopharma.com
Quinine

**INDICATIONS AND DOSE**

**Nocturnal leg cramps**
- **BY MOUTH**
- Adult: 200–300 mg once daily, to be taken at bedtime

**Non-falciparum malaria**
- **BY INTRAVENOUS INFUSION**
- Adult: 10 mg/kg every 8 hours (max. per dose 700 mg), infused over 4 hours, given if patient is unable to take oral therapy. Change to oral chloroquine as soon as the patient’s condition permits, reduce dose to 5–7 mg/kg if parenteral treatment is required for more than 48 hours

**Falciparum malaria**
- **BY MOUTH**
- Child: 10 mg/kg every 8 hours (max. per dose 600 mg) for 7 days, to be given together with or followed by either doxycycline (in children over 12 years), or clindamycin
- Adult: 600 mg every 8 hours for 5–7 days, to be given together with or followed by either doxycycline or clindamycin
- **BY INTRAVENOUS INFUSION**
- Adult: Loading dose 20 mg/kg (max. per dose 1.4 g), infused over 4 hours, the loading dose of 20 mg/kg should not be used if the patient has received quinine or mefloquine during the previous 12 hours, then maintenance 10 mg/kg every 8 hours (max. per dose 700 mg) until patient can swallow tablets to complete the 7-day course, maintenance dose to be given 8 hours after the start of the loading dose and infused over 4 hours, to be given together with or followed by either doxycycline or clindamycin, reduce maintenance dose to 5–7 mg/kg if parenteral treatment is required for more than 48 hours

**Falciparum malaria (in intensive care unit)**
- **BY INTRAVENOUS INFUSION**
- Adult: Loading dose 7 mg/kg, infused over 30 minutes, followed immediately by 10 mg/kg, infused over 4 hours, then maintenance 10 mg/kg every 8 hours (max. per dose 700 mg) until patient can swallow tablets to complete the 7-day course, maintenance dose to be given 8 hours after the start of the loading dose and infused over 4 hours, to be given together with or followed by either doxycycline or clindamycin, reduce maintenance dose to 5–7 mg/kg if parenteral treatment is required for more than 48 hours

**DOSE EQUIVALENCE AND CONVERSION**
- When using quinine for malaria, doses are valid for quinine hydrochloride, dihydrochloride, and sulfate; they are not valid for quinine bisulfate which contains a correspondingly smaller amount of quinine.
- Quinine (anhydrous base) 100 mg = quinine bisulfate 169 mg; quinine dihydrochloride 122 mg; quinine hydrochloride 122 mg; and quinine sulfate 121 mg. Quinine bisulfate 300 mg tablets are available but provide less quinine than 300 mg of the dihydrochloride, hydrochloride, or sulfate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Tablet**

| CAUTIONARY AND ADVISORY LABELS | 21 |
| Paludrine (Alliance Pharmaceuticals Ltd) | 98 tablet | £11.95 DF + £13.95 |

**REFERENCES**

- European Medicines Agency (EMEA), 2002 (for Proguanil Supplementary Monograph).
- European Medicines Agency (EMEA), 2006 (for Mefloquine Supplementary Monograph).
620  Viral infection

6.1  Hepatitis

Overview

Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely symptomatic. Early treatment of acute hepatitis C with interferon alfa p. 956 [unlicensed indication] may reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. Active or passive immunisation against hepatitis A and B infections can be given.

Chronic hepatitis B

Peginterferon alfa p. 623 is an option for the initial treatment of chronic hepatitis B and may be preferable to interferon alfa. The use of peginterferon alfa and interferon alfa is limited by a response rate of 30–40% and relapse is frequent. Treatment should be discontinued if no improvement occurs after 4 months. The manufacturers of peginterferon alfa-2a and interferon alfa contraindicate use in decompensated liver disease, but low doses can be used with great caution in these patients. Although interferon alfa is contra-indicated in patients receiving immunosuppressant treatment (or who have received it recently), cautious use of peginterferon alfa-2a may be justified in some cases.

Entecavir p. 621 or tenofovir disoproxil p. 654 are options for the initial treatment of chronic hepatitis B. If the response is inadequate after 6–9 months of treatment, a change in treatment should be considered. Other drugs that are licensed for the treatment of chronic hepatitis B include adefovir dipivoxil p. 623, lamivudine p. 653, or telbivudine p. 622.

Entecavir alone, tenofovir disoproxil alone, or a combination of lamivudine with either adefovir dipivoxil or tenofovir disoproxil can be used in patients with decompensated liver disease.

5.3  Toxoplasmosis

ANTIPROTOZOAIS

Pyrimethamine

- **INDICATIONS AND DOSE**
  - **Toxoplasmosis in pregnancy (in combination with sulfadiazine and folinic acid)**
    - **BY MOUTH**
      - Adult: 50 mg once daily until delivery
If drug-resistant hepatitis B virus emerges during treatment, another antiviral drug to which the virus is sensitive should be added. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. Adefovir dipivoxil or tenofovir disoproxil can be given with lamivudine in lamivudine-resistant chronic hepatitis B; telbivudine or entecavir should not be used because cross-resistance can occur.

If there is no toxicity or loss in efficacy, treatment with adefovir dipivoxil, entecavir, lamivudine, telbivudine, or tenofovir disoproxil is usually continued until 6 months after adequate seroconversion has occurred. Treatment is usually continued long-term in patients with decompensated liver disease.

Tenofovir disoproxil, or a combination of tenofovir disoproxil with either emtricitabine p. 651 or lamivudine may be used with other antiretrovirals, as part of 'highly active antiretroviral therapy' in patients who require treatment for both HIV and chronic hepatitis B. If patients infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa or adefovir dipivoxil. Treatment may be continued long-term, even if adequate seroconversion has occurred. Management of these patients should be coordinated between HIV and hepatology specialists.

### Chronic hepatitis C

Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load measured as this may affect the choice and duration of treatment. A combination of ribavirin p. 626 and peginterferon alfa is used for the treatment of chronic hepatitis C. The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

Daclatasvir is licensed for use in combination with sofosbuvir p. 628 for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis; the addition of ribavirin should be considered for patients with advanced liver disease or with other negative prognostic factors, such as prior treatment experience. It is also licensed in combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment experienced, with or without compensated cirrhosis, and in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C infection of genotype 4. Daclatasvir must not be given as monotherapy.

Ombitasvir with paritaprevir and ritonavir p. 625 (Viekirax®), is licensed for use in combination with dasabuvir p. 631, with or without ribavirin, for the treatment of chronic hepatitis C infection of genotype 1 in patients with or without compensated cirrhosis; it is also licensed for use in combination with ribavirin for the treatment of chronic hepatitis C infection of genotype 4 with or without compensated cirrhosis.

Ribavirin inhibits a wide range of DNA and RNA viruses. It is given by mouth for the treatment of chronic hepatitis C infection, in double therapy with peginterferon alfa, interferon alfa, or sofosbuvir, or in triple therapy with peginterferon alfa and one protease inhibitor or sofosbuvir. Ribavirin is also effective in Lassa fever [unlicensed indication].

Sofosbuvir is a pro-drug of a nucleoside inhibitor that is effective against hepatitis C virus polymerase NS5B. It is licensed for use in combination with ribavirin, with or without peginterferon alfa, for the treatment of chronic hepatitis C infection of genotypes 1, 2, 3, 4, 5, or 6 in patients with compensated liver disease. Sofosbuvir monotherapy is not recommended because it is less effective than combination therapy.

Ledipasvir is licensed for use in combination with sofosbuvir (ledipasvir with sofosbuvir p. 628), with or without ribavirin, for the treatment of chronic hepatitis C infections of genotypes 1, 3, 4, 5 or 6. Sofosbuvir with velpatasvir and voxilaprevir p. 630 is licensed for the treatment of chronic hepatitis C of all genotypes.

### 6.2 Hepatitis infections

#### 6.2a Chronic hepatitis B

**Other drugs used for Chronic hepatitis B**

- Interferon alfa, p. 956
- Lamivudine, p. 653
- Tenofovir disoproxil, p. 654

#### Entecavir

**NUCLEOSIDE ANALOGUES**

**INDICATIONS AND DOSE**

- Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) not previously treated with nucleoside analogues
  - **BY MOUTH**
  - Adult: 500 micrograms once daily

- Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) and lamivudine-resistance
  - **BY MOUTH**
  - Adult: 1 mg once daily, consider other treatment if inadequate response after 6 months

**SIDE-EFFECTS**

- Diarrhoea
- Fatigue
- Headache
- Insomnia
- Nausea
- Vomiting

**CAUTIONS**

- HIV infection—risk of HIV resistance in patients not receiving 'highly active antiretroviral therapy'—lamivudine-resistant chronic hepatitis B—risk of entecavir resistance

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Caution: May cause birth defects. Use only if potential benefit outweighs risk.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**RENAL IMPAIRMENT**

Consult product literature.

- **Dose adjustments**
  - Reduce dose if eGFR less than 50 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

**CAUTIONS, FURTHER INFORMATION**

Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

**COMMON OR VERY COMMON**

- Diarrhoea
- Dizziness
- Dyspepsia
- Fatigue
- Headache
- Insomnia
- Nausea
- Vomiting

**COMMON**

- Alopecia
- Rash

**SIDE-EFFECTS**

- Diarrhoea
- Fatigue
- Insomnia
- Nausea
- Vomiting

**FREQUENCY NOT KNOWN**

- Lactic acidosis

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**RENAAL IMPAIRMENT**

Consult product literature.

- **Dose adjustments**
  - Reduce dose if eGFR less than 50 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
Telbivudine

- **INDICATIONS AND DOSE**
  Chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis, when other treatment is not appropriate
  - **BY MOUTH**
  - Adult: 25 mg once daily (for duration of treatment consult product literature)

- **CAUTIONS**
  Laminudine-resistant chronic hepatitis B—risk of telbivudine resistance

- **INTERACTIONS**
  → Appendix 1: telbivudine

- **SIDE-EFFECTS**
  - **Common or very common**
    - Abdominal pain
    - Cough
    - Diarrhoea
    - Dizziness
    - Fatigue
    - Headache
    - Nausea
    - Rash
  - **Uncommon**
    - Arthralgia
    - Malaise
    - Muscle complaints
    - Nerve disorders
    - Pain
    - Sensation abnormal
    - Taste altered
  - **Rare or very rare**
    - Lactic acidosis
  - **PREGNANCY**
    - Manufacturer advises use only if potential benefit outweighs risk.
  - **BREAST FEEDING**
    - Manufacturer advises avoid—present in milk in animal studies.
  - **RENAL IMPAIRMENT**
    - Dose adjustments
    - 600 mg every 48 hours if eGFR 30–49 mL/minute/1.73 m²; 600 mg every 72 hours if eGFR less than 30 mL/minute/1.73 m².
  - **MONITORING REQUIREMENTS**
    - Monitor liver function tests every 3 months and viral markers of hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation.

- **PATIENT AND CARER ADVICE**
  Muscle effects and peripheral neuropathy

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE decisions**
  Telbivudine is not recommended for the treatment of chronic hepatitis B. Patients currently receiving telbivudine can continue treatment until they and their clinician consider it appropriate to stop.

- **MEDICINAL FORMS**
  Tablets
  - Sebivo (Novartis Pharmaceuticals UK Ltd)
  - Telbivudine 600 mg Sebivo 600mg tablets | 28 tablet £25.30

**Antivirals > Nucleoside Reverse Transcriptase Inhibitors**

**Tenofovir alafenamide**

- **INDICATIONS AND DOSE**
  Chronic hepatitis B (initiated by a specialist)
  - **BY MOUTH**
  - Adult: 25 mg once daily (for duration of treatment consult product literature)

- **CAUTIONS**
  Decompensated liver disease - HIV co-infection

- **INTERACTIONS**
  → Appendix 1: tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common
  - Abdominal distension
  - Frequency not known
  - Hepatitis aggravated (during or following treatment)

- **BREAST FEEDING**
  Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in decompensated hepatic disease (no information available).

- **PRE-TREATMENT SCREENING**
  Manufacturer advises HIV antibody testing should be offered to those with unknown HIV-1 status before initiation of treatment.

- **MONITORING REQUIREMENTS**
  Manufacturer advises monitor liver function tests at repeated intervals during treatment and for at least 6 months after last dose—recurrent hepatitis may occur on discontinuation.

- **PATIENT AND CARER ADVICE**
  Missed doses
  - Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**INDICATIONS AND DOSE**
Chronic hepatitis B (initiated by a specialist)
- **BY MOUTH**
- Adult: 25 mg once daily (for duration of treatment consult product literature)

- **CAUTIONS**
  Decompensated liver disease - HIV co-infection

- **INTERACTIONS**
  → Appendix 1: tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common
  - Abdominal distension
  - Frequency not known
  - Hepatitis aggravated (during or following treatment)

- **BREAST FEEDING**
  Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in decompensated hepatic disease (no information available).

- **PRE-TREATMENT SCREENING**
  Manufacturer advises HIV antibody testing should be offered to those with unknown HIV-1 status before initiation of treatment.

- **MONITORING REQUIREMENTS**
  Manufacturer advises monitor liver function tests at repeated intervals during treatment and for at least 6 months after last dose—recurrent hepatitis may occur on discontinuation.

- **PATIENT AND CARER ADVICE**
  Missed doses
  - Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**INDICATIONS AND DOSE**
Chronic hepatitis B (initiated by a specialist)
- **BY MOUTH**
- Adult: 25 mg once daily (for duration of treatment consult product literature)

- **CAUTIONS**
  Decompensated liver disease - HIV co-infection

- **INTERACTIONS**
  → Appendix 1: tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common
  - Abdominal distension
  - Frequency not known
  - Hepatitis aggravated (during or following treatment)

- **BREAST FEEDING**
  Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in decompensated hepatic disease (no information available).

- **PRE-TREATMENT SCREENING**
  Manufacturer advises HIV antibody testing should be offered to those with unknown HIV-1 status before initiation of treatment.

- **MONITORING REQUIREMENTS**
  Manufacturer advises monitor liver function tests at repeated intervals during treatment and for at least 6 months after last dose—recurrent hepatitis may occur on discontinuation.

- **PATIENT AND CARER ADVICE**
  Missed doses
  - Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

**INDICATIONS AND DOSE**
Chronic hepatitis B (initiated by a specialist)
- **BY MOUTH**
- Adult: 25 mg once daily (for duration of treatment consult product literature)

- **CAUTIONS**
  Decompensated liver disease - HIV co-infection

- **INTERACTIONS**
  → Appendix 1: tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common
  - Abdominal distension
  - Frequency not known
  - Hepatitis aggravated (during or following treatment)

- **BREAST FEEDING**
  Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  Manufacturer advises caution in decompensated hepatic disease (no information available).

- **PRE-TREATMENT SCREENING**
  Manufacturer advises HIV antibody testing should be offered to those with unknown HIV-1 status before initiation of treatment.

- **MONITORING REQUIREMENTS**
  Manufacturer advises monitor liver function tests at repeated intervals during treatment and for at least 6 months after last dose—recurrent hepatitis may occur on discontinuation.

- **PATIENT AND CARER ADVICE**
  Missed doses
  - Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
**ANTIVIRALS**

**Nucleotide Analougues**

**Adefovir dipivoxil**

- **INDICATIONS AND DOSE**
  Chronic hepatitis B infection with either compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis, when other treatment not appropriate or decompensated liver disease in combination with another antiviral for chronic hepatitis B that has no cross-resistance to adefovir
  - **BY MOUTH**
    - Adults: 10 mg once daily

- **CAUTIONS**
  Elderly

- **INTERACTIONS**
  - Appendix 1: adefovir

- **SIDE-EFFECTS**
  - Common or very common: Asthenia, diarrhoea, flatulence, gastrointestinal discomfort, headache, nausea, renal impairment, skin reactions, vomiting
  - Frequency not known: Bone fracture, bone pain, hypophosphataemia, myopathy, nephrotoxicity, osteomalacia, pancreatitis, proximal renal tubulopathy

- **CONCEPTION AND CONTRACEPTION**
  Effective contraception required during treatment.

- **PREGNANCY**
  Toxicity in animal studies — manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING**
  Manufacturer advises avoid — no information available.

- **RENAI IMPAIRMENT**
  No information available if eGFR less than 10 mL/minute/1.73 m².
  **Dose adjustments**
  - 10 mg every 48 hours if eGFR 30–50 mL/minute/1.73 m²;
  - 10 mg every 72 hours if eGFR 10–30 mL/minute/1.73 m².

- **Monitoring**
  Monitor renal function more frequently in patients with renal impairment.

- **MONITORING REQUIREMENTS**
  - Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation — recurrent hepatitis may occur on discontinuation).
  - Monitor renal function before treatment then every 3 months, more frequently in patients receiving nephrotoxic drugs.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  **Tablet**
  - Hepsera (Gilead Sciences International Ltd)
    - Adefovir dipivoxil 10 mg: Hepsera 10 mg tablets | 30 tablet | £252.22

**IMMUNOSTIMULANTS**

**Interferons**

**Peginterferon alfa**

- **DRUG ACTION**
  Polyethylene glycol-conjugated (‘pegylated’) derivatives of interferon alfa (peginterferon alfa-2a and peginterferon alfa-2b) are available; pegylation increases the persistence of the interferon in the blood.

- **INDICATIONS AND DOSE**
  **PEGASYS®**
  Combined with ribavirin for chronic hepatitis C | Monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated | Monotherapy for chronic hepatitis B
  - **BY SUBCUTANEOUS INJECTION**
    - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  **CONTRA-INDICATIONS, FURTHER INFORMATION**
  For contra-indications consult product literature.

- **CAUTIONS**
  **CAUTIONS, FURTHER INFORMATION**
  For cautions consult product literature.

- **INTERACTIONS**
  - Appendix 1: interferons

- **SIDE-EFFECTS**
  - Common or very common: Alopecia, anaemia, anxiety, appetite abnormal, arthralgias, arthralgia, arthritis, asthenia, ataxia, behaviour abnormal, breathlessness, chest discomfort, chills, concentration impaired, confusion, constipation, cough, crying, dehydration, depression, diarrhoea, dizziness, dryness, dry eye, dry mouth, dysphagia, dysphonia, dysphoria, ear pain, eye discomfort, eye disorders, eye inflammation, feeling abnormal, fever, gastrointestinal discomfort, gastrointestinal disorders, haemolytic anaemia, haemorrhage, hair texture abnormal, headaches, hearing impairment, hyperbiliarinaemia, hypertension, hyperthyroidism, hyperuricaemia, hypertension, hypothyroidism, increased risk of infection, influenza like illness, leucopenia, lymphadenopathy, malaise, memory loss, menorrhea, menstrual cycle irregularities, mood altered, muscle complaints, muscle tone increased, muscle weakness, nail disorder, nasal complaints, nausea, neutropenia, oedema, oral disorders, ovarian disorder, pain, palpitations, photosensitivity reaction, prostatitis, respiratory disorders, sensation abnormal, sepsis, sexual dysfunction, skin reactions, sleep disorders, sweat changes, syncope, taste altered, thirst, throat complaints, thrombocytopenia, tinnitus, tremor, urinary disorders, urine abnormal, vaginal disorder, vasodilatation, vertigo, vision disorders, vomiting, weight decreased
  - Uncommon: Diabetes mellitus, hallucination, hypersensitivity, hypertriglyceridaemia, myocardial infarction, nerve disorders, pancreatitis, psychosis, sarcoidosis, suicidal tendencies, thyroiditis
  - Rare or very rare: Angioedema, bone marrow disorder, cardiac inflammation, cardiomyopathy, cerebral ischaemia, CNS haemorrhage, coma, congestive heart failure, diabetic ketoacidosis, embolism and thrombosis, encephalopathy, facial paralysis, injection site necrosis, ischaemic heart disease, myopathy, renal failure, retinopathy, seizure (more common with high doses in the elderly), severe cutaneous adverse reactions (SCARs), systemic lupus erythematosus (SLE), ulcerative colitis, vasculitis
  - Frequency not known: Homicidal ideation, pericardial effusion, peripheral ischaemia, pulmonary arterial hypertension, pure red cell aplasia, solid organ transplant rejection, tongue discoloration

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6.2b Chronic hepatitis C

Other drugs used for Chronic hepatitis C

Interferon alfa, p. 956 · Peginterferon alfa, p. 623

**ANTIVIRALS > HCV INHIBITORS**

**Elbasvir with grazoprevir**

**DATE** 24-Apr-2017

**DRUG ACTION** Elbasvir is an HCV NSSA inhibitor and grazoprevir is an HCV NS3/4A protease inhibitor; they reduce viral load by inhibiting hepatitis C virus RNA replication.

**INDICATIONS AND DOSE**

Chronic Hepatitis C infection of genotypes 1 or 4 (with or without ribavirin) (initiated by a specialist)

- **BY MOUTH**
  - Adult: 50/100 mg once daily for 12 weeks (may extend to 16 weeks in some circumstances—consult product literature)

**DOSE EQUIVALENCE AND CONVERSION**

- Dose expressed as x/y mg elbasvir/grazoprevir.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVISE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF INTERACTION WITH VITAMIN K ANTAGONISTS AND CHANGES IN INR (JANUARY 2017)

An EU-wide review has identified that changes in liver function, secondary to hepatitis C treatment with direct-acting antivirals, may affect the efficacy of vitamin K antagonists; the MHRA has advised that INR should be monitored closely in patients receiving concomitant treatment.

MHRA/CHM ADVISE: DIRECT-ACTING ANTIVIRAL INTERFERON-FREE REGIMENS TO TREAT CHRONIC HEPATITIS C: RISK OF HEPATITIS B REACTIVATION (JANUARY 2017)

An EU-wide review has concluded that direct-acting antiviral interferon-free regimens for chronic hepatitis C can cause hepatitis B reactivation in patients co-infected with hepatitis B and C viruses; the MHRA recommends to screen patients for hepatitis B before starting treatment—patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines.

MHRA/CHM ADVISE: DIRECT-ACTING ANTIVIRALS TO TREAT HEPATITIS B REACTIVATION (DECEMBER 2018)

MHRA advises healthcare professionals:

- to monitor glucose levels closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C, especially within the first 3 months of treatment and modify diabetic medication or doses when necessary;
- to be vigilant for changes in glucose tolerance and advise patients of the risk of hypoglycaemia;
- to inform the healthcare professional in charge of the diabetic care of the patient when direct-acting antiviral therapy is initiated.

**CAUTIONS**

- Hepatitis B co-infection re-treatment following previous exposure to elbasvir with grazoprevir, or to drugs of the same classes (NS5A inhibitors or NS3/4A inhibitors other than telaprevir, simeprevir, boceprevir)—efficacy not demonstrated

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Benzyl alcohol

- **Pegasys** (Roche Products Ltd)
  - Peginterferon alfa-2a 180 microgram per 1 ml Pegasys 90micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PS) £76.51
  - Peginterferon alfa-2a 270 microgram per 1 ml Pegasys 135micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PS) £107.76 DT + £107.76
  - Peginterferon alfa-2a 360 microgram per 1 ml Pegasys 180micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PS) £497.60

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment—consult product literature.

**PREGNANCY**

Manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in animal studies).

**BREAST FEEDING**

Manufacturers advise avoid—no information available.

**HEPATIC IMPAIRMENT**

Avoid in severe impairment.

**RENAIL IMPAIRMENT**

For further information on peginterferon alfa use in renal impairment consult product literature.

Dose adjustments: Reduce dose in moderate to severe hepatic impairment.

- **MONITORING REQUIREMENTS**
  - Monitoring Close monitoring required in mild to moderate hepatic impairment.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010) NICE TA200
  - The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage (‘watchful waiting’). Peginterferon alfa alone can be used if ribavirin is contra-indicated or not tolerated.

- Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200
  - The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years;
  - not previously treated with interferon alfa or peginterferon alfa;
  - treated previously with interferon alfa alone or in combination with ribavirin;
  - whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
  - co-infected with HIV.
  - Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk.
  - Patients receiving interferon alfa may be switched to peginterferon alfa. www.nice.org.uk/TA200

**BNF**

**624 Viral infection**

- **Pegasys** (Roche Products Ltd) Peginterferon alfa-2a 270 microgram per 1 ml filled disposable injection (PS) £76.51
- **Pegasys** (Roche Products Ltd) Peginterferon alfa-2a 180 microgram per 1 ml filled disposable injection (PS) £497.60
**INTERACTIONS**  
Appendix 1: elbasvir - grazoprevir

**SIDE-EFFECTS**

- **Common or very common**  
  Alopæia · anxiety · appetite decreased · arthralgia · asthenia · constipation · depression · diarrhoea · dizziness · dry mouth · gastrointestinal discomfort · headache · insomnia · irritability · myalgia · nausea · pruritus · vomiting

- **Uncommon**  
  Anæmia · transient ischaemic attack

- **PREGNANCY**  
  Uncommon

- **INTERACTIONS**  
  Manufacturer advises if a dose is more than 800 000 IU/mL.

**MORBIDITY**  
Adult: 2 tablets once daily for duration of treatment consult product literature, to be taken with food.

**ANTIVIRALS**  
NON-STRUCTURAL PROTEIN 5A INHIBITORS

**Ombitasvir with paritaprevir and ritonavir**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ritonavir p. 659.

- **INDICATIONS AND DOSE**  
  Chronic hepatitis C of genotype 1 (in combination with dasabuvir, with or without ribavirin) · Chronic hepatitis C of genotype 4 (in combination with ribavirin)

- **BY MOUTH**
  - Adult: 2 tablets once daily for duration of treatment consult product literature, to be taken with food.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF INTERACTION WITH VITAMIN K ANTAGONISTS AND CHANGES IN INR (JANUARY 2017)

An EU-wide review has identified that changes in liver function, secondary to hepatitis C treatment with direct-acting antivirals, may affect the efficacy of vitamin K antagonists; the MHRA has advised that INR should be monitored closely in patients receiving concomitant treatment.

MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRAL INTERFERON-FREE REGIMENS TO TREAT CHRONIC HEPATITIS C: RISK OF HEPATITIS B REACTIVATION (JANUARY 2017)

An EU-wide review has concluded that direct-acting antiviral interferon-free regimens for chronic hepatitis C can cause hepatitis B reactivation in patients co-infected with hepatitis B and C viruses; the MHRA recommends to screen patients for hepatitis B before starting treatment—patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines.

MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF HYPOGLYCAEMIA IN PATIENTS WITH DIABETES (DECEMBER 2018)

Rapid reduction in hepatitis C viral load during direct-acting antiviral therapy for hepatitis C may improve glucose metabolism in patients with diabetes and result in symptomatic hypoglycaemia if diabetic treatment is continued at the same dose.

The MHRA advises healthcare professionals:

- to monitor glucose levels closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C, especially within the first 3 months of treatment and modify diabetic medication or doses when necessary;
- to be vigilant for changes in glucose tolerance and advise patients of the risk of hypoglycaemia;
- to inform the healthcare professional in charge of the diabetic care of the patient when direct-acting antiviral therapy is initiated.

**CONTRA-INDICATIONS**  
HIV co-infection without suppressive antiretroviral therapy

**CAUTIONS**  
Retreatment—efficacy not established

**INTERACTIONS**  
 Appendix 1: HIV- protease inhibitors · ombitasvir · paritaprevir

**SIDE-EFFECTS**

- **Common or very common**  
  Anaemia · asthenia · insomnia · nausea · pruritus

- **Rare or very rare**  
  Angioedema

- **Frequency not known**  
  Depression · suicidal behaviour

**SIDE-EFFECTS, FURTHER INFORMATION**  
Side-effects listed are reported when ombitasvir with paritaprevir and grazoprevir are used.


**626  Viral infection**

ritonavir is used in combination with dasabuvir, with or without ribavirin.

**CONCEPTION AND CONCEPTION** For women of childbearing potential, exclude pregnancy before initiation of treatment; effective contraception should be used during treatment.

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid—risk of growth retardation in children, the risk of rejection.

**PATIENT AND CARER ADVICE**

**HEPATIC IMPAIRMENT**

**BREAST FEEDING**

**CONCEPTION AND CONTRACEPTION**

**UNLICENSED USE**

When used by inhalation in children Inhalation licensed for use in children (age range not specified by manufacturer).

With intravenous use in children Intravenous preparation not licensed.

**CONTRA-INDICATIONS**

With systemic use Active severe psychiatric condition (in children) · autoimmune disease (in children) · autoimmune hepatitis (in children) · consult product literature for specific contra-indications when ribavirin used in combination with other medicinal products · haemoglobinopathies · history of severe psychiatric condition (in children) · severe cardiac disease (in adults) · severe debilitating medical conditions · severe, uncontrolled cardiac disease in children with chronic hepatitis C (in children) · unstable or uncontrolled cardiac disease in previous 6 months (in adults).

**CAUTIONS**

When used by inhalation Maintain standard supportive respiratory and fluid management therapy.

With systemic use Anaemia (haemoglobin concentration should be monitored during the treatment and corrective action taken) (in adults) · cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration) · consult product literature for specific cautions when ribavirin used in combination with other medicinal products · gout (in adults) · haemolysis (haemoglobin concentration should be monitored during the treatment and corrective action taken) (in adults) · patients with a transplant—risk of rejection · risk of growth retardation in children, the

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

**Ribavirin**

(Tribavirin)

**INDICATIONS AND DOSE**

**Bronchiolitis**

**By Inhalation of Aerosol, or by Inhalation of Nebulised Solution**

Child 1-23 months: Inhalate a solution containing 20 mg/mL for 12–18 hours for at least 3 days, maximum of 7 days, to be administered via small particle aerosol generator.

Life-threatening RSV, parainfluenza virus, and adenovirus infection in immunocompromised children (administered on expert advice)

**By Intravenous Infusion**

Child: 33 mg/kg for 1 dose, to be administered over 15 minutes, then 16 mg/kg every 6 hours for 4 days, then 8 mg/kg every 8 hours for 3 days.

**COPEGUS® Tablets**

Chronic hepatitis C (in combination with direct acting antivirals, or interferon alfa 2a, or peginterferon alfa 2a with or without direct acting antivirals)

**By Mouth**

Adult (body-weight up to 75 kg): 400 mg, to be taken in the morning and 600 mg, dose to be taken in the evening.

Adult (body-weight 75 kg and above): 600 mg twice daily.
reversibility of which is uncertain—if possible, consider starting treatment after pubertal growth spurt (in children).
- severe dental disorders (in adults).
- severe ocular disorders (in adults).
- severe periodontal disorders (in adults).
- severe psychiatric effects (in adults).
- **INTERACTIONS** → Appendix 1: ribavirin

- **SIDE-EFFECTS**
  - **Uncommon**. Dehydration - diabetes mellitus - hallucination - hearing loss - hepatic disorders - hypertension - nerve disorders - sarcoidosis - suicidal tendencies - thyroiditis
  - **Rare or very rare**. Angina pectoris - angioedema - bone marrow disorders - cardiac inflammation - cerebral ischaemia - cholangitis - coma - congestive heart failure - facial paralysis - hepatic failure (discontinue) - hypersensitivity - intracranial haemorrhage - myocardial infarction - myopathy - pancreatitis - psychotic disorder - pulmonary embolism - retinopathy - seizure - severe cutaneous adverse reactions (SCARs) - systemic lupus erythematosus (SLE) - vasculitis
  - **Frequency not known**. Haemolytic anaemia - homicidal ideaion - nephrotic syndrome - pure red cell aplasia - renal failure - solid organ transplant rejection - tongue discolouration - ulcerative colitis

**SIDE-EFFECTS, FURTHER INFORMATION**. Side effects listed are reported when oral ribavirin is used in combination with peginterferon alfa or interferon alfa, consult product literature for details.

- **CONCEPTION AND CONTRACEPTION**
  - With systemic use: Exclude pregnancy before treatment in females of childbearing age. Effective contraception essential during treatment and for 4 months after treatment in females and for 7 months after treatment in males of childbearing age. Routine monthly pregnancy tests recommended. Condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen).
  - When used by inhalation: Women planning pregnancy should avoid exposure to aerosol.

- **PREGNANCY**. Avoid; teratogenicity in animal studies.
  - When used by inhalation: Pregnant women should avoid exposure to aerosol.

- **BREAST FEEDING**. Avoid—no information available.

- **HEPATIC IMPAIRMENT**. Avoid oral ribavirin in severe hepatic dysfunction or decompensated cirrhosis.
- **Dose adjustments**. No dosage adjustment required.

- **RENAL IMPAIRMENT**. Plasma-ribavirin concentration increased.
  - In adults: Manufacturer advises avoid oral ribavirin unless essential if eGFR less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely.
  - In children: Manufacturer advises avoid oral ribavirin if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely. Manufacturer advises use intravenous preparation with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - When used by inhalation: Monitor electrolytes closely. Monitor equipment for precipitation.
  - With systemic use in children: Determine full blood count, platelets, electrolytes, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature).
  - With systemic use in adults: Determine full blood count, platelets, electrolytes, glucose, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature).
  - With systemic use in children: Test thyroid function before treatment and then every 3 months.
  - With oral use in children: Eye examination recommended before treatment. Eye examination also recommended during treatment if pre-existing ophthalmological disorder or if decrease in vision reported—discontinue treatment if ophthalmological disorder deteriorates or if new ophthalmological disorder develops.

- **PRESCRIBING AND DISPENSING INFORMATION**. Flavours of oral liquid formulations may include bubble-gum.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010) NICE TA200
      - In adults: The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage (‘watchful waiting’).
      - www.nice.org.uk/TA200
    - Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200
      - In adults: The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:—not previously treated with interferon alfa or peginterferon alfa;—treated previously with interferon alfa alone or in combination with ribavirin;—whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;—co-infected with HIV.
      - Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa.
      - www.nice.org.uk/TA200
    - Peginterferon alfa and ribavirin for chronic hepatitis C (November 2013) NICE TA300
      - In children: Peginterferon alfa in combination with ribavirin is recommended (within the marketing authorisation) as an option for treating chronic hepatitis C in children.
      - www.nice.org.uk/TA300
  - **LESS SUITABLE FOR PRESCRIBING**. Ribavirin inhalation is less suitable for prescribing.
628  Viral infection

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **ViraZole (Meda Pharmaceuticals Ltd)**
  - Ribavirin 100 mg per 1 ml
  - ViraZole 1.2g/12ml solution for injection vials | 5 vial pack | £3.600.00

**Oral solution**
- **Rebetol (Merck Sharp & Dohme Ltd)**
  - Ribavirin 40 mg per 1 ml
  - Rebetol 40mg/ml oral solution | 100 ml | £67.08

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 21**
  - **Rebetol (Roche Products Ltd)**
    - Ribavirin 200 mg | 112 tablet pack | £233.58
    - 168 tablet pack | £350.37
  - **Ribavirin 400 mg** | 56 tablet pack | £233.58

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS 21**
  - **Rebetol (Merck Sharp & Dohme Ltd)**
    - Ribavirin 200 mg | 168 capsule pack | £321.38

**ANTIVIRALS > NUCLEOTIDE ANALOGUES**

**Ledipasvir with sofosbuvir**  11-Jul-2018

The properties listed below are those particular to the combination only. For the properties of the components please consider, sofosbuvir below.

**DRUG ACTION**  Sofosbuvir is a nucleotide analogue inhibitor and ledipasvir is an HCV inhibitor; they reduce viral load by inhibiting hepatitis C virus RNA replication.

**INDICATIONS AND DOSE**

- **Chronic hepatitis C infection (initiated by a specialist)**
  - **BY MOUTH**
    - **Adult:** 90/400 mg once daily, for duration of treatment consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- **Manufacturer advises reduce dose of concurrent H2-receptor antagonist if above a dose comparable to famotidine 40 mg twice daily.**
- **Manufacturer advises reduce dose of concurrent proton pump inhibitor if above a dose comparable to omeprazole 20 mg; take at the same time as sofosbuvir with ledipasvir.**

**DOSE EQUIVALENCE AND CONVERSION**
- **Dose expressed as x/y mg ledipasvir/sofosbuvir.**

**CAUTIONS**  Retreatment following treatment failure—efficacy not established

**INTERACTIONS**  → Appendix 1: ledipasvir - sofosbuvir

**SIDE-EFFECTS**
- **Common or very common**  Fatigue · headache · rash
- **Frequency not known**  Angioedema · arthralgia

**PRESCRIBING AND DISPENSING INFORMATION**  Dispense in original container (contains desiccant).

**PATIENT AND CARER ADVICE**

**Vomiting**  If vomiting occurs within 5 hours of administration, an additional dose should be taken.

**Missed doses**  If a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- **Ledipasvir - sofosbuvir for treating chronic hepatitis C (November 2015) NICE TA363**
  - Ledipasvir with sofosbuvir is recommended as an option for treating adults with chronic hepatitis C infection:
    - of genotype 1 without cirrhosis (treatment naive patients)—8 weeks' treatment
    - of genotype 1 or 4 with cirrhosis (treatment naive patients)—12 weeks' treatment
    - of genotype 1 or 4 without cirrhosis (or with cirrhosis but only if the person has a low risk of the disease getting worse) that has not responded adequately to previous treatment—12 weeks' treatment
  - In addition, ledipasvir with sofosbuvir is only recommended in patients with cirrhosis for the durations mentioned above if the following criteria are met:
    - Child-Pugh class A
    - platelet count of 75,000/mm³ or more
    - no features of portal hypertension
    - no history of an HCV-associated decompensation episode
    - not previously treated with an NSA inhibitor
  - Patients whose treatment with ledipasvir with sofosbuvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
  - www.nice.org.uk/guidance/ta363

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1030/15
The Scottish Medicines Consortium has advised (March 2015) that ledipasvir with sofosbuvir (Harvoni®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis C infection of genotypes 1 and 4 only.

SMC No. 1084/15
The Scottish Medicines Consortium has advised (September 2015) that ledipasvir with sofosbuvir (Harvoni®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis C infection of genotype 3 in patients who are ineligible for, or unable to tolerate interferon.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 25**
  - **Harvoni (Gilead Sciences International Ltd)**
    - Ledipasvir 90 mg, Sofosbuvir 400 mg | Harvoni 90mg/400mg tablets | 28 tablet pack | £12,993.33

**Sofosbuvir**  26-Mar-2019

**INDICATIONS AND DOSE**

- **Chronic hepatitis C infection**
  - **BY MOUTH**
    - **Adult:** 400 mg once daily, for duration of treatment consult product literature

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF INTERACTION WITH VITAMIN K ANTAGONISTS AND CHANGES IN INR (JANUARY 2017)**

An EU-wide review has identified that changes in liver function, secondary to hepatitis C treatment with direct-acting antivirals, may affect the efficacy of vitamin K antagonists; the MHRA has advised that INR should be monitored closely in patients receiving concomitant treatment.

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRAL INTERFERON-FREE REGIMENS TO TREAT CHRONIC HEPATITIS C: RISK OF HEPATITIS B REACTIVATION (JANUARY 2017)**

An EU-wide review has concluded that direct-acting antiviral interferon-free regimens for chronic hepatitis C can cause hepatitis B reactivation in patients co-infected with hepatitis B and C viruses; the MHRA recommends to screen patients for hepatitis B before starting treatment—patients infected with both hepatitis B and C
viruses must be monitored and managed according to current clinical guidelines.

MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS FOR CHRONIC HEPATITIS C: RISK OF HYPOGLYCAEMIA IN PATIENTS WITH DIABETES (DECEMBER 2018)

Rapid reduction in hepatitis C viral load during direct-acting antiviral therapy for hepatitis C may improve glucose metabolism in patients with diabetes and result in symptomatic hypoglycaemia if diabetic treatment is continued at the same dose.

The MHRA advises healthcare professionals:
- to monitor glucose levels closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C, especially within the first 3 months of treatment and modify diabetic medication or doses when necessary;
- to be vigilant for changes in glucose tolerance and advise patients of the risk of hypoglycaemia;
- to inform the healthcare professional in charge of the diabetic care of the patient when direct-acting antiviral therapy is initiated.

- CAUTIONS, FURTHER INFORMATION Manufacturer advises in chronic hepatitis C of genotype 1, 4, 5, or 6, only use sofosbuvir with ribavirin dual therapy in those with intolerance or contra-indications to peginterferon alfa who require urgent treatment.

- INTERACTIONS Appendix 1: sofosbuvir

- SIDE-EFFECTS

- Common or very common Alopecia, anaemia, anxiety, appetite decreased, arthralgia, asthma, chest pain, chills, concentration impaired, constipation, cough, depression, diarrhoea, dizziness, dry mouth, dysphonia, fever, gastrointestinal discomfort, gastrooesophageal reflux disease, headaches, influenza like illness, insomnia, irritability, memory loss, muscle complaints, nasopharyngitis, nausea, neutropenia, pain, skin reactions, vision blurred, vomiting, weight decreased

- Frequency not known Arrhythmia

SIDE-EFFECTS, FURTHER INFORMATION Side-effects listed are reported when sofosbuvir is used in combination with ribavirin or with ribavirin and peginterferon alfa.

- PREGNANCY Manufacturer advises avoid—limited information available.

- BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

- RENAL IMPAIRMENT Safety and efficacy not established if eGFR less than 30 mL/minute/1.73 m² — accumulation may occur.

- PRESCRIBING AND DISPENSING INFORMATION Dispense in original container (contains desiccant).

- PATIENT AND CARER ADVICE

- Missed doses Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- NATIONAL FUNDING/ACCESS DECISIONS

- NICE decisions

- Sofosbuvir for treating chronic hepatitis C (February 2015) NICE TA330 Sofosbuvir (Sovaldi®) in combination with peginterferon alfa and ribavirin is an option for treating adults with chronic hepatitis C infection:
  - of genotype 1
  - of genotype 3 with cirrhosis (treatment naive patients)
  - of genotype 3 that has not adequately responded to interferon-based treatment
  - of genotype 4, 5, or 6 with cirrhosis.

- Sofosbuvir (Sovaldi®) in combination with ribavirin is an option for treating adults with chronic hepatitis C infection:
  - of genotype 2 who are intolerant to or ineligible for interferon (treatment naive patients)
  - of genotype 2 that has not adequately responded to interferon-based treatment
  - of genotype 3 with cirrhosis who are intolerant to or ineligible for interferon (treatment naive patients)
  - of genotype 3 with cirrhosis that has not adequately responded to interferon-based treatment

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta330

- Sofosbuvir for treating chronic hepatitis C (February 2015) NICE TA330

- Sofosbuvir (Sovaldi®) in combination with ribavirin is not recommended for the treatment of adults with chronic hepatitis C infection of genotypes 1, 4, 5, or 6.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta330

Scottish Medicines Consortium (SMC) decisions

SMC No. 964/14

The Scottish Medicines Consortium has advised (June 2014) that sofosbuvir (Sovaldi®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis C infection of genotypes 1 to 6; its use in combination with ribavirin as dual therapy for chronic hepatitis C infection of either genotype 2 (in treatment naive patients) or genotype 3 is restricted to those who cannot use peginterferon alfa because of intolerance or contra-indications.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>21, 25</th>
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<tbody>
<tr>
<td>Sofosbuvir 400 mg</td>
<td>Sovaldi 400mg tablets</td>
</tr>
<tr>
<td>£11,850.98</td>
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Sofosbuvir with velpatasvir

The properties listed below are those particular to the combination only. For the properties of the components please consider, sofosbuvir p. 628.

- DRUG ACTION Sofosbuvir is a nucleotide analogue inhibitor and velpatasvir is an HCV inhibitor; they reduce viral load by inhibiting hepatitis C virus RNA replication.

- INDICATIONS AND DOSE

Chronic hepatitis C infection, with or without ribavirin (initiated by a specialist)

- BY MOUTH

- Adult: 400/100 mg once daily for 12 weeks (may extend to 24 weeks in some circumstances—consult product literature)

- DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Manufacturer advises reduce dose of concurrent H2-receptor antagonist if above a dose comparable to famotidine 40 mg twice daily.

- Manufacturer advises reduce dose of concurrent proton pump inhibitor if above a dose comparable to
Sofosbuvir with velpatasvir and voxilaprevir

The properties listed below are those particular to the combination only. For the properties of the components please consider, sofosbuvir p. 628.

**INDICATIONS AND DOSE**

Chronic hepatitis C infection (specialist use only)

- **BY MOUTH**
  - Adult: 1 tablet once daily, for duration of treatment, consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises reduce dose of concurrent H₂-receptor antagonist if above a dose comparable to famotidine 40 mg twice daily.
- Manufacturer advises reduce dose of concurrent proton pump inhibitor if above a dose comparable to omeprazole 20 mg.

**CAUTIONS**

- Hepatitis B co-infection
- INTERACTIONS → Appendix 1: sofosbuvir - velpatasvir
- SIDE-EFFECTS Atrioventricular block - bradycardia - fatigue - headache - nausea

**PATIENT AND CARER ADVICE**

Vomiting Manufacturer advises if vomiting occurs within 3 hours of administration, an additional dose should be taken.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Sofosbuvir-velpatasvir for treating chronic hepatitis C (January 2017) NICE TA430

Sofosbuvir with velpatasvir is recommended as an option for treating chronic hepatitis C infection in adults, if the following criteria are met:

- of genotype 1, 3, 4, 5 or 6 with or without cirrhosis (previously treated or treatment naive patients);
- of genotype 2 with cirrhosis (previously treated or treatment naive patients);
- of genotype 2 without cirrhosis (treatment naive patients), only if interferon not suitable or not tolerated, or without cirrhosis (previously treated patients). This is contingent on the manufacturer providing the drug with the discount agreed in the simple discount agreement.

Patients whose treatment was started within the NHS before this guidance was published should continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta430

**Scottish Medicines Consortium (SMC) decisions**

**SMC No. 1195/16**

The Scottish Medicines Consortium has advised (November 2016) that sofosbuvir with velpatasvir (Epclusa®) is accepted for restricted use within NHS Scotland for the treatment of adults with chronic hepatitis C infection of genotype 3 only.

**SMC No. 1271/17**

The Scottish Medicines Consortium has advised (October 2017) that sofosbuvir with velpatasvir (Epclusa®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis C virus (HCV) infection in adults with genotype 2, 5 or 6 or decompensated cirrhosis, irrespective of chronic HCV genotype. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**NMC No. 1271/17**

The Scottish Medicines Consortium has advised (April 2018) that sofosbuvir with velpatasvir (Epclusa®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis C virus (HCV) infection in adults with genotype 1 or 4. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 25

- Epclusa (Gilead Sciences International Ltd) ▼
- Velpatasvir 100 mg, Sofosbuvir 400 mg Epclusa 400mg/100mg tablets 1 28 tablet (box) £12,993.33
**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21, 25**

- Vosevi (Gilead Sciences International Ltd) ▼
  - Velpatasvir 100 mg, Voxilaprevir 100 mg, Sofosbuvir 400 mg 
  - Vosevi 400mg/100mg/100mg tablets ▼
  - 28 tablet ▼
  - £14,924.33

**ANTIVIRALS › PROTEASE INHIBITORS, HEPATITIS**

**Glecaprevir with pibrentasvir** 25-Oct-2017

**INDICATIONS AND DOSE**

**Chronic hepatitis C (specialist use only)**

- **BY MOUTH**
  - Adult: 300/120 mg once daily, for duration of treatment, consult product literature
  - **DOSE EQUIVALENCE AND CONVERSION**
  - Dose expressed as x/y mg glecaprevir/pibrentasvir.

**IMPORTANT SAFETY INFORMATION**

**HEPATITIS B INFECTION**

Cases of hepatitis B reactivation, sometimes fatal, have been reported in patients co-infected with hepatitis B and C viruses; manufacturer advises to assess patients for hepatitis B prior to initiation of therapy and manage according to current clinical guidelines.

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF INTERACTION WITH VITAMIN K ANTAGONISTS AND CHANGES IN INR (JANUARY 2017)**

An EU-wide review has identified that changes in liver function, secondary to hepatitis C treatment with direct-acting antivirals, may affect the efficacy of vitamin K antagonists; the MHRA has advised that INR should be monitored closely in patients receiving concomitant treatment.

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS FOR CHRONIC HEPATITIS C: RISK OF HYPOGLYCAEMIA IN PATIENTS WITH DIABETES (DECEMBER 2018)**

Rapid reduction in hepatitis C viral load during direct-acting antiviral therapy for hepatitis C may improve glucose metabolism in patients with diabetes and result in symptomatic hypoglycaemia if diabetic treatment is continued at the same dose.

The MHRA advises healthcare professionals:

- to monitor glucose levels closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C, especially within the first 3 months of treatment and modify diabetic medication or doses when necessary;
- to be vigilant for changes in glucose tolerance and advise patients of the risk of hypoglycaemia;
- to inform the healthcare professional in charge of the diabetic care of the patient when direct-acting antiviral therapy is initiated.

**NICE decisions**

- **Glecaprevir-pibrentasvir for treating chronic hepatitis C**
  - (January 2018) NICE TA499
  - Glecapsrevir with pibrentasvir is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in adults, only if the manufacturer provides the drug at the same price or lower than that agreed with the Commercial Medicines Unit.
  - www.nice.org.uk/guidance/ta499

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (November 2017) that glecaprevir with pibrentasvir (Maviret®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis C virus (HCV) infection in adults. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21, 25**

- **Maviret (AbbVie Ltd) ▼**
  - **Pibrentasvir 40 mg, Glecaprevir 100 mg**
  - Maviret 100mg/40mg tablets ▼
  - 84 tablet ▼
  - £12,993.66

**ANTIVIRALS › OTHER**

**Dasabuvir** 28-Mar-2019

**DRUG ACTION**

Dasabuvir is a non-nucleoside inhibitor of hepatitis C virus polymerase NS5B, which is an essential component of the hepatitis C virus replication process.

**INDICATIONS AND DOSE**

**Chronic hepatitis C infection of genotype 1, in combination with other antiviral drugs (ombitasvir with paritaprevir and ritonavir, with or without ribavirin)**

- **BY MOUTH**
  - Adult: 250 mg twice daily for details of duration of treatment, consult product literature, dose to be taken in the morning and evening

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRALS TO TREAT CHRONIC HEPATITIS C: RISK OF INTERACTION WITH VITAMIN K ANTAGONISTS AND CHANGES IN INR (JANUARY 2017)**

A EU-wide review has identified that changes in liver function, secondary to hepatitis C treatment with direct-acting antivirals, may affect the efficacy of vitamin K antagonists; the MHRA has advised that INR should be monitored closely in patients receiving concomitant treatment.

**MHRA/CHM ADVICE: DIRECT-ACTING ANTIVIRAL INTERFERON-FREE REGIMENS TO TREAT CHRONIC HEPATITIS C: RISK OF HEPATITIS B REACTIVATION (JANUARY 2017)**

An EU-wide review has concluded that direct-acting antiviral interferon-free regimens for chronic hepatitis C can cause hepatitis B reactivation in patients co-infected with hepatitis B and C viruses; the MHRA recommends to screen patients for hepatitis B before starting treatment—patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines.

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**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in moderate to severe impairment (risk of increased exposure).

**PATIENT AND CARER ADVICE**

- **Missed doses** Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**PATIENT AND CARER ADVICE**

- Manufacturer advises avoid in limited efficacy not established

**SIDE-EFFECTS**

- **Common or very common** Asthenia, diarrhoea, headache, nausea
- **Frequency not known** Pruritus, transient ischaemic attack
- **PREGNANCY** Manufacturer advises avoid—limited information available.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
632 Viral infection

6.3 Herpesvirus infections

Herpes simplex and varicella–zoster infection

The two most important herpesvirus pathogens are herpes simplex virus (herpesvirus hominis) and varicella–zoster virus.

Herpes simplex infections

Herpes infections of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection.

In individuals with good immune function, mild infection of the eye (ocular herpes) and of the lips (herpes labialis or cold sores) is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics. Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised patient may signal the development of resistance.

Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.

Varicella-zoster infections

Regardless of immune function and the use of any immunoglobulins, neonates with chickenpox should be treated with a parenteral antiviral to reduce the risk of severe disease. Oral therapy in children is not recommended as absorption is variable. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required.

Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents.

Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.

Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella–zoster immunoglobulin (see under Disease Specific Immunoglobulins). In herpes zoster (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days.

Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.

Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management.

Choice

Aciclovir p. 633 is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of...
Herpes simplex infections of the skin and mucous membranes. It is used by mouth for severe herpetic stomatitis. Aciclovir ointment is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.

Famiclovir p. 635, a prodrug of penciclovir, is similar to aciclovir and is licensed for use in herpes zoster and genital herpes.

Valaciclovir p. 636 is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed for preventing cytomegalovirus disease following solid organ transplantation. Famiclovir or valaciclovir are suitable alternatives to aciclovir for oral lesions associated with herpes zoster. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought.

Foscarnet sodium p. 637 is used for mucocutaneous herpes simplex virus infection unresponsive to aciclovir in immunocompromised patients; it is toxic and can cause renal impairment.

Inosine pranobex below has been used by mouth for herpes simplex infections; its effectiveness remains unproven.

Cytomegalovirus infection

Ganciclovir p. 637 is related to aciclovir but it is more active against cytomegalovirus (CMV); it is also much more toxic than aciclovir and should therefore be prescribed only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the initial treatment of CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine p. 655; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration.

Valaciclovir is licensed for prevention of cytomegalovirus disease following renal transplantation.

Valganciclovir p. 638 is an ester of ganciclovir which is licensed for the initial treatment and maintenance treatment of CMV retinitis in AIDS patients. Valganciclovir is also licensed for preventing CMV disease following solid organ transplantation from a cytomegalovirus-positive donor.

Foscarnet sodium is also active against cytomegalovirus; it is toxic and can cause renal impairment.

See local treatment of CMV retinitis.

Antiviral Proceedings

Inosine pranobex (Inosine acedoben dimepranol)

Indications and dose

Mucocutaneous herpes simplex

- **By mouth**
  - Adult: 1 g 4 times a day for 7–14 days

Adjunctive treatment of genital warts

- **By mouth**
  - Adult: 1 g 3 times a day for 14–28 days

Subacute sclerosing panencephalitis

- **By mouth**
  - Adult: 50–100 mg/kg daily in 6 divided doses

Caution

History of gout, history of hyperuricaemia

Side-effects

Arthralgia, constipation, diarrhoea, drowsiness, epigastric discomfort, fatigue, headache, insomnia, malaise, nausea, nervousness, polyuria, skin reactions, vertigo, vomiting

Pregnancy

Manufacturer advises avoid.

Renal impairment

Manufacturer advises caution; metabolised to uric acid.

Less suitable for prescribing

Inosine pranobex is less suitable for prescribing.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Table

General dosage

- **Imunovir** (KoRa Healthcare)
  - Inosine acedoben dimepranol 500 mg Imunovir 500 mg tablets | 100 tablet 950 £39.50

Antiviral Proceedings

Aciclovir

(Acyclovir)

Indications and dose

Herpes simplex, suppression

- **By mouth**
  - Child 12–17 years: 400 mg twice daily, alternatively 200 mg 4 times a day; increased to 400 mg 3 times a day, dose may be increased if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation), therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
  - Adult: 400 mg twice daily, alternatively 200 mg 4 times a day; increased to 400 mg 3 times a day, dose may be increased if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation), therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Herpes simplex, prophylaxis in the immunocompromised

- **By mouth**
  - Child 1–5 years: 200 mg 4 times a day
  - Child 6–12 years: 400 mg 4 times a day
  - Adult: 400 mg 4 times a day

- **By intravenous infusion**
  - Adult: 5 mg/kg every 8 hours

Herpes simplex, treatment (non-genital)

- **By mouth**
  - Adult: 200 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)

Herpes simplex, treatment (non-genital) in immunocompromised or if absorption impaired

- **By mouth**
  - Adult: 400 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)

Herpes simplex, treatment

- **By mouth**
  - Child 1–5 years: 100–200 mg 4 times a day
  - Child 6–12 years: 200–400 mg 4 times a day
  - Adult: 200–400 mg 4 times a day

- **By intravenous infusion**
  - Adult: 5 mg/kg every 8 hours

Herpes simplex, treatment in immunocompromised or if absorption impaired

- **By mouth**
  - Child 1–5 years: 200 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
  - Child 6–12 years: 400 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)
Varicella zoster (chickenpox), attenuation of infection if varicella–zoster immunoglobulin not indicated

- **BY MOUTH**
  - Child: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure
  - Adult: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure

**DOSES AT EXTREMES OF BODY-WEIGHT**
- With intravenous use: To avoid excessive dosage in obese patients parenteral dose should be calculated on the basis of ideal weight for height.

- **UNLICENSED USE**
  - With oral use in children: Tablets and suspension not licensed for suppression of herpes simplex or for treatment of herpes zoster in children (age range not specified by manufacturer).
  - With oral use: Aciclovir doses in BNF may differ from those in product literature. Attenuation of chickenpox is an unlicensed indication.

- **CAUTIONS**
  - Elderly (risk of neurological reactions) - maintain adequate hydration (especially with infusion or high doses)

- **INTERACTIONS** → Appendix 1: aciclovir

- **SIDE-EFFECTS**
  - **Common or very common**
    - With intravenous use: Abdominal pain, diarrhea, dizziness, fatigue, fever, headache, nausea, photosensitivity reaction, skin reactions, vomiting
  - With oral use: Abdominal pain, diarrhea, dizziness, drowsiness, dysarthria, dysphagia, encephalopathy, fatigue, fever, hallucination, headache, hepatic disorders, inflammation localised, psychosis, renal impairment, renal pain, seizure, tremor
  - Uncommon: Abdominal pain, ataxia, coma, confusion, diarrhea, dizziness, dysarthria, dysphagia, encephalopathy, hallucination, hepatic disorders, leucopenia, psychosis, renal impairment, renal pain, seizure, thrombocytopenia, tremor
  - **Rare or very rare**
    - With intravenous use: Abdominal pain, agitation, angioedema, ataxia, coma, confusion, diarrhea, dizziness, drowsiness, dysarthria, dysphagia, encephalopathy, fever, hallucination, headache, hepatic disorders, inflammation localised, psychosis, renal impairment, renal pain, seizure, tremor
  - With oral use: Abdominal pain, ataxia, coma, confusion, diarrhea, dizziness, drowsiness, dysarthria, dysphagia, encephalopathy, hallucination, hepatic disorders, leucopenia, psychosis, renal impairment, renal pain, seizure, tremor
  - Frequency not known: Abdominal pain, ataxia, coma, confusion, diarrhea, dizziness, drowsiness, dysarthria, dysphagia, encephalopathy, hallucination, hepatic disorders, leucopenia, psychosis, renal impairment, renal pain, seizure, tremor
  - With intravenous use: Crystalluria
  - With oral use: Alopecia, crystalluria
  - **PREGNANCY** Not known to be harmful — manufacturers advise use only when potential benefit outweighs risk.
  - **BREAST FEEDING** Significant amount in milk after systemic administration — not known to be harmful but manufacturer advises caution.

- **RENAL IMPAIRMENT** Risk of neurological reactions increased. Maintain adequate hydration (especially during renal impairment).

**Dose adjustments**
- With intravenous use in adults: Use normal intravenous dose every 12 hours if eGFR 25–50 mL/minute/1.73 m² (every 24 hours if eGFR 10–25 mL/minute/1.73 m²). Consult product literature for intravenous dose if eGFR less than 10 mL/minute/1.73 m².
- With oral use in adults: For herpes zoster, use normal oral dose every 8 hours if eGFR 10–25 mL/minute/1.73 m² (every 12 hours if eGFR less than 10 mL/minute/1.73 m²).
- For herpes simplex, use normal oral dose every 12 hours if eGFR less than 10 mL/minute/1.73 m².
- With oral use in children: For herpes zoster, use normal oral dose every 8 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m² (every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²).
For herpes simplex, use normal dose every 12 hours if estimated glomerular filtration rate less than 10.0/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use in adults For intravenous Zovirax IV®, Aciclovir IV (Genus), give intermittently in Sodium chloride 0.9% or Sodium chloride and glucose; initially reconstitute to 25 mg/mL in water for injection or sodium chloride 0.9% then dilute to not more than 5 mg/mL with the infusion fluid; to be given over 1 hour; alternatively, may be administered in a concentration of 25 mg/mL using a suitable infusion pump and given over 1 hour; for Aciclovir IV (Hospira) dilute to not more than 5 mg/mL with infusion fluid; give over 1 hour.

**PRESCRIBING AND DISPENSING INFORMATION**
- With oral use Flavours of oral liquid preparations may include banana, or orange.

**PATIENT AND CARER ADVICE**
- Medicines for Children leaflet: Aciclovir (oral) for viral infections
  - With oral use www.medicinesforchildren.org.uk/aciclovir-oral-viral-infections-

**PROFESSION SPECIFIC INFORMATION**
- Dental practitioners’ formulary
  - With oral use Aciclovir Tablets 200 mg or 800 mg may be prescribed. Aciclovir Oral Suspension 200 mg/5mL may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Aciclovir (Non-proprietary) | Aciclovir 200 mg Aciclovir 200mg tablets | 25 tablet [POD] £1.25 OT  
|                           | Aciclovir 400 mg Aciclovir 400mg tablets | 56 tablet [POD] £3.30 OT  
|                           | Aciclovir 800 mg Aciclovir 800mg tablets | 35 tablet [POD] £4.35 OT  

**Dispersible tablet**

| Aciclovir (Non-proprietary) | Aciclovir 200 mg Aciclovir 200mg dispersible tablets | 25 tablet [POD] £1.05 OT  
|                           | Aciclovir 400 mg Aciclovir 400mg dispersible tablets | 56 tablet [POD] £1.98 OT  
|                           | Aciclovir 800 mg Aciclovir 800mg dispersible tablets | 35 tablet [POD] £1.98 OT  
|                           | Zovirax (GlaxoSmithKline Ltd) | Aciclovir 200 mg Zovirax 200mg dispersible tablets | 25 tablet [POD] £2.83 OT  
|                           | Aciclovir 800 mg Zovirax 800mg dispersible tablets | 35 tablet [POD] £5.00 OT  

**Oral suspension**

| Aciclovir (Non-proprietary) | Aciclovir 40 mg per 1 ml Aciclovir 200mg/5ml oral suspension sugar-free sugar-free | 25 ml [POD] £3.75 OT  
|                           | Aciclovir 80 mg per 1 ml Aciclovir 400mg/5ml oral suspension sugar-free sugar-free | 100 ml [POD] £3.94 OT  
|                           | Zovirax (GlaxoSmithKline Ltd) | Aciclovir 80 mg per 1 ml Zovirax Double Strength 400mg/5ml oral suspension sugar-free | 125 ml [POD] £5.56 OT  
|                           | Aciclovir 80 mg per 1 ml Zovirax Double Strength 400mg/5ml oral suspension sugar-free | 200 ml [POD] £5.56 OT  

**Solution for infusion**

| ELECTROLYTES: | May contain Sodium  
| Aciclovir (as Aciclovir sodium) 25 mg per 1 ml Aciclovir 1g/40ml solution for infusion vials | 1 vial [POD] £4.00 (Hospital only)  
| Aciclovir 250mg/10ml concentrate for solution for infusion vials | 5 vial [POD] £5.00 (Hospital only)  
| Aciclovir 500mg/20ml solution for infusion vials | 5 vial [POD] £10.00 (Hospital only)  
| Aciclovir 500mg/20ml concentrate for solution for infusion vials | 5 vial [POD] £10.00 (Hospital only)  

**Powder for solution for infusion**

| ELECTROLYTES: | May contain Sodium  
| Aciclovir (as Aciclovir sodium) 250 mg Aciclovir 250mg powder for solution for infusion vials | 5 vial [POD] £16.50 (Hospital only)  
| Aciclovir 250mg powder for solution for infusion vials | 10 vial [POD] £39.30 (Hospital only)  
| Aciclovir (as Aciclovir sodium) 500 mg Aciclovir 500mg powder for solution for infusion vials | 5 vial [POD] £82.00 (Hospital only)  
| Zovirax IV. (GlaxoSmithKline Ltd) | Aciclovir (as Aciclovir sodium) 250 mg Zovirax IV. 250mg powder for solution for infusion vials | 5 vial [POD] £16.70  
| Aciclovir (as Aciclovir sodium) 500 mg Zovirax IV. 500mg powder for solution for infusion vials | 5 vial [POD] £17.00  

**Famciclovir**

| INDICATIONS AND DOSE |  
| Herpes zoster infection, treatment |  
| BY MOUTH | Adult: 500 mg 3 times a day for 7 days, alternatively 750 mg 1–2 times a day for 7 days  
| Herpes zoster infection, treatment in Immunocompromised patients |  
| BY MOUTH | Adult: 500 mg 3 times a day for 10 days, continue for 2 days after crusting of lesions  
| Genital herpes, suppression |  
| BY MOUTH | Adult: 250 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences  
| Genital herpes, suppression in immunocompromised or HIV-positive patients |  
| BY MOUTH | Adult: 500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences  
| Genital herpes infection, treatment of first episode |  
| BY MOUTH | Adult: 250 mg 3 times a day for 5 days or longer if new lesions appear during treatment or if healing incomplete  
| Genital herpes infection, treatment of first episode in immunocompromised or HIV-positive patients |  
| BY MOUTH | Adult: 500 mg twice daily for 10 days  
| Genital herpes infection, treatment of recurrent infection |  
| BY MOUTH | Adult: 125 mg twice daily for 5 days, alternatively 1 g twice daily for 1 day  
| Genital herpes infection, treatment of recurrent infections in immunocompromised or HIV-positive patients |  
| BY MOUTH | Adult: 500 mg twice daily for 5–10 days  
| Herpes simplex infection (non-genital), treatment in Immunocompromised patients |  
| BY MOUTH | Adult: 500 mg twice daily for 7 days  

| UNLICENSED USE |  
| Famciclovir doses in BNF may differ from those in product literature.  
| SIDE-EFFECTS |  
| Common or very common | Abdominal pain - diarrhoea - dizziness - headache - nausea - skin reactions - vomiting  
| Uncommon | Angioedema - confusion - drowsiness  
| Rare or very rare | Hallucination - jaundice cholestatic - palpitations - thrombocytopenia  
| PREGNANCY | Manufacturers advise avoid unless potential benefit outweighs risk.  

www.getintopharma.com
HERPES SIMPLEX

Herpes simplex, suppression of infections in immunocompromised or HIV-positive patients
► BY MOUTH
► Adult: 500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Genital herpes, reduction of transmission (administered on expert advice)
► BY MOUTH
► Adult: 500 mg once daily, to be taken by the infected partner

Prevention of cytomegalovirus disease following solid organ transplantation when valganciclovir or ganciclovir cannot be used
► BY MOUTH
► Adult: 2 g 4 times a day usually for 90 days, preferably starting within 72 hours of transplantation

CAUTIONS
Elderly (risk of neurological reactions) - maintain adequate hydration (especially with high doses)

INTERACTIONS
► Appendix 1: valaciclovir

SIDE-EFFECTS
Common or very common
Diarrhoea, dizziness, headache, nausea, photosensitivity reaction - skin reactions - vomiting

Uncommon
Abdominal discomfort, agitation, confusion, dyspnoea, haematuria, hallucination, leucopenia, level of consciousness decreased, renal pain, thrombocytopenia, tremor

Rare or very rare
Angioedema, ataxia, coma, delirium, dysarthria, encephalopathy, nephrolithiasis, psychosis, renal impairment, seizure

Frequency not known
Microangiopathic haemolytic anaemia

SIDE-EFFECTS, FURTHER INFORMATION
Neurological reactions more frequent with higher doses.

PREGNANCY
Not known to be harmful—manufacturers advise use only when potential benefit outweighs risk.

BREAST FEEDING
Significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution.

HEPATIC IMPAIRMENT
Manufacturer advises caution with doses of 4 g or more per day (no information available).

RENAL IMPAIRMENT
Maintain adequate hydration.
Dose adjustments
In adults For herpes zoster, 1 g every 12 hours if eGFR 30–50 mL/minute/1.73 m²; (1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m²; 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m²). For treatment of herpes simplex, 500 mg (1 g in immunocompromised or HIV-positive patients) every 24 hours if eGFR less than 30 mL/minute/1.73 m². For treatment of herpes labialis, if eGFR 30–50 mL/minute/1.73 m², initially 1 g, then 1 g 12 hours after initial dose (if eGFR 10–30 mL/minute/1.73 m², initially 500 mg, then 500 mg 12 hours after initial dose; if estimated glomerular filtration rate 10–30 mL/minute/1.73 m², initially 500 mg, then 500 mg 12 hours after initial dose; if estimated glomerular filtration rate 7.5–10 mL/minute/1.73 m², initially 250 mg, then 250 mg 12 hours after initial dose; if estimated glomerular filtration rate < 7.5 mL/minute/1.73 m², initially 125 mg, then 125 mg 12 hours after initial dose).

Valaciclovir

INDICATIONS AND DOSE
Herpes zoster infection, treatment
► BY MOUTH
► Adult: 1 g 3 times a day for 7 days
Herpes zoster infection, treatment in immunocompromised patients
► BY MOUTH
► Adult: 1 g 3 times a day for at least 7 days and continued for 2 days after crusting of lesions
Herpes simplex, treatment of first infective episode
► BY MOUTH
► Adult: 500 mg twice daily for 5 days (longer if new lesions appear during treatment or healing is incomplete)
Herpes simplex infections treatment of first episode in immunocompromised or HIV-positive patients
► BY MOUTH
► Adult: 1 g twice daily for 10 days
Herpes simplex, treatment of recurrent infections
► BY MOUTH
► Adult: 500 mg twice daily for 3–5 days
Treatment of recurrent herpes simplex infections in immunocompromised or HIV-positive patients
► BY MOUTH
► Adult: 1 g twice daily for 5–10 days
Herpes labialis treatment
► BY MOUTH
► Child 12-17 years: Initially 2 g, then 2 g after 12 hours
► Adult: Initially 2 g, then 2 g after 12 hours
Herpes simplex, suppression of infections
► BY MOUTH
► Adult: 500 mg daily in 1–2 divided doses, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
Cytomegalovirus infections

6.3a Cytomegalovirus infections

ANTIVIRALS  NUCLEOSIDE ANALOGUES

Cidofovir

DRUG ACTION Cidofovir is a selective inhibitor of human cytomegalovirus (HCMV) DNA polymerase which inhibits viral DNA synthesis and thereby suppresses HCMV replication.

INDICATIONS AND DOSE Cytomegalovirus retinitis in patients with AIDS (in combination with probenecid) (specialist use only)

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg once weekly for 2 weeks, then maintenance 5 mg/kg every 2 weeks, maintenance treatment to be started 2 weeks after completion of induction treatment

CONTRA-INDICATIONS Concomitant administration with potentially nephrotoxic drugs—discontinue potentially nephrotoxic drugs at least 7 days before starting cidofovir. Patients unable to receive probenecid

CAUTIONS Diabetes mellitus (increased risk of ocular hypotony), ensure concomitant use of probenecid and Sodium Chloride 0.9%

CAUTIONS, FURTHER INFORMATION

Probenecid and Sodium Chloride 0.9%. Manufacturer advises oral probenecid and intravenous Sodium Chloride 0.9% must be administered with each cidofovir dose to prevent nephrotoxicity (consult cidofovir product literature for information on probenecid dosing and recommendations on intravenous hydration); see Prescribing and dispensing information for details on obtaining probenecid.

INTERACTIONS Appendix 1: cidofovir

SIDE-EFFECTS

Common or very common Alopecia · asthenia · chills · diarrhoea · dyspnoea · eye inflammation · fever · headache · nausea · neutropenia · ocular hypotony · proteinuria · rash · renal failure · vomiting

Uncommon Fanconi syndrome acquired

Frequency not known Hearing impairment · nephrotoxicity · pancreatitis

SIDE-EFFECTS, FURTHER INFORMATION

Manufacturer advises intravenous sodium chloride 0.9% prehydration and concomitant oral probenecid for prevention of nephrotoxicity; consider treatment interruption, or discontinuation if changes in renal function occur—consult product literature.

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and after treatment in women; men should be advised to use barrier contraception during and for 3 months after treatment. Cidofovir may cause impaired fertility in males—reduced testes weight and hypospermatia observed in animal studies.

PREGNANCY Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING Manufacturer advises avoid (no information available).

HEPATIC IMPAIRMENT Manufacturer advises caution (no information available).

RENAL IMPAIRMENT Manufacturer advises avoid if creatinine clearance is less than or equal to 55 mL/minute or if proteinuria is greater than or equal to 100 mg/dL.

MONITORING REQUIREMENTS

Manufacturer advises monitor serum creatinine, urine electrolytes, creatinine clearance and creatinine half-life; review drug interactions regularly; consider monitoring proteinuria; monitor liver function tests; review information on interactions.

HANDLING AND STORAGE

Caution in handling. Manufacturer advises cidofovir should be considered a potential carcinogen and must be handled with caution (consult product literature); if contact with skin or mucous membranes occurs, wash thoroughly with water.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

ELECTROLYTES: May contain Sodium

Cidofovir (non-proprietary)

Cidofovir 75 mg per 1 ml Cidofovir 375mg/5ml concentrate for solution for infusion vials 1 vial

Ganciclovir

INDICATIONS AND DOSE Prevention of cytomegalovirus disease [pre-emptive therapy in patients with drug-induced immunosuppression]

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg every 12 hours for 7–14 days, then maintenance 6 mg/kg once daily, on 5 days of the week, alternatively maintenance 5 mg/kg once daily

Prevention of cytomegalovirus disease [universal prophylaxis in patients with drug-induced immunosuppression]

BY INTRAVENOUS INFUSION

Adult: 6 mg/kg once daily, on 5 days of the week, alternatively 5 mg/kg once daily

Treatment of cytomegalovirus disease [in immunocompromised patients]

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg every 12 hours for 14–21 days, then maintenance 6 mg/kg once daily, on 5 days of the week, alternatively maintenance continued →
5 mg/kg once daily, maintenance only for patients at risk of relapse; if disease progresses initial induction treatment may be repeated

- **CONTRA-INDICATIONS** Abnormally low haemoglobin count (consult product literature) - abnormally low neutrophil count (consult product literature) - abnormally low platelet count (consult product literature)

- **CAUTIONS** History of cytopenia - potential carcinogen (including long-term carcinogenicity) - potential teratogen (including long-term teratogenicity) - radiotherapy

- **INTERACTIONS** → Appendix 1: ganciclovir

- **SIDE-EFFECTS**
  - Uncommon Alopecia - arrhythmia - deafness - haematura - hypotension - infertility male - oral ulceration - pancreatitis - psychotic disorder - tremor - visual impairment
  - Rare or very rare Agranulocytosis - hallucination

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients hypersensitive to valganciclovir, aciclovir, or valaciclovir.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises women of childbearing potential should use effective contraception during and for at least 90 days after treatment; men with partners of childbearing potential should be advised to use barrier contraception during and for at least 90 days after treatment. Ganciclovir may cause temporary or permanent inhibition of spermatogenesis — impaired fertility observed in animal studies.

- **PREGNANCY** Women of childbearing potential should use effective contraception during and for at least 90 days after treatment.

- **BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.

- **RENAI IMPAIRMENT**
  - **DOSE ADJUSTMENTS** Manufacturer advises reduce dose for patients receiving mg/kg dosing if creatinine clearance less than 70 mL/minute — consult product literature.
  - **MONITORING REQUIREMENTS** Monitor full blood count closely (sd - bone deterioration may require correction and possibly treatment interruption).

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises, for intravenous infusion, give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute with Water for Injections (500 mg/10 mL) then dilute requisite dose to a concentration of not more than 10 mg/mL with infusion fluid; give over 1 hour into a vein with adequate flow, preferably using a plastic cannula.

- **HANDLING AND STORAGE** Caution in handling Ganciclovir is a potential teratogen and carcinogen. Manufacturer advises avoid inhalation of the powder or direct contact of the powder or reconstituted solution with the skin or mucous membranes; if contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.

**Valganciclovir**

**INDICATIONS AND DOSE**

Cytopathic virus retinitis [induction and maintenance treatment in patients with AIDS]

- **BY MOUTH**
  - Adult: Initially 900 mg twice daily for 21 days, then maintenance 900 mg daily, induction regimen may be repeated if retinitis progresses

Prevention of cytopathic virus disease [following solid organ transplantation from a cytopathic virus positive donor]

- **BY MOUTH**
  - Adult: 900 mg daily for 100 days (for 100 – 200 days following kidney transplantation), to be started within 10 days of transplantation

**DOSE EQUIVALENCE AND CONVERSION**

- Oral valganciclovir 900 mg twice daily is equivalent to intravenous ganciclovir 5 mg/kg twice daily.

**CONTRA-INDICATIONS** Abnormally low haemoglobin count (consult product literature) - abnormally low neutrophil count (consult product literature) - abnormally low platelet count (consult product literature)

**CAUTIONS** History of cytopenia - potential carcinogen (including long-term carcinogenicity) - potential teratogen (including long-term teratogenicity) - radiotherapy

**INTERACTIONS** → Appendix 1: valganciclovir

**SIDE-EFFECTS**


- Uncommon Alopecia - arrhythmia - deafness - haematura - hypotension - infertility male - oral ulceration - pancreatitis - psychotic disorder - tremor - visual impairment

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients hypersensitive to ganciclovir, aciclovir, or valaciclovir.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises women of childbearing potential should use effective contraception during and for at least 90 days after treatment; men with partners of childbearing potential should be advised to use barrier contraception during and for at least 90 days after treatment. Ganciclovir may cause temporary or permanent inhibition of spermatogenesis — impaired fertility observed in animal studies.
Cytomegalovirus infections | 639

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—teratogenicity observed with ganciclovir in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—ganciclovir present in milk in animal studies.
- **RENAL IMPAIRMENT**
  - Dose adjustments Manufacturer advises reduce dose if creatinine clearance less than 60 mL/minute—consult product literature.
- **MONITORING REQUIREMENTS** Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Valganciclovir is a pro-drug of ganciclovir. Flavours of oral liquid formulations may include tutti-frutti.
  - Caution in handling the powder, reconstituted solution, or broken tablets and avoid inhalation of powder; if contact with skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.
  - If exposure to foscarnet sodium occurs, wash hands with soap and water.
- **HANDLING AND STORAGE**
  - Manufacturer advises reconstituted powder for oral solution should be stored in a refrigerator (2–8°C) for up to 49 days.
  - Caution in handling Valganciclovir is a potential teratogen and carcinogen. Manufacturer advises caution when handling the powder, reconstituted solution, or broken tablets and avoid inhalation of powder; if contact with skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
  - **Oral solution**
    - CAUTIONARY AND ADVISORY LABELS 21
    - Valcyte (Roche Products Ltd)
      - Valganciclovir (as Valganciclovir hydrochloride) 50 mg per 1 ml Valcyte 50mg/ml oral solution sugar-free | 100 ml (POS) £230.32
    - Valcyte (Roche Products Ltd)
      - Valganciclovir (as Valganciclovir hydrochloride) 450 mg Valganciclovir 450mg tablets | 60 tablet (POS) £865.17–£1,081.46 DT = £1,027.39
    - Valcyte (Roche Products Ltd)
      - Valganciclovir (as Valganciclovir hydrochloride) 450 mg Valcyte 450mg tablets | 60 tablet (POS) £1,081.46 DT = £1,027.39

### Antibacterials

#### Foscarnet sodium

- **INDICATIONS AND DOSE**
  - **Cytomegalovirus disease**
    - **BY INTRAVENOUS INFUSION**
      - Adult: Initially 60 mg/kg every 8 hours for 2–3 weeks, alternatively initially 90 mg/kg every 12 hours for 2–3 weeks, then maintenance 60 mg/kg daily, then increased if tolerated to 90–120 mg/kg daily, if disease progresses on maintenance dose, repeat induction regimen
      - **Muco-cutaneous herpes simplex virus infections unresponsive to aciclovir in immunocompromised patients**
        - **BY INTRAVENOUS INFUSION**
          - Adult: 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal
  - **UNLICENSED USE** Licensed for CMV retinitis in AIDS patients only. Foscarnet doses in BNF may differ from those in product literature.
  - **CAUTIONS** Ensure adequate hydration
  - **INTERACTIONS** → Appendix 1: foscarnet

- **SIDE-EFFECTS**
  - Common or very common Aggression, anaemia, anxiety, appetite decreased, arrhythmias, chest pain, chills, confusion, constipation, coordination abnormal, dehydration, depression, diarrhoea, dizziness, electrolyte imbalance, fever, gastrointestinal discomfort, genital discomfort (due to high concentrations excreted in urine), genital ulceration (due to high concentrations excreted in urine), haemorrhage, headache, hepatic function abnormal, hypertension, hypotension, leucopenia, malaise, muscle contractions involuntary, myalgia, nausea (reduce infusion rate), neutropenia, numbness, oedema, palpitations, pancreatitis, paraesthesia (reduce infusion rate), peripheral neuropathy, proteinuria, renal impairment, seizure, sepsis, skin reactions, thrombocytopenia, thrombophlebitis, tremor, urinary disorders, vomiting
  - Uncommon Acidosis, angioedema, glomerulonephritis, nephropathy, pancytopenia
  - Frequency not known Anaphylactoid reaction, diabetes insipidus, muscle weakness, myopathy, oesophageal ulcer, QT interval prolongation, renal pain, renal tubular acidosis, severe cutaneous adverse reactions (SCARs)
  - **CONCEPTION AND CONTRACEPTION** Men should avoid fathering a child during and for 6 months after treatment.
- **PREGNANCY** Manufacturer advises avoid.
- **BREAST FEEDING** Reduce dose; consult product literature.
- **RENAL IMPAIRMENT**
  - Dose adjustments Reduce dose; consult product literature.
- **MONITORING REQUIREMENTS**
  - Monitor electrolytes, particularly calcium and magnesium.
  - Monitor serum creatinine every second day during induction and every week during maintenance.
  - **DIRECTIONS FOR ADMINISTRATION** Avoid rapid infusion. For intravenous infusion (Foscavir®), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 12 mg/mL for infusion into peripheral vein (undiluted solution via central venous line only); infuse over at least 1 hour (infuse doses greater than 60 mg/kg over 2 hours).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - ELECTROLYTES: May contain Sodium
      - Foscavir (Clinigen Healthcare Ltd)
        - Foscarnet sodium 24 mg per 1 ml Foscavir 6g/250ml solution for infusion bottles | 1 bottle (POS) £119.85 (Hospital only)

#### Letermovir

- **DRUG ACTION** Letermovir is a cytomegalovirus DNA terminase complex inhibitor that interferes with cytomegalovirus genome formation and virion maturation.

- **INDICATIONS AND DOSE**
  - Prevention of cytomegalovirus reactivation and disease (in recipients of an allogeneic haematopoietic stem cell transplant who are seropositive for the human cytomegalovirus) (initiated by a specialist)
    - **BY MOUTH**
      - Adult: 480 mg once daily for 100 days post-transplant, start within 28 days post-transplant, treatment beyond 100 days may be considered in some patients—consult product literature
      - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
        - Manufacturer advises reduce dose to 240 mg once daily with concurrent use of ciclosporin.
      - **INTERACTIONS** → Appendix 1: letermovir

www.getintopharma.com
Infection in their use. remain slightly higher than in uninfected individuals. associated with premature ageing, mortality and morbidity (antiretrovirals) may be associated with serious side-effects. is not responding. to the Antiretroviral Pregnancy Registry at www.apregistry.com. HIV infection in Pregnancy and Childhood at www.ucl.ac.uk/nshpc/ and to the Antiretroviral Pregnancy Registry at www.apregistry.com.

HIV infection, switching therapy
Deterioration of the condition (including clinical and virological changes) may require a change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

HIV infection in pregnancy
Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although information on the teratogenic potential of most antiretroviral drugs is limited), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. All treatment options require careful assessment by a specialist. Combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother. However, it may be associated with a greater risk of preterm delivery. Pregnancies in HIV-positive women and babies born to them should be reported prospectively to the National Study of HIV in Pregnancy and Childhood at www.ucl.ac.uk/nshpc/ and to the Antiretroviral Pregnancy Registry at www.apregistry.com.

HIV infection and breast-feeding
Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

HIV infection, pre-exposure prophylaxis
The risk of acquiring HIV is increased in:
- men or transgender individuals who have unprotected anal intercourse with men;
- sexual partners of people who are HIV-positive with a detectable viral load; and
- HIV-negative heterosexual individuals who have unprotected intercourse with a HIV-positive person, and are likely to repeat this with the same person or another person with a similar status.

Emtricitabine with tenofovir disoproxil p. 652 may be appropriate for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in combination with safer sex practices in adults at high risk; recommendations developed by the British Association for Sexual Health and HIV are available at: www.bashh.org.
HIV infection, post-exposure prophylaxis

Prophylaxis with antiretroviral drugs [unlicensed indication] may be appropriate following exposure to HIV-infected material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer’s Expert Advisory Group on AIDS), www.gov.uk/dh and local ones may also be available. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Prompt prophylaxis with antiretroviral drugs [unlicensed indication] is also appropriate following potential sexual exposure to HIV; recommendations have been developed by the British Association for Sexual Health and HIV, www.bashh.org.

Drug treatment

Zidovudine p. 655, a nucleoside reverse transcriptase inhibitor (or ‘nucleoside analogue’), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine p. 648, emtricitabine, lamivudine, stavudine p. 654, and tenofovir disoproxil.

The protease inhibitors include atazanavir, darunavir, fosamprenavir (a pro-drug of amprenavir), lopinavir (available as lopinavir with ritonavir), ritonavir, saquinavir p. 660, and tipranavir p. 660. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, lopinavir (available as lopinavir with ritonavir), saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects.

The non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine p. 645, nevirapine, and rilpivirine are used in the treatment of HIV-1 infection, but not against the subtype HIV-2, a subtype that is rare in the UK. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz; CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2-4 weeks of treatment). Efavirenz has also been associated with an increased plasma-cholesterol concentration. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide below, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.

Maraviroc p. 660 is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV.

Dolutegravir p. 642, elvitegravir p. 643 and raltegravir p. 643 are inhibitors of HIV integrase. They are licensed for the treatment of HIV infection in combination with other antiretroviral drugs.

Cobicistat p. 661 is a pharmacokinetic enhancer that boosts the concentrations of other antiretrovirals, but it has no antiretroviral activity itself.

Immune reconstitution syndrome

Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms; these reactions may occur within the first few weeks or months of initiating treatment. Autoimmune disorders (such as Graves’ disease) have also been reported many months after initiation of treatment.

Osteonecrosis

Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

HIV infection in children

HIV disease in children has a different natural progression to adults. Children infected with HIV should be managed within a formal paediatric HIV clinical network by specialists with access to guidelines and information on antiretroviral drugs for children.

Antivirals > HIV-fusion inhibitors

**Enfuvirtide**

**DRUG ACTION** Enfuvirtide inhibits the fusion of HIV to the host cell.

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypersensitivity**

Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge.

**Osteonecrosis**

Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution— no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects).

**DIRECTIONS FOR ADMINISTRATION** For subcutaneous injection, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial.

**PATIENT AND CARER ADVICE**

Hypersensitivity reactions Patients or carers should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop.
Dolutegravir

**DRUG ACTION** Dolutegravir is an inhibitor of HIV integrase.

**INDICATIONS AND DOSE**

HIV infection without resistance to other inhibitors of HIV integrase, in combination with other antiretroviral drugs

- **BY MOUTH**
  - Adult: 50 mg once daily

HIV infection in patients where resistance to other inhibitors of HIV integrase suspected, in combination with other antiretroviral drugs

- **BY MOUTH**
  - Adult: 50 mg twice daily, dose to be taken with food

HIV infection in combination with other antiretroviral drugs (with concomitant carbamazepine, efavirenz, etravirine (without boosted protease inhibitors, but see also Interactions), fosphenytoin, phenobarbital, phenytoin, primidone, nevirapine, oxcarbazepine, St John's wort, rifampicin, or tipranavir)

- **BY MOUTH**
  - Adult: 50 mg twice daily, avoid concomitant use with these drugs if resistance to other inhibitors of HIV integrase suspected

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: DOLUTEGRAVIR (TIVICAY®), TRIUMEQ®, JULUCA®: SIGNAL OF INCREASED RISK OF NEURAL TUBE DEFECTS; DO NOT PRESCRIBE TO WOMEN SEEKING TO BECOME PREGNANT; EXCLUDE PREGNANCY BEFORE INITIATION AND ADVISE USE OF EFFECTIVE CONTRACEPTION (JUNE 2018)

New safety recommendations have been issued while an EU review evaluates cases of neural tube defects in babies born to mothers who became pregnant while taking dolutegravir. The MHRA advises:

- dolutegravir should not be prescribed to women who are trying to become pregnant;
- pregnancy should be excluded in women of childbearing potential with pregnancy testing before starting dolutegravir;
- women of childbearing potential should be advised to use effective contraception throughout treatment with dolutegravir;
- if pregnancy is confirmed in the first trimester while a woman is taking dolutegravir, switch to an alternative treatment unless there is no suitable alternative;
- women taking dolutegravir for HIV should be advised not to stop taking their medicine without first consulting their doctor.

**INTERACTIONS**

Appendix 1: dolutegravir

**SIDE-EFFECTS**

- Common or very common Depresssion · diarrhoea · dizziness · fatigue · flatulence · gastrointestinal discomfort · headache · nausea · skin reactions · sleep disorders · vomiting
- Uncommon Arthralgia · hepatitis · hypersensitivity · immune reconstitution inflammatory syndrome · myalgia · suicidal tendencies

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypersensitivity

Hypersensitivity reactions (including severe rash, or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, oral lesions, conjunctivitis, angioedema, eosinophilia, or raised liver enzymes) reported uncommonly. Discontinue immediately if any sign or symptoms of hypersensitivity reactions develop.

**Osteonecrosis** Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

**PREGNANCY** Manufacturer advises avoid, see Important Safety Information.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer dolutegravir tablets.

**Missed doses** If a dose is more than 20 hours late on the once daily regimen (or more than 8 hours late on the twice daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (May 2014) that dolutegravir (Tivicay®) is accepted for use within NHS Scotland when used in combination with other anti-retroviral medicines for the treatment of HIV infected adults. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

All Wales Medicines Strategy Group (AWMSG) decisions

The All Wales Medicines Strategy Group has advised (October 2017) that dolutegravir (Tivicay®) is recommended as an option for use within NHS Wales in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Tivicay (ViiV Healthcare UK Ltd)
  - Dolutegravir (as Dolutegravir sodium) 10 mg
    - 30 tablet pack £39.75 OT + £39.75
  - Dolutegravir (as Dolutegravir sodium) 25 mg
    - 30 tablet pack £249.38 OT + £249.38
  - Dolutegravir (as Dolutegravir sodium) 50 mg
    - 30 tablet pack £498.75 OT + £498.75

**Combinations available**: Abacavir with dolutegravir and lamivudine, p. 647

**Dolutegravir with rilpivirine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dolutegravir above, rilpivirine p. 646.

**INDICATIONS AND DOSE**

HIV-1 infection (initiated by a specialist)

- **BY MOUTH**
  - Adult: 50/25 mg once daily

**DOSE EQUIVALENCES AND CONVERSION**

- Dose expressed as x/y mg dolutegravir/rilpivirine.

**INTERACTIONS**

Appendix 1: dolutegravir - rilpivirine

**PATIENT AND CARER ADVICE**

Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and
HIV infection 643

HIV infection without resistance to other inhibitors of HIV integrase, in combination with low-dose ritonavir and atazanavir or lopinavir

BY MOUTH

Adult: 85 mg once daily, take at the same time as a once daily ritonavir-boosted regimen or with the first dose of a twice daily ritonavir-boosted regimen

HIV infection without resistance to other inhibitors of HIV integrase, in combination with low-dose ritonavir and darunavir or fosamprenavir

BY MOUTH

Adult: 150 mg once daily, take with the first dose of a twice daily ritonavir-boosted regimen

CAUTIONS Elderly—limited information available

INTERACTIONS → Appendix 1: elvitegravir

SIDE-EFFECTS

Common or very common Diarrhoea, fatigue, headache, nausea, rash, vomiting

Uncommon Depression, dizziness, drowsiness, flatulence, gastrointestinal discomfort, insomnia, paraesthesia

suicidal ideation (in patients with history of depression or psychiatric illness) - taste altered

Frequency not known Hyperglycaemia, osteonecrosis - weight increased

SIDE-EFFECTS, FURTHER INFORMATION For further information regarding osteonecrosis see HIV infection p. 640

CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective contraception during treatment (if using a hormonal contraceptive, it must contain norgestimate as the progestogen and at least 30 micrograms ethinylestradiol).

PREGNANCY Manufacturer advises avoid unless essential—limited data available.

PATIENT AND CARER ADVICE Missed doses Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. If vomiting occurs within 1 hour of taking a dose, a replacement dose should be taken.

MEDICINAL FORMS No licensed medicines listed.

Combinations available: Elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide, p. 649 - Elvitegravir with cobicistat, emtricitabine and tenofovir disoproxil, p. 650

Elvitegravir 14-Jul-2018

DRUG ACTION Elvitegravir is an inhibitor of HIV integrase.

INDICATIONS AND DOSE

HIV-1 infection (initiated by a specialist)

BY MOUTH USING TABLETS

Adult: 400 mg twice daily, alternatively 1200 mg once daily, once daily dosing for use in patients who are treatment naive or virologically suppressed on an initial regimen of 400 mg twice daily—use 600 mg tablets only

CONTRA-INDICATIONS Pre-term neonates—no information available

CAUTIONS Psychiatric illness (may exacerbate underlying illness including depression) - risk factors for myopathy - risk factors for rhabdomyolysis

INTERACTIONS → Appendix 1: elvitegravir

SIDE-EFFECTS

Common or very common Akathisia, appetite abnormal, asthenia, behaviour abnormal, depression, diarrhoea, dizziness, fever, gastrointestinal discomfort, gastrointestinal disorders, headaches, nausea, skin reactions, sleep disorders, vertigo, vomiting

Uncommon Alopecia, anaemia, anxiety, arrhythmias, arthralgia, arthritis, body fat disorder, burning, cachexia, chest discomfort, chills, cognitive disorder, concentration impaired, confusion, constipation, diabetes mellitus, drowsiness, dry mouth, dyslipidaemia, dysphonia, erectile dysfunction, feeling jittery, glosisits, gynaecomastia, haemorrhage, hepatic disorders, hot flush, hyperglycaemia, hypersensitivity, hypertension, immune reconstitution inflammatory syndrome, increased risk of infection, lipodystrophy, lymph node abscess, lymphatic abnormalities, malaise, memory loss, menopausal symptoms, mood altered, myalgia, myopathy, nasal congestion, nephritis, nephrolithiasis, nerve disorders, neutropenia, nocturia, odynophagia, oedema, osteopenia, pain, palpitations, pancreatitis acute, polydipsia, psychiatric disorder, renal cyst, renal impairment, sensation abnormal, severe cutaneous adverse reactions (SCARs), skin papilloma, submandibular mass, suicidal tendencies, sweat changes, taste altered...
tendinitis • thrombocytopenia • tinnitus • tremor • visual impairment • weight increased

▶ Frequency not known Osteonecrosis

SIDE-EFFECTS, FURTHER INFORMATION Rash occurs commonly. Discontinue if severe rash or rash accompanied by fever, malaise, arthralgia, myalgia, blisters, mouth ulceration, conjunctivitis, angioedema, hepatitis, or eosinophilia.

For further information regarding lipodystrophy and osteonecrosis see HIV infection p. 640

▶ PREGNANCY Manufacturer advises avoid—toxicity in animal studies.

▶ HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment—no information available. Use with caution in patients with chronic hepatitis B or C (at greater risk of hepatic side-effects).

▶ PRESCRIBING AND DISPENSING INFORMATION Dispense raltegravir chewable tablets in original container (contains desiccant).

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SMC No. 613/10

The Scottish Medicines Consortium has advised (May 2010) that raltegravir (Isentress®) is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

SMC No. 1280/17

The Scottish Medicines Consortium has advised (November 2017) that raltegravir 600 mg film-coated tablets (Isentress®) are accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection in adults and paediatric patients weighing at least 40 kg when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25

Isentress (Merck Sharp & Dohme Ltd)

Raltegravir 400 mg Isentress 400mg tablets | 60 tablet

POM £471.41

Raltegravir 600 mg Isentress 600mg tablets | 60 tablet

POM £471.41

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Doravirine

28-May-2019

INDICATIONS AND DOSE

HIV-1 infection in combination with other antiretroviral drugs (initiated by a specialist)

▶ BY MOUTH

Adult: 100 mg once daily

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Manufacturer advises if concurrent use of moderate inducers of CYP3A4, dabrafenib, modafinil, or telotristat ethyl is unavoidable, increase dose to 100 mg twice daily. Manufacturer advises 100 mg twice daily with rifabutin.

INTERACTIONS → Appendix 1: doravirine

SIDE-EFFECTS

Common or very common Asthenia • diarrhoea • dizziness • drowsiness • gastrointestinal discomfort • gastrointestinal disorders • headache • hepatic cellular injury • nausea • skin reactions • sleep disorders • vomiting

Uncommon Anxiety • arthralgia • concentration impaired • confusion • constipation • depression • electrolyte imbalance • hypertension • malaise • memory loss • mood altered • muscle tone increased • myalgia • paraesthesia • suicidal ideation

Rare or very rare Acute kidney injury • adjustment disorder • aggression • chest pain • chills • dyspnoea • hallucination • pain • rash pustular • renal disorder • thirst • tonsillar hypertrophy • urolithiasis

PREGNANCY Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).

PATIENT AND CARER ADVICE

Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue, dizziness, and somnolence.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25, 3

Pifeltro (Merck Sharp & Dohme Ltd)

Doravirine 100 mg Pifeltro 100mg tablets | 30 tablet

POM £471.41

Combinations available: Lamivudine with tenofovir disoproxil and doravirine, p. 653

Efavirenz

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs

▶ BY MOUTH USING CAPSULES

Adult: 600 mg once daily

▶ BY MOUTH USING TABLETS

Adult: 600 mg once daily

CAUTIONS Acute porphyrias p. 1058 • elderly • history of psychiatric disorders • history of seizures

INTERACTIONS → Appendix 1: efavirenz

SIDE-EFFECTS

Common or very common Abdominal pain • anxiety • concentration impaired • depression • diarrhoea • dizziness • drowsiness • dyslipidaemia • fatigue • headache • movement disorders • nausea • skin reactions • sleep disorders • vomiting

Uncommon Behaviour abnormal • confusion • flushing • gynaecomastia • hallucination • hepatic disorders • memory loss • mood altered • pancreatitis • psychosis • seizure • Stevens-Johnson syndrome • suicidal tendencies • thinking abnormal • tinnitus • tremor • vertigo • vision blurred

Rash Rare or very rare Delusions • photosensitivity reaction

SIDE-EFFECTS, FURTHER INFORMATION For further information regarding osteonecrosis, immune reconstitution syndrome and lipodystrophy, see HIV infection p. 640

Rash Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—usually resolves within 1 month.

CNS effects Administration at bedtime especially in first 2–4 weeks reduces CNS effects.

www.getintopharma.com
● PREGNANCY Reports of neural tube defects when used in first trimester.
● HEPATIC IMPAIRMENT Greater risk of hepatic side-effects in chronic hepatitis B or C. Avoid in moderate to severe impairment.

Monitoring In mild liver disease, monitor for dose related side-effects (e.g. CNS effects) and monitor liver function.
● RENAL IMPAIRMENT Manufacturer advises caution in severe renal failure—no information available.
● MONITORING REQUIREMENTS Monitor liver function if receiving other hepatotoxic drugs.

● DIRECTIONS FOR ADMINISTRATION For patients who cannot swallow capsules, the capsule may be opened and contents added to a small amount of food—consult product literature. No additional food should be consumed for up to 2 hours after administration of efavirenz.

● PATIENT AND CARER ADVICE Psychiatric disorders Patients or their carers should be advised to seek immediate medical attention if symptoms such as severe depression, psychosis or suicidal ideation occur.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 23
Efavirenz 600 mg Efavirenz 600mg tablets | 30 tablet PEA £31.35–£452.94 | 30 tablet PEA £28.55 (Hospital only)
Sustiva (Bristol-Myers Squibb Pharmaceuticals Ltd)
Efavirenz 600 mg Sustiva 600mg tablets | 30 tablet PEA £200.27 (Hospital only)
Capsule
CAUTIONARY AND ADVISORY LABELS 23
Sustiva (Bristol-Myers Squibb Pharmaceuticals Ltd)
Efavirenz 50 mg Sustiva 50mg capsules | 30 capsule PEA £16.73 (Hospital only)
Efavirenz 100 mg Sustiva 100mg capsules | 30 capsule PEA £33.41 (Hospital only)
Efavirenz 200 mg Sustiva 200mg capsules | 90 capsule PEA £200.27 (Hospital only)
Combinations available: Efavirenz with emtricitabine and tenofovir disoproxil, p. 649

Etravirine
12-Jul-2018

● INDICATIONS AND DOSE HIV infection resistant to other non-nucleoside reverse transcriptase inhibitor and protease inhibitors in combination with other antiretroviral drugs (including a boosted protease inhibitor)
  ▶ BY MOUTH
  Adult: 200 mg twice daily, to be taken after food

● CONTRA-INDICATIONS Acute porphyrias p. 1058

● INTERACTIONS
  → Appendix 1: etravirine

● SIDE-EFFECTS
  Common or very common Diabetes mellitus, diarrhoea, headache, hyperglycaemia, myocardial infarction, nausea, skin reactions, vomiting
  Uncommon Angioedema, bronchospasm, dry mouth, dyslipidaemia, gynaecomastia, haematemesis, hepatic disorders, hyperhidrosis, hypersensitivity, hyposomnia, numbness, pancreatitis, slughness, vision blurred
  Rare or very rare Severe cutaneous adverse reactions (SCARs)
  Frequency not known Haemorrhagic stroke, osteonecrosis, weight increased

SIDE-EFFECTS, FURTHER INFORMATION For further information regarding osteonecrosis, immune reconstitution syndrome and lipodystrophy, see HIV infection p. 640

Hypersensitivity reactions Rash, usually in the second week, is the most common side-effect and appears more frequently in females. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterised by rash, eosinophilia, and systemic symptoms (including fever, general malaise, myalgia, arthralgia, blistering, oral lesions, conjunctivitis, and hepatitis). Discontinue permanently if hypersensitivity reaction or severe rash develop. If rash mild or moderate (without signs of hypersensitivity reaction), may continue without interruption—usually resolves within 2 weeks.

● HEPATIC IMPAIRMENT Manufacturer advises caution in moderate impairment and in patients with hepatitis B or C (increased risk of hepatic side effects); avoid in severe impairment (no information available).

● DIRECTIONS FOR ADMINISTRATION Patients with swallowing difficulties may disperse tablets in a glass of water just before administration.

● PRESCRIBING AND DISPENSING INFORMATION Dispense in original container (contains desiccant).

● PATIENT AND CARER ADVICE

Hypersensitivity reactions Patients or carers should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develop.

Missed doses If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 21
Intenice (Janssen-Cilag Ltd)
Etravirine 25 mg Etravirine 25mg tablets | 120 tablet PEA £75.32
Etravirine 100 mg Etravirine 100mg tablets | 120 tablet PEA £301.27
Etravirine 200 mg Etravirine 200mg tablets | 60 tablet PEA £301.27

Nevirapine
12-Jul-2018

● INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs (initial dose)
  ▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  Adult: Initially 200 mg once daily for first 14 days, initial dose titration using ‘immediate-release’ preparation should not exceed 28 days; if rash occurs and is not resolved within 28 days, alternative treatment should be sought. If treatment interrupted for more than 7 days, restart using the lower dose of the ‘immediate-release’ preparation for the first 14 days as for new treatment

HIV infection in combination with other antiretroviral drugs (maintenance dose following initial dose titration if no rash present)
  ▶ BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
  Adult: 200 mg twice daily
  ▶ BY MOUTH USING MODIFIED-RELEASE MEDICINES
  Adult: 400 mg once daily

● CONTRA-INDICATIONS Acute porphyrias p. 1058 * post-exposure prophylaxis

● CAUTIONS Females (at greater risk of hepatic side effects) * high CD4 cell count (at greater risk of hepatic side effects)

CAUTIONS, FURTHER INFORMATION
  Hepatic effects Patients with chronic hepatitis B or C, high CD4 cell count, and women are at increased risk of hepatic
side effects— if plasma HIV-1 RNA detectable, manufacturer advises avoid in women with CD4 cell count greater than 250 cells/mm³ or in men with CD4 cell count greater than 400 cells/mm³ unless potential benefit outweighs risk.

- INTERACTIONS → Appendix 1: nevirapine
- SIDE-EFFECTS
  - Common or very common Abdominal pain - angioedema - diarrhoea - fatigue - fever - headache - hepatic disorders - hypersensitivity - hypotension - nausea - pain - pruritus - vomiting
  - Uncommon Anaemia - arthralgia - myalgia - severe cutaneous adverse reactions (SCARs)
  - Frequency not known Eosinophilia - osteonecrosis - weight increased

SIDE-EFFECTS, FURTHER INFORMATION

Hepatic effects
Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 6 weeks; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction.

Rash
Rash, usually in first 6 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually (after 14 days); Discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves.

Osteonecrosis
Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

- HEPATIC IMPAIRMENT
  For modified-release preparations, manufacturer advises avoid (no information available). For immediate-release preparations, manufacturer advises caution in moderate impairment and chronic hepatitis (increased risk of hepatic side effects; consider interrupting or discontinuing treatment if hepatic function worsens); avoid in severe impairment (no information available).

- RENAL IMPAIRMENT
  Manufacturer advises avoid modified-release preparation—no information available.

- MONITORING REQUIREMENTS
  Hepatic disease
  Close monitoring of liver function required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly.
  Rash
  Monitor closely for skin reactions during first 18 weeks.

- PATIENT AND CARER ADVICE
  Hypersensitivity reactions
  Patients or carers should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions, or symptoms of hepatitis develop.
  Missed doses
  If a dose is more than 8 hours late with the ‘immediate-release’ preparation (or more than 12 hours late with the modified-release preparation), the missed dose should not be taken and the next dose should be taken at the usual time.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Oral suspension
  → Viramune (Boehringer Ingelheim Ltd)
  Nevirapine (as Nevirapine hemihydrate) 10 mg per 1 ml Viramune 50mg/5ml oral suspension | 240 ml £50.40
  Modified-release tablet
  CAUTIONARY AND ADVISORY LABELS
  25
  → Nevirapine (Non-proprietary)
  Nevirapine 400 mg Nevirapine 400mg modified-release tablets | 30 tablet | £21.45–£170.00
  → Viramune (Boehringer Ingelheim Ltd)
  Nevirapine 100 mg Viramune 100mg modified-release tablets | 90 tablet | £12.75 (Hospital only)

Tablet

- Nevirapine (Non-proprietary)
  Nevirapine 200 mg Nevirapine 200mg tablets | 60 tablet £21.45–£170.00

Rilpivirine

- INDICATIONS AND DOSE
  HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy and if plasma HIV-1 RNA concentration less than or equal to 100 000 copies/ml.
  → BY MOUTH
  → Adult: 25 mg once daily

- CAUTIONS
  Acute porphyrias p. 1058

- INTERACTIONS → Appendix 1: rilpivirine

- SIDE-EFFECTS
  - Common or very common Appetite decreased - depression - dizziness - drowsiness - dry mouth - fatigue - gastrointestinal discomfort - headache - nausea - rash - sleep disorders - vomiting
  - Uncommon Immune reconstitution inflammatory syndrome

SIDE-EFFECTS, FURTHER INFORMATION
For further information regarding lipodystrophy, see HIV infection p. 640

- PREGNANCY
  Manufacturer advises avoid unless essential—no information available.

- HEPATIC IMPAIRMENT
  Manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

- RENAL IMPAIRMENT
  Manufacturer advises caution in severe impairment.

- PATIENT AND CARER ADVICE
  Patients or carers should be given advice on how to administer rilpivirine tablets.
  Missed doses
  If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

Tablet
  CAUTIONARY AND ADVISORY LABELS
  3, 21, 25
  → Edurant (Janssen-Cilag Ltd)
  Rilpivirine (as Rilpivirine hydrochloride) 25 mg Edurant 25mg tablets | 30 tablet | £200.27

Combinations available: Dolaggravir with rilpivirine, p. 642 - Etricitabine with rilpivirine and tenofovir alafenamide, p. 651 - Etricitabine with rilpivirine and tenofovir disoproxil, p. 652

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ANTIVIRALS > NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside reverse transcriptase inhibitors

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain - anaemia (may require transfusion) - appetite decreased - asthenia - diarrhoea - dizziness - headache - myalgia - nausea - skin reactions - vomiting
  - Uncommon: Hepatic steatosis - lactic acidosis - pancreatitis - thrombocytopenia
  - Frequency not known: Immune reconstitution inflammatory syndrome - osteonecrosis - weight increased

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

- **PRECAUTIONS**
  - Monitoring: Mitochondrial dysfunction has been reported in infants exposed to nucleoside reverse transcriptase inhibitors in utero; the main effects include haematological, metabolic, and neurological disorders; all infants whose mothers received nucleoside reverse transcriptase inhibitors during pregnancy should be monitored for relevant signs or symptoms.

- **HEPATIC IMPAIRMENT**
  - In general, manufacturers advise caution in patients with chronic hepatitis B or C (increased risk of hepatic side-effects).

### Abacavir

#### INDICATIONS AND DOSE

**HIV infection in combination with other antiretroviral drugs**

- **BY MOUTH**
  - Adult: 600 mg daily in 1–2 divided doses

- **CAUTIONS**
  - HIV load greater than 100,000 copies/mL - patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%)

- **INTERACTIONS**
  - Appendix 1: abacavir

- **SIDE-EFFECTS**
  - Common or very common: Fever - lethargy
  - Rare or very rare: Severe cutaneous adverse reactions (SCARs)
  - Frequency not known: Hypersensitivity

#### Abacavir with dolutegravir and lamivudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir above, lamivudine p. 653, dolutegravir p. 642.

- **INDICATIONS AND DOSE**
  - HIV infection
  - **BY MOUTH**
    - Adult (body-weight 40 kg and above): 1 tablet once daily

- **INTERACTIONS**
  - Appendix 1: abacavir - dolutegravir - lamivudine

- **RENAL IMPAIRMENT**
  - Avoid Triumeq® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

- **PATIENT AND CARER ADVICE**
  - Misseled doses: If a dose is more than 2 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

#### Abacavir with dolutegravir and lamivudine

- **Tablet**
  - Triumeq (ViiV Healthcare UK Ltd)
    - Dolutegravir (as Dolutegravir sodium) 50 mg, Lamivudine 300 mg, Abacavir (as Abacavir sulfate) 600 mg
    - 50 mg/600 mg/300 mg tablets | £798.16
Abacavir with lamivudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 647, lamivudine p. 653.

- **INDICATIONS AND DOSE**
  - HIV infection in combination with other antiretrovirals
    - **BY MOUTH**
      - Adult: body-weight 40 kg and above: 1 tablet once daily

- **INTERACTIONS**
  - **RENAL IMPAIRMENT** Avoid Kivexa® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).
  - **INTERACTIONS** → Appendix 1: abacavir · lamivudine

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Abacavir with lamivudine (Non-proprietary)
      - Lamivudine 300 mg, Abacavir 600 mg Abacavir 600mg / Lamivudine 300mg tablets | 30 tablet [P] £190.00–£299.41 | 30 tablet [P] £224.56 (Hospital only)
    - Kivexa® (ViiV Healthcare UK Ltd)
      - Lamivudine 300 mg, Abacavir 600 mg Kivexa 600mg/300mg tablets | 30 tablet [P] £352.25

Abacavir with lamivudine and zidovudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 647, lamivudine p. 653, zidovudine p. 655.

- **INDICATIONS AND DOSE**
  - HIV infection (use only if patient is stabilised for 6–8 weeks on the individual components in the same proportions)
    - **BY MOUTH**
      - Adult: 1 tablet twice daily

- **INTERACTIONS** → Appendix 1: abacavir · lamivudine · zidovudine
  - **RENAL IMPAIRMENT** Avoid Trizivir® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Trizivir® (ViiV Healthcare UK Ltd)
      - Lamivudine 150 mg, Abacavir (as Abacavir sulfate) 300 mg, Zidovudine 300 mg Trizivir tablets | 60 tablet [P] £509.06

Bictegravir with emtricitabine and tenofovir alafenamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 651, tenofovir alafenamide p. 622.

- **INDICATIONS AND DOSE**
  - HIV-1 infection (initiated by a specialist)
    - **BY MOUTH**
      - Adult: 1 tablet once daily

- **INTERACTIONS** → Appendix 1: bictegravir · tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common Depression · diarrhoea · dizziness · fatigue · headache · nausea · sleep disorders
  - Uncommon Anaemia · angioedema · anxiety · arthralgia · flatulence · gastrointestinal discomfort · hyperbilirubinaemia · skin reactions · suicidal behaviour · vomiting

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

- **RENAL IMPAIRMENT** Manufacturer advises avoid if creatinine clearance is less than 30 mL/minute—limited information available.

- **PATIENT AND CARER ADVICE**
  - **Missed doses** Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - SMC No. SMC2093
    - The Scottish Medicines Consortium has advised (September 2018) that bictegravir with emtricitabine and tenofovir alafenamide (Biktarvy®) is accepted for use within NHS Scotland for the treatment of adults infected with human immunodeficiency virus type 1 without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

  - **All Wales Medicines Strategy Group (AWMSG) decisions**
    - AWMSG No. 3414
    - The All Wales Medicines Strategy Group has advised (December 2018) that bictegravir with emtricitabine and tenofovir alafenamide (Biktarvy®) is recommended as an option for restricted use within NHS Wales for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir, and who are either unsuitable for or unable to tolerate abacavir with dolutegravir and lamivudine (Triumeq®).
    - Bictegravir with emtricitabine and tenofovir alafenamide (Biktarvy®) is not recommended for use within NHS Wales outside of this subpopulation. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Bictegravir with emtricitabine and tenofovir alafenamide (Biktarvy®) is accepted for use within NHS Wales.

Didanosine

(HDV; DDI)

- **INDICATIONS AND DOSE**
  - HIV infection in combination with other antiretroviral drugs
    - **BY MOUTH**
      - Adult (body-weight up to 60 kg): 250 mg daily in 1–2 divided doses
      - Adult (body-weight 60 kg and above): 400 mg daily in 1–2 divided doses
Efavirenz with emtricitabine and tenofovir disoproxil

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 654, efavirenz p. 644, tenofovir p. 651.

**INDICATIONS AND DOSE**

**HIV infection stabilised on antiretroviral therapy for more than 3 months**
- **BY MOUTH**
  - Adult: 1 tablet once daily

**INTERACTIONS**
- Appendix 1: efavirenz, tenofovir disoproxil

**HEPATIC IMPAIRMENT**
Manufacturer of Atripla® advises caution in mild impairment; avoid Atripla® in moderate to severe impairment.

**RENAI IMPAIRMENT**
Avoid Atripla® if eGFR less than 50 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**
Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 23, 25
- Efavirenz with emtricitabine and tenofovir disoproxil (Non-proprietary)
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg, Efavirenz 600 mg
    - Elvitegravir 245mg tablets | 30 tablet (PO) 847.58-532.87
  - Atripla® (Gilead Sciences International Ltd)
    - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg, Efavirenz 600 mg
      - Atripla 600mg/200mg/245mg tablets | 30 tablet (PO) £532.87

Elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 651, elvitegravir p. 643, cobicistat p. 661, tenofovir alafenamide p. 622.

**INDICATIONS AND DOSE**

**HIV-1 infection (specialist use only)**
- **BY MOUTH**
  - Adult: 1 tablet once daily

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**

**CAUTIONARY AND ADVISORY LABELS** 25
- Videx EC (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Didanosine 125 mg Videx EC 125mg capsules | 30 capsule (PO)
  - Didanosine 250 mg Videx EC 250mg capsules | 30 capsule (PO) £36.37 (Hospital only)
  - Didanosine 400 mg Videx EC 400mg capsules | 30 capsule (PO) £154.19 (Hospital only)

**INTERACTIONS**
- Appendix 1: cobicistat, elvitegravir, tenofovir alafenamide

**IMPORRNT SAFETY INFORMATION**
MHRA/CHM ADVICE: ELVITEGRAVIR BOOSTED WITH COBICISTAT: AVOID USE IN PREGNANCY DUE TO RISK OF TREATMENT FAILURE AND MATERINAL-TO-CHILD TRANSMISSION OF HIV-1 (APRIL 2019)
Pharmacokinetic data show mean exposure of elvitegravir boosted with cobicistat (available in combination in Genvoya® and Stribild®) to be lower during the second and third trimesters of pregnancy than postpartum. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child. For further information, see Pregnancy.
Elvitegravir with cobicistat, emtricitabine and tenofovir disoproxil

22-May-2019

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 654, emtricitabine p. 651, cobicistat p. 661, elvitegravir p. 643.

**INDICATIONS AND DOSE**

**HIV infection**

- **BY MOUTH**
- Adult: 1 tablet once daily

**SIDE-EFFECTS**

- Common or very common Abnormal dreams, diarrhoea, dizziness, fatigue, flatulence, gastrointestinal discomfort, headache, nausea, skin reactions, vomiting
- Uncommon Anaemia, angioedema, depression
- Frequency not known Nephrototoxicity, osteonecrosis, weight increased

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception in women of childbearing potential; if using a hormonal contraceptive, it must contain drospirenone or norgestimate as the progestogen and at least 30 micrograms ethinylestradiol.

**PREGNANCY** Manufacturer advises not to be initiated during pregnancy due to low elvitegravir exposure; women who become pregnant during therapy should be switched to an alternative regimen.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (increased risk of hepatic side-effects); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT** Manufacturer advises avoid if creatinine clearance less than 30 mL/minute—limited information available.

**PRESCRIBING AND DISPENSING INFORMATION** Dispense in original container—contains desiccant.

**PATIENT AND CARER ADVICE**

- Missed doses Manufacturer advises if a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
- Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

SNC No. 1142/16
The Scottish Medicines Consortium has advised (May 2016) that elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide (Genvoya®) is accepted for use within NHS Scotland for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1), without known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**All Wales Medicines Strategy Group (AWMSG) decisions**

AWMSG No. 2248
The All Wales Medicines Strategy Group has advised (July 2016) that elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide (Genvoya®) is recommended as an option for use within NHS Wales for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1), without known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. The recommendation applies only if the approved Wales Patient Access Scheme (WPAS) is used or where the list price is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Genvoya** (Gilead Sciences International Ltd) ▼
  - Tenofovir alafenamide 10 mg, Cobicistat 150 mg, Elvitegravir 150 mg, Emtricitabine 200 mg (Genvoya 150mg/150mg/200mg/10mg tablets | 30 tablet [PO] 5879.51)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: ELVITEGRAVIR BOOSTED WITH COBICISTAT: AVOID USE IN PREGNANCY DUE TO RISK OF TREATMENT FAILURE AND MATERNL-TO-CHILD TRANSMISSION OF HIV-1 (APRIL 2019)
Pharmacokinetic data show mean exposure of elvitegravir boosted with cobicistat (available in combination in Genvoya® and Stribild®) to be lower during the second and third trimesters of pregnancy than postpartum. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child. For further information, see Pregnancy.

**INTERACTIONS** → Appendix 1: cobicistat - elvitegravir - tenofovir disoproxil

**SIDE-EFFECTS**

- Common or very common Appetite decreased, asthenia, constipation, diarrhoea, dizziness, electrolyte imbalance, flatulence, gastrointestinal discomfort, headache, hyperbilirubinaemia, hyperglycaemia, hypersensitivity, hypertriglyceridaemia, nausea, neutropenia, pain, rash pustular, skin reactions, sleep disorders, vomiting
- Uncommon Anaemia, angioedema, depression (in patients with history of depression or psychiatric illness), muscle weakness, myopathy, pancreatitis, proteinuria, renal failure, renal tubular disorders, suicidal ideation (in patients with history of depression or psychiatric illness)
- Rare or very rare Acute tubular necrosis, hepatic disorders, lactic acidosis, nephritis, nephrogenic diabetes insipidus, osteomalacia
- Frequency not known Autoimmune disorder, Grave’s disease, inflammation, osteonecrosis, weight increased

**CONCEPTION AND CONTRACEPTION** Women of childbearing potential should use effective contraception during treatment (if using a hormonal contraceptive, it must contain norgestimate as the progestogen and at least 30 micrograms ethinylestradiol).

**PREGNANCY** Manufacturer advises not to be initiated during pregnancy due to low elvitegravir exposure; women who become pregnant during therapy should be switched to an alternative regimen.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (increased risk of hepatic side-effects); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT** If eGFR less than 90 mL/minute/1.73 m², only initiate Stribild® if other treatments cannot be used (avoid initiating Stribild® if eGFR less than 70 mL/minute/1.73 m²); if eGFR less than 70 mL/minute/1.73 m², only continue Stribild® if potential benefit outweighs risk (discontinue Stribild® if eGFR less than 50 mL/minute/1.73 m²).

**MONITORING REQUIREMENTS** Test urine glucose before treatment, then every 4 weeks for 1 year and then every 3 months.

**PRESCRIBING AND DISPENSING INFORMATION** Dispense in original container (contains desiccant).

**www.getintopharma.com**
**Emtricitabine (FTC)**

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**
- **BY MOUTH USING CAPSULES**
  - Adult: 200 mg once daily
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 240 mg once daily

**DOSE EQUIVALENCE AND CONVERSION**
- 240 mg oral solution = 200 mg capsule; where appropriate the capsule may be used instead of the oral solution.

**SIDE-EFFECTS**
- **Common or very common** Dyspepsia, hyperbilirubinaemia, hyperglycaemia, hypersensitivity, hypertriglyceridaemia, neutropenia, pain, rash pustular, sleep disorders, systemic symptoms
- **Uncommon** Angioedema

**HEPATIC IMPAIRMENT**

**RENAL IMPAIRMENT**
- **Dose adjustments** Reduce dose if eGFR less than 50 ml/minute/1.73 m²; consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral liquid formulations may include candy.

**PATIENT AND CARER ADVICE**
- **Missed doses** If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**
- **ELECTROLYTES:** May contain Sodium
  - Emtricitabine 10 mg per 1 ml (Emtriva 10mg/ml oral solution sugar-free)
  - 170 ml (PO) £39.53

**Capsule**
- Emtriva (Gilead Sciences International Ltd)
  - Emtricitabine 200 mg (Emtriva 200mg capsules)
  - 30 capsule (PO) £138.98

**Combinations available:** Darunavir with cobicistat, emtricitabine and tenofovir alafenamide, p. 658

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**Emtricitabine with rilpivirine and tenofovir alafenamide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine above, rilpivirine p. 646, tenofovir alafenamide p. 622.

**INDICATIONS AND DOSE**

**HIV infection in patients with plasma HIV-1 RNA concentration of 100 000 copies/mL or less (specialist use only)**
- **BY MOUTH**
  - Adult: 1 tablet once daily

**SIDE-EFFECTS**
- **Common or very common** Appetite decreased, depression, diarrhoea, dizziness, drowsiness, dry mouth, fatigue, flatulence, gastrointestinal discomfort, headache, nausea, skin reactions, sleep disorders, vomiting
- **Uncommon** Anaemia, angioedema, arthralgia, immune reconstitution inflammatory syndrome
- **Frequency not known** Conjunctivitis, drug reaction with eosinophilia and systemic symptoms (DRESS), eosinophilia, fever, osteonecrosis, QT interval prolongation, weight increased

**SIDE-EFFECTS, FURTHER INFORMATION**
- Systemic symptoms reported with severe skin reactions include fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and eosinophilia.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in moderate impairment (increased risk of hepatic side-effects); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**
- Manufacturer advises avoid if creatinine clearance less than 30 ml/minute—no information available.

**PATIENT AND CARER ADVICE**
- Vomiting: Manufacturer advises if vomiting occurs within 4 hours of taking a dose, a replacement dose should be taken.
- Driving and skilled tasks: Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**
- The Scottish Medicines Consortium has advised (October 2016) that emtricitabine with rilpivirine and tenofovir alafenamide (Odefsey®) is accepted for use within NHS Scotland for the treatment of human immunodeficiency virus type 1 (HIV-1), without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with viral load HIV-1 RNA of 100 000 copies/mL or less.

**All Wales Medicines Strategy Group (AWMSG) decisions**
- The All Wales Medicines Strategy Group has advised (November 2016) that emtricitabine with rilpivirine and tenofovir alafenamide (Odefsey®) is recommended as an option for use within NHS Wales for the treatment of human immunodeficiency virus type 1, without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with viral load HIV-1 RNA of 100 000 copies/mL or less.
Emtricitabine with rilpivirine and tenofovir disoproxil

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 651, rilpivirine p. 646.

- **INDICATIONS AND DOSE**
- **HIV infection in patients with plasma HIV-1 RNA concentration less than 100,000 copies/mL**
  - **BY MOUTH**
  - Adult: 1 tablet once daily

- **INTERACTIONS** → Appendix 1: rilpivirine - tenofovir disoproxil

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment (increased risk of hepatic side-effects); avoid in severe impairment (no information available).

- **RENAL IMPAIRMENT** Avoid Eviplera® if eGFR less than 50 mL/minute/1.73 m².

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer Eviplera®.

  - Missed doses: If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - Eviplera (Gilead Sciences International Ltd) |
    - Rilpivirine (as Rilpivirine hydrochloride) 25 mg, Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 25 mg, Emtricitabine 200 mg/Odyssey 200 mg/25 mg/25 mg tablets |
    - 30 tablet pack £52.35

Emtricitabine with tenofovir alafenamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 651, tenofovir alafenamide p. 622.

- **INDICATIONS AND DOSE**
- **HIV infection in combination with other antiretroviral drugs (specialist use only)**
  - **BY MOUTH**
  - Adult: 200/10–200/25 mg once daily, dose is dependent on drug regimen—consult product literature

  - **DOSE EQUIVALENCE AND CONVERSION**
  - Dose expressed as x/y mg emtricitabine/tenofovir alafenamide.

- **INTERACTIONS** → Appendix 1: tenofovir alafenamide

- **SIDE-EFFECTS**
  - Common or very common Abnormal dreams, diarrhoea, dizziness, fatigue, flatulence, gastrointestinal discomfort, headache, nausea, skin reactions, vomiting

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

   - **Tablet**
     - Descovy (Gilead Sciences International Ltd) |
     - Tenofovir alafenamide (as Tenofovir alafenamide fumarate) 25 mg, Emtricitabine 200 mg, Descovy 200 mg/25 mg tablets |
     - 30 tablet pack £355.73

Emtricitabine with tenofovir disoproxil

The properties listed below are those particular to the combination only. For the properties of the components please consider, tenofovir disoproxil p. 654, emtricitabine p. 651.

- **INDICATIONS AND DOSE**
- **HIV-1 infection (initiated by a specialist)**
  - **BY MOUTH**
  - Adult: 200/245 mg once daily

- **Pre-exposure prophylaxis of HIV-1 infection (initiated by a specialist)**
  - **BY MOUTH**
  - Adult: 200/245 mg once daily

  - **DOSE EQUIVALENCE AND CONVERSION**
  - Dose expressed as x/y mg emtricitabine/tenofovir disoproxil.

- **INTERACTIONS** → Appendix 1: tenofovir disoproxil

- **RENAL IMPAIRMENT**
  - When used for HIV-1 infection: Manufacturer advises avoid in severe impairment.
  - When used for Pre-exposure prophylaxis of HIV-1 infection: Manufacturer advises avoid if creatinine clearance less than 60 mL/minute.

  - **Dose adjustments**
  - When used for HIV-1 infection: Manufacturer advises use normal dose every 2 days in moderate impairment.

- **DIRECTIONS FOR ADMINISTRATION** Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste).

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**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer emtricitabine with tenofovir tablets.

**Missed doses** If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (April 2017) that emtricitabine/tenofovir disoproxil (Truvada®) is accepted for use within NHS Scotland in combination with safer sex practices for pre-exposure prophylaxis of sexually acquired HIV-1 infection in adults at high risk.

**All Wales Medicines Strategy Group (AWMSG) decisions**

The All Wales Medicines Strategy Group has advised (September 2017) that emtricitabine/tenofovir disoproxil (Truvada®) is not recommended for use within NHS Wales in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV 1 infection in adults at high risk. The case for cost-effectiveness has not been proven.

Subsequent to this AWMSG recommendation, Truvada® has been made available in Wales and is being provided through NHS Wales from 17 July 2017 for up to three years for use as pre-exposure prophylaxis. During this time, eligible patients will receive Truvada® and data will be collected to assess its effectiveness at preventing HIV and address some of the concerns of AWMSG in relation to cost-effectiveness.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- **Emtricitabine with tenofovir disoproxil (Non-proprietary)**
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg: Truvada® 245mg tablets | 30 tablet (PO) £355.73 DT = £355.73 (Hospital only)
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg: Truvada® 30 tablet (PO) £106.72-£355.73 DT = £355.73
- **Ictastan (Actavis UK Ltd)**
  - Emtricitabine 300 mg: Ictastan 300mg tablets | 30 tablet (PO) £74.43 DT = £74.43
- **Truvada (Gilead Sciences International Ltd)**
  - Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg: Truvada® 200mg/245mg tablets | 30 tablet (PO) £355.73 DT = £355.73

**Lamivudine**

**Tablet**

**INDICATIONS AND DOSE**

**EPIVIR® ORAL SOLUTION**

**HIV infection in combination with other antiretroviral drugs**

- **By mouth**
  - Adult: 150 mg every 12 hours, alternatively 300 mg once daily

**EPIVIR® TABLETS**

**HIV infection in combination with other antiretroviral drugs**

- **By mouth**
  - Adult: 150 mg every 12 hours, alternatively 300 mg once daily

**ZEFFIX®**

Chronic hepatitis B infection either with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used, or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease

- **By mouth**
  - Adult: 100 mg once daily, patients receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

**CAUTIONS**

- Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine

**INTERACTIONS** → Appendix 1: lamivudine

**SIDE-EFFECTS**

- Common or very common: Hepatitis aggravated - muscle cramps - myopathy
- Rare or very rare: Angioedema
- Frequency not known: Abdominal discomfort - malaise - respiratory tract infection - throat complaints

**BREATFEEDING**

Can be used with caution in women infected with chronic hepatitis B alone, providing that adequate measures are taken to prevent hepatitis B infection in infants.

**RENAL IMPAIRMENT**

Dose adjustments: Reduce dose if eGFR less than 50 mL/minute/1.73 m²; consult product literature.

**MONITORING REQUIREMENTS**

When treating chronic hepatitis B with lamivudine, monitor liver function tests every 3 months, and viral markers of hepatitis B every 3–6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue for at least 1 year after discontinuation — recurrent hepatitis may occur on discontinuation).

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of oral liquid formulations may include banana and strawberry.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

**EXCIPIENTS:** May contain Sucrose

- **EPIVIR® (ViiV Healthcare UK Ltd)**
  - Lamivudine 10 mg per 1 ml Epivir 50mg/5ml oral solution | 240 ml (PO) £39.01

**Tablet**

- **EPIVIR® (ViiV Healthcare UK Ltd)**
  - Lamivudine 150 mg Epivir 150mg tablets | 60 tablet (PO) £143.32 DT = £143.32
  - Lamivudine 300 mg Epivir 300mg tablets | 30 tablet (PO) £157.51 DT = £157.51
- **Zeffix (GliaSmidKihline UK Ltd)**
  - Lamivudine 100 mg Zeffix 100mg tablets | 28 tablet (PO) £78.09 DT = £74.11

**Lamivudine with tenofovir disoproxil and doravirine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, lamivudine above, tenofovir disoproxil p. 654, doravirine p. 644.

**INDICATIONS AND DOSE**

**HIV-1 infection (initiated by a specialist)**

- **By mouth**
  - Adult: 1 tablet once daily
DOSE ADJUSTMENTS DUE TO INTERACTIONS
- Manufacturer advises if concurrent use of moderate inducers of CYP3A4, dabrafenib, modafinil or telotristat ethyl is unavoidable, increase doravirine dose to 100 mg twice daily. Manufacturer advises increasing doravirine dose to 100 mg twice daily with rifabutin. The extra doravirine 100 mg dose should be taken approximately 12 hours after the dose of Delstrigo™.

INTERACTIONS → Appendix 1: doravirine • lamivudine • tenofovir disoproxil

PREGNANCY
- Manufacturer advises avoid.

HEPATIC IMPAIRMENT
- Manufacturer advises caution in severe impairment—no information available.

RENAI IMPAIRMENT
- Manufacturer advises caution in creatinine clearance less than 50 mL/minute.

PATIENT AND CARER ADVICE
- Missed doses: If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
- Driving and skilled tasks: Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue, dizziness, and somnolence.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Tablet
- CAUTIONARY AND ADVISORY LABELS 25, 3
  - De Facto (McKesson Sharp & Dohme Ltd) ▼
  - Doravirine 100 mg, Tenofovir disoproxil fumarate (as Tenofovir disoproxil fumarate) 245 mg, Lamivudine 300 mg Delstrigo 100mg/300mg/245mg tablets | 30 tablet (PO) £57.55

Stavudine (d4T)

INDICATIONS AND DOSE
HIV infection in combination with other antiretroviral drugs when no suitable alternative available and when prescribed for shortest period possible
- BY MOUTH
  - Adult (body-weight up to 60 kg): 30 mg every 12 hours, to be taken preferably at least 1 hour before food
  - Adult (body-weight 60 kg and above): 40 mg every 12 hours, to be taken preferably at least 1 hour before food

CAUTIONS
- Excessive alcohol intake • history of pancreatitis • history of peripheral neuropathy • lactic acidosis (especially when used in combination with didanosine)—use only if alternative regimens are not suitable

CAUTIONS, FURTHER INFORMATION
- Lactic acidosis: Lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with stavudine. Use with caution in patients with hepatomegaly, hepatitis, or other risk factors for liver disease and hepatic steatosis (including obesity and alcohol abuse). Discontinue treatment if symptoms of hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function become apparent.

INTERACTIONS → Appendix 1: stavudine

SIDE-EFFECTS
- Common or very common: Depression • drowsiness • dyspepsia • hyperlactataemia • lipopatrophy • nerve disorders • paraesthesia • peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops) • sleep disorders • thinking abnormal

SIDE-EFFECTS, FURTHER INFORMATION
- Metabolic effects may occur with stavudine; plasma lipids and blood glucose concentrations should be measured routinely.

PREGNANCY
- Manufacturer advises use only if potential benefit outweighs risk.

RENAI IMPAIRMENT
- Risk of peripheral neuropathy.
- Dose adjustments: Use half normal dose every 12 hours if eGFR 25–50 mL/minute/1.73 m².
- Use half normal dose every 24 hours if eGFR less than 25 mL/minute/1.73 m².

PRESCRIBING AND DISPENSING INFORMATION
- Flavours of oral liquid formulations may include cherry.
- LESS SUITABLE FOR PRESCRIBING
  - Stavudine (especially in combination with didanosine) is associated with a higher risk of lipoatrophy and should be used only if alternative regimens are not suitable; it is considered to be less suitable for prescribing.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Capsule
- Zerit (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Zerit 20 mg Zerit 20mg capsules | 56 capsule (PO) £13.96
  - Zerit 30 mg Zerit 30mg capsules | 56 capsule (PO) £14.25
  - Zerit 40 mg Zerit 40mg capsules | 56 capsule (PO) £15.66

Tenofiev disoproxil

INDICATIONS AND DOSE
HIV infection in combination with other antiretroviral drugs
- Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis).
- Chronic hepatitis B infection with decompensated liver disease
  - BY MOUTH
  - Adult: 245 mg once daily

DOSE EQUIVALENCE AND CONVERSION
- 7.5 scoops of granules contains approx. 245 mg tenofovir disoproxil (as fumarate).

INTERACTIONS → Appendix 1: tenofovir disoproxil

SIDE-EFFECTS
- Common or very common
  - Abdominal distension • flatulence
  - Uncommon: Proximal renal tubulopathy
  - Rare or very rare
    - Acute tubular necrosis • angioedema • hepatitis • nephritis • nephrogenic diabetes insipidus • renal impairment

HEPATIC IMPAIRMENT
- Manufacturer advises caution in uncompensated hepatic disease (limited information available).

RENAI IMPAIRMENT
- Dose adjustments
  - Granules: 132 mg once daily if eGFR 30–50 mL/minute/1.73 m²; 66 mg once daily if eGFR 20–30 mL/minute/1.73 m²; 33 mg once daily if eGFR 10–20 mL/minute/1.73 m².
  - Tablets: 245 mg every 2 days if eGFR 30–50 mL/minute/1.73 m²; 245 mg every 3–4 days if eGFR 10–30 mL/minute/1.73 m².

MONITORING: Monitor renal function—interrupt treatment if further deterioration.

MONITORING REQUIREMENTS
- Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at

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increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases.

- When treating chronic hepatitis B with tenofovir, monitor liver function tests every 3 months and viral markers for hepatitis B every 3–5 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

- **DIRECTIONS FOR ADMINISTRATION** *Granules*: mix 1 scoop of granules with 1 tablespoon of soft food (e.g. yoghurt, apple sauce) and take immediately without chewing. Do not mix granules with liquids.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer tenofovir granules. Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Tenofovir disoproxil for the treatment of chronic hepatitis B (July 2009) NICE TAI73
    - Tenofovir is an option for the treatment of chronic hepatitis B. [www.nice.org.uk/TAI73](http://www.nice.org.uk/TAI73)

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Granules**
    - CAUTIONARY AND ADVISORY LABELS 21
    - [Viread](Gilead Sciences International Ltd)
      - Tenofovir disoproxil (as Tenofovir disopropil fumarate) 33 mg per 1 gram
        - Viread 33mg/g granules | 60 gram | £4.50
    - **Tablet**
      - CAUTIONARY AND ADVISORY LABELS 21
      - [Tenofovir disoproxil (Non-proprietary)]
        - Tenofovir disoproxil 245 mg
          - Tenofovir 245mg tablets | 30 tablet | £16.84–£204.59 DT | £102.60 DT | £102.60
        - [Viread](Gilead Sciences International Ltd)
          - Tenofovir disoproxil 245mg tablets | 30 tablet | £135.98 DT | £135.98
      - Tenofovir disoproxil 163 mg
        - Viread 163mg tablets | 30 tablet | £102.60 DT | £102.60
      - Tenofovir disoproxil 204 mg
        - Viread 204mg tablets | 30 tablet | £170.19 DT | £170.19
      - Tenofovir disoproxil 245 mg
        - Viread 245mg tablets | 30 tablet | £204.39 DT | £30.25

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**Zidovudine**

(Azidothymidine; AZT)

- **INDICATIONS AND DOSE**
  - **HIV infection in combination with other antiretroviral drugs**
    - **BY MOUTH**
      - Adult: 250–300 mg twice daily
  - **Prevention of maternal-fetal HIV transmission**
    - **BY MOUTH, OR BY INTRAVENOUS INFUSION**
    - Adult: Seek specialist advice (combination therapy preferred) (consult local protocol)
  - **HIV infection in combination with other antiretroviral drugs in patients temporarily unable to take zidovudine by mouth**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 0.8–1 mg/kg every 4 hours usually for not more than 2 weeks, dose approximating to 1.2–1.5 mg/kg every 4 hours by mouth

- **CONTRA-INDICATIONS** Abnormally low haemoglobin concentration (consult product literature) - abnormally low neutrophil counts (consult product literature)

- **CAUTIONS**
  - Elderly - lactic acidosis - risk of haematological toxicity particularly with high dose and advanced disease - vitamin B12 deficiency (increased risk of neutropenia)

- **CAUTIONS, FURTHER INFORMATION**
  - Lactic acidosis Lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with zidovudine. Use with caution in patients with hepatomegaly, hepatitis, or other risk factors for liver disease and hepatic steatosis (including obesity and alcohol abuse). Discontinue treatment if symptoms of hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function become apparent.

- **INTERACTIONS** → Appendix 1: zidovudine

- **SIDE-EFFECTS**
  - **Common or very common** Leucopenia - malaise - neutropenia
  - **Uncommon** Bone marrow disorders - dyspnoea - fever - flatulence - generalised pain - myopathy
  - **Rare or very rare** Alertness decreased - anxiety - cardiomyopathy - chest pain - chills - cough - depression - drowsiness - dyspepsia - gynaecomastia - hepatic disorders - hyperhidrosis - influenza like illness - insomnia - nail discoulouration - oral discoulouration - paraesthesia - pure red cell aplasia - seizure - taste altered - urinary frequency increased.

- **Frequency not known** Lipatrophies

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Anaemia and myelosuppression**
  - If anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment.

- **Lipodystrophy syndrome**
  - Metabolic effects may occur with zidovudine; plasma lipids and blood glucose concentrations should be measured routinely.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in moderate to severe impairment (increased risk of accumulation).
  - **Dose adjustments**
    - Manufacturer advises consider dose reduction in moderate to severe impairment—consult product literature.

- **RENAL IMPAIRMENT**
  - **Dose adjustments**
    - Reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if eGFR is less than 10 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor full blood count after 4 weeks of treatment, then every 3 months.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use For *intermittent intravenous infusion*, dilute to a concentration of 2 mg/mL or 4 mg/mL with Glucose 5% and give over 1 hour.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- [Retrovir](ViiV Healthcare UK Ltd)
  - [Zidovudine 10 mg per 1 ml](Retrovir IV 200mg/20ml concentrate for solution for infusion vials | 5 vial) | £52.48

**Oral solution**

- [Retrovir](ViiV Healthcare UK Ltd)
  - Zidovudine 10 mg per 1 ml
    - [Retrovir 50mg/5ml oral solution sugar-free](Retrovir 50mg/5ml oral solution sugar-free | 200 ml) | £20.91
Infection

HEPATIC IMPAIRMENT

▶ Uncommon
▶ Common or very common

SIDE-EFFECTS

PROTEASE INHIBITORS, HIV

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs—Zidovudine with lamivudine

BY MOUTH
Adult: 1 tablet twice daily

INTERACTIONS
Appendix 1: lamivudine - zidovudine

RENAL IMPAIRMENT
Avoid if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

DIRECTIONS FOR ADMINISTRATION

COMBIVIR ® TABLETS Tablets may be crushed and mixed with semi-solid food or liquid just before administration.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Zidovudine with lamivudine (Non-proprietary)
Lamivudine 150 mg, Zidovudine 300 mg
Zidovudine 300mg / Lamivudine 150mg tablets | 60 tablet £240.10-£255.10
Combivir (ViiV Healthcare UK Ltd)
Lamivudine 150 mg, Zidovudine 300 mg
Combivir 150mg/300mg tablets | 60 tablet £300.12

ANTIVIRALS > PROTEASE INHIBITORS, HIV

Protease inhibitors

CONTRA-INDICATIONS
Acute porphyrias p. 1058

CAUTIONS
Haemophilia (increased risk of bleeding)

SIDE-EFFECTS

Common or very common

Uncommon
Drowsiness - immune reconstitution inflammatory syndrome - osteonecrosis - Stevens-Johnson syndrome - weight increased

HEPATIC IMPAIRMENT
In general, manufacturers advise use with caution in patients with chronic hepatitis B or C (increased risk of hepatic side-effects).

Atazanavir

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs—Atazanavir with cobicistat

BY MOUTH
Adult: 300 mg daily

CAUTIONS
Cardiac conduction disorders - electrolyte disturbances - predisposition to QT interval prolongation

INTERACTIONS
Appendix 1: HIV- protease inhibitors

SIDE-EFFECTS

Uncommon
Chest pain - depression - disorientation - drug reaction with eosinophilia and systemic symptoms (DRESS) - gallbladder disorders - gynaecomastia - haematuria - memory loss - myopathy - nephritis - tubulointerstitial nephritis - nephrolithiasis - proteinuria - syncope - torsade de pointes - urinary frequency increased

Rare or very rare
Gait abnormal - oedema - palpitations - QT interval prolongation - renal pain - vasodilation

SIDE-EFFECTS, FURTHER INFORMATION
Mild to moderate rash occurs commonly, usually within the first 3 weeks of therapy. Severe rash occurs less frequently and may be accompanied by systemic symptoms. Discontinue if severe rash develops.

PREGNANCY
Theoretical risk of hyperbilirubinaemia in neonate if used at term.

Monitoring
In pregnancy, monitor viral load and plasma-atazanavir concentration during third trimester.

HEPATIC IMPAIRMENT
Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment (no information available).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 5, 21
Reyataz (Bristol-Myers Squibb Pharmaceuticals Ltd)
Atazanavir (as Atazanavir sulfate) 150 mg
Reyataz 150mg capsules | 60 capsule £303.38 (Hospital only)
Atazanavir (as Atazanavir sulfate) 200 mg
Reyataz 200mg capsules | 60 capsule £303.38 (Hospital only)
Atazanavir (as Atazanavir sulfate) 300 mg
Reyataz 300mg capsules | 30 capsule £303.38 (Hospital only)

Atazanavir with cobicistat

The properties listed below are those particular to the combination only. For the properties of the components please consider, atazanavir above, cobicistat p. 661.

INDICATIONS AND DOSE

HIV infection, in combination with other antiretroviral drugs (initiated by a specialist)

BY MOUTH
Adult: 300/150 mg once daily

DOSE EQUIVALENCE AND CONVERSION

Dose expressed as x/y mg of atazanavir/cobicistat.

CONTRA-INDICATIONS
Haemodialysis

INTERACTIONS
Appendix 1: cobicistat - HIV- protease inhibitors

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 5, 21
Evotaz (Bristol-Myers Squibb Pharmaceuticals Ltd) Capsule
Atazanavir (as Atazanavir sulfate) 150 mg
Evotaz 300mg/150mg tablets | 30 tablet £223.38
Darunavir

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral therapy—with low-dose ritonavir

BY MOUTH
Adult: 600 mg twice daily, alternatively 800 mg once daily, once daily dose only to be used if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells x 10^9/litre

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral therapy—with cobicistat

BY MOUTH
Adult: 800 mg once daily

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy—with low-dose ritonavir

BY MOUTH
Adult: 800 mg once daily

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy—with cobicistat

BY MOUTH
Adult: 800 mg once daily

INTERACTIONS

Appendix 1: HIV–protease inhibitors

SIDE-EFFECTS

Uncommon Angina pectoris • arrhythmias • burping • chest pain • concentration impaired • confusion • constipation • cough • depression • dry eye • eye erythema • feeling hot • flushing • gout • gynaecomastia • haemorrhage • herpes simplex • hyperglycaemia • hypothyroidism • leucopenia • memory loss • mood altered • muscle weakness • myocardial infarction • nail discolouration • nephrolithiasis • oral disorders • osteoporosis • pain • peripheral oedema • polydipsia • QT interval prolongation • renal impairment • sensation abnormal • sexual dysfunction • sweat changes • throat irritation • thrombocytopenia • urinary disorders • urine abnormalities • vertigo

Rare or very rare Arthritis • chills • feeling abnormal • joint stiffness • musculoskeletal stiffness • palpitations • rhinorrhoea • severe cutaneous adverse reactions (SCARs) • syncope • visual impairment

SIDE-EFFECTS, FURTHER INFORMATION

Mild to moderate rash occurs commonly, usually within the first 4 weeks of therapy and resolves without stopping treatment. Severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) occurs less frequently and may be accompanied by fever, malaise, arthralgia, myalgia, oral lesions, conjunctivitis, hepatitis, or eosinophilia; treatment should be stopped if this develops.

ALLERGY AND CROSS-SENSITIVITY

Use with caution in patients with sulfonamide sensitivity.

PREGNANCY

Manufacturer advises use only if potential benefit outweighs risk; if required, use the twice daily dose regimen. For use with cobicistat, see darunavir with cobicistat below or darunavir with cobicistat, emtricitabine and tenofovir alafenamide p. 658.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

MONITORING REQUIREMENTS

Monitor liver function before and during treatment.
Fosamprenavir

- **DRUG ACTION** Fosamprenavir is a pro-drug of amprenavir.

- **INDICATIONS AND DOSE** HIV infection in combination with other antiretroviral drugs—with low-dose ritonavir
  - **BY MOUTH**
  - Adult: 700 mg twice daily

- **SIDE-EFFECTS**
  - **Common or very common** Oral paraesthesia

- **DOSAGE AND ADMINISTRATION**
  - In adults, oral suspension should be taken on an empty stomach.
  - **Prescribing and dispensing information** Flavours of oral liquid formulations may include grape, bubblegum, or peppermint.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer fosamprenavir oral suspension.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  
  **Tablet**
  
<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezolsta (Janssen-Cilag Ltd) ▼</td>
</tr>
<tr>
<td>Tenofovir alafenamide (as Tenofovir alafenamide fumarate)</td>
</tr>
<tr>
<td>10 mg, Cobicistat 150 mg, Emtricitabine 200 mg, Darunavir (as Darunavir ethanolate) 800 mg</td>
</tr>
<tr>
<td>800mg/150mg/200mg/10mg tablets</td>
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</tbody>
</table>

- **IMPORTANT SAFETY INFORMATION**
  - **Mhra/chm advice: Darunavir boosted with cobicistat—Avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1 (July 2018)**
  
  Pharmacokinetic data show mean exposure of darunavir boosted with cobicistat (available in combination in Rezolsta® and Symtuza®) to be lower during the second and third trimesters of pregnancy than during 6–12 weeks postpartum. Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child. For further information, see Pregnancy.

- **INTERACTIONS**
  - Appendix 1: HIV-protease inhibitors · tenofovir alafenamide
  
  **PREGNANCY**
  - Manufacturer advises not to be initiated during pregnancy due to low darunavir exposure; women who become pregnant during therapy should be switched to an alternative regimen.

  **RENAL IMPAIRMENT**
  - Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m²—no information available.

  **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
  
  SMC No. 1290/18
  
  The Scottish Medicines Consortium advises (January 2018) that darunavir with cobicistat, emtricitabine and tenofovir alafenamide (Symtuza®) is accepted for use within NHS Scotland for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg).

- **All Wales Medicines Strategy Group (AWMSG) decisions**
  
  AWMSG No. 2418
  
  The All Wales Medicines Strategy Group has advised (March 2018) that darunavir with cobicistat, emtricitabine and tenofovir alafenamide (Symtuza®) is recommended as an option for use within NHS Wales for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg).

Darunavir with cobicistat, emtricitabine and tenofovir alafenamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, darunavir p. 657, cobicistat p. 661, emtricitabine p. 651, tenofovir alafenamide p. 622.

- **INDICATIONS AND DOSE**
  - HIV infection (initiated by a specialist)
    - **BY MOUTH**
    - Adult: 1 tablet once daily

- **INTERACTIONS**
  - Appendix 1: cobicistat · HIV-protease inhibitors · tenofovir alafenamide

- **PREGNANCY**
  - Manufacturer advises not to be initiated during pregnancy due to low darunavir exposure; women who become pregnant during therapy should be switched to an alternative regimen.

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m²—no information available.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
  
  SMC No. 1081/15
  
  The Scottish Medicines Consortium has advised (August 2015) that darunavir with cobicistat (Rezolsta®) is accepted for use within NHS Scotland for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults, in combination with other antiretrovirals. Genotypic testing should guide its use.
**Lopinavir with ritonavir**

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**

- **By mouth using tablets**
  - Adult: 400/100 mg twice daily, alternatively 800/200 mg once daily, once daily dose to be used only in adults with a HIV strain that has less than 3 mutations to protease inhibitors
  - **By mouth using oral solution**
  - Adult: 5 mL twice daily

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Side-effects**
  - **Common or very common**
    - Increased risk of infection - leucopenia - lymphadenopathy - menstrual cycle irregularities - migraine - muscle weakness - myopathy - night sweats - pain - sexual dysfunction
  - **Uncommon**
    - Atherosclerosis - atroventricular block - cholangitis - constipation - deep vein thrombosis - haemorrhage - hyperbilirubinemia - hypogonadism - myocardial infarction - nephritis - stomatitis - stroke - tinnitus - tremor - tricuspid valve incompetence - vasculitis - vertigo - visual impairment

**CAUTIONS**

- Cardiac conduction disorders, pancreatitis - patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%) - structural heart disease

**INTERACTIONS**

- Appendix 1: HIV-protease inhibitors

**DOSE EQUIVALENCE AND CONVERSION**

- Oral solution contains 400 mg lopinavir, 100 mg ritonavir/5 mL (or 80 mg lopinavir, 20 mg ritonavir/mL).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- **Cautionary and advisory labels**
  - **21**
  - **Excipients:** May contain Alcohol, propylene glycol
  - **Kaletra (AbbVie Ltd)**
    - Ritonavir 20 mg per 1 ml, Lopinavir 80 mg per 1 ml
    - | Kaletra 80 mg/200 mg/1 ml oral solution | 120 ml PTFE | £122.96
    - | 300 ml PTFE | £307.39

**Tablet**

- **Cautionary and advisory labels**
  - **25**
  - **Kaletra (AbbVie Ltd)**
    - Ritonavir 25 mg, Lopinavir 100 mg
    - | Kaletra 100 mg/25 mg tablets | 40 tablet PTFE | £76.85
    - | Kaletra 200 mg/50 mg tablets | 120 tablet PTFE | £285.41

**Ritonavir**

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs (high-dose ritonavir)**

- **By mouth**
  - Adult: Initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days; increased to 600 mg every 12 hours

**Low-dose booster to increase effect of other protease inhibitors**

- **By mouth**
  - Adult: 100–200 mg 1–2 times a day

**CAUTIONS**

- Cardiac conduction disorders, pancreatitis, structural heart disease

**INTERACTIONS**

- Appendix 1: HIV-protease inhibitors

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Side-effects**
  - **Common or very common**
  - **Uncommon**
    - Myocardial infarction
  - **Rare or very rare**
    - Hyperglycaemia - toxic epidermal necrolysis

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Cautionary and advisory labels**
  - **21, 25**
  - **Kaletra (Non-proprietary)**
    - Ritonavir 100 mg
    - | Ritonavir 100 mg tablets | 30 tablet PTFE | £16.52–£19.40
    - | Norvir (AbbVie Ltd) Ritonavir 100 mg | 30 tablet PTFE | £19.44

www.getintopharma.com
**Viral infection**

### Saquinavir

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretrovirals in patients previously treated with antiretroviral therapy—

- **BY MOUTH**
  - Adult: 1 g every 12 hours

HIV infection in combination with other antiretrovirals in patients not previously treated with antiretroviral therapy—

- **BY MOUTH**
  - Adult: 500 mg every 12 hours for 7 days, then increased to 1 g every 12 hours

**CONTRA-INDICATIONS**

Bradydysrythmias · congenital QT prolongation · electrolyte disturbances · heart failure with reduced left ventricular ejection fraction · history of symptomatic arrhythmias · predisposition to cardiac arrhythmias

**INTERACTIONS**

▶ Appendix 1: HIV-protease inhibitors

**SIDE-EFFECTS**

- Common or very common · Burping · constipation · dry lips · libido decreased · lipatrophy · paraesthesia
- Uncommon · Mucosal ulceration · renal impairment · visual impairment
- Frequency not known · QT interval prolongation

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment (limited information available); avoid in decompensated liver disease.

**RENAL IMPAIRMENT**

Use with caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Monitor ECG before starting treatment (do not initiate treatment if QT interval over 450 milliseconds; if baseline QT interval less than 450 milliseconds, monitor ECG during treatment (particularly 10 days after starting treatment in patients not previously treated with antiretroviral therapy)—discontinue if QT interval increases over 480 milliseconds, if QT interval more than 20 milliseconds above baseline, if prolongation of PR interval, or if arrhythmias occur.

**PATIENT AND CARER ADVICE**

Arrhythmias · Patients should be told how to recognize signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncpe develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 21
  - **Invirase** (Roche Products Ltd)
    - Saquinavir (as Saquinavir mesilate) 500 mg · Invirase 500 mg tablets · 120 tablet [PDR] £251.26

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 5, 21
  - **Aptivus** (Boehringer Ingelheim Ltd)
    - Tipranavir 250 mg · Aptivus 250 mg capsules · 120 capsule [PDS]
      - £441.00

### Tipranavir

**INDICATIONS AND DOSE**

HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals—

- **BY MOUTH**
  - Adult: 500 mg twice daily

**DOSE EQUIVALENCE AND CONVERSION**

- The bioavailability of tipranavir oral solution is higher than that of the capsules; the oral solution is not interchangeable with the capsules on a milligram-for-milligram basis.

**CAUTIONS**

Abnormal liver function tests and/or signs or symptoms of liver injury (consider delaying treatment if serum transaminase levels are greater than 5 times the upper limit of normal—consult product literature) · patients at risk of increased bleeding from trauma, surgery or other pathological conditions

**INTERACTIONS**

▶ Appendix 1: HIV-protease inhibitors

**SIDE-EFFECTS**

- Uncommon · Hyperamylasaemia · hyperglycaemia · influenza like illness · renal failure · thrombocytopenia
- Rare or very rare · Dehydration · hyperbilirubinaemia · intracranial haemorrhage
- Frequency not known · Bleeding tendency

**SIDE-EFFECTS, FURTHER INFORMATION**

Potentially life-threatening hepatotoxicity reported. Discontinue if signs or symptoms of hepatitis develop or if liver function abnormality develops (consult product literature).

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in mild impairment (risk of increased exposure)—monitor liver function before treatment, then every two weeks for 3 months, then monthly until 48 weeks, then every 8 to 12 weeks thereafter, and discontinue if liver function worsens; avoid in moderate to severe impairment.

**MONITORING REQUIREMENTS**

Monitor liver function before treatment, then every 2 weeks for 1 month, then every 4 weeks until 24 weeks, then every 8 to 12 weeks thereafter.

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of oral liquid formulations may include toffee and mint.

**PATIENT AND CARER ADVICE**

Patients or carers should be told to observe the oral solution for crystallisation; the bottle should be replaced if more than a thin layer of crystals form (doses should continue to be taken at the normal time until the bottle is replaced).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 5, 21
  - **INCIPIENTS**: May contain Ethanol
  - **Aptivus** (Boehringer Ingelheim Ltd)
    - Tipranavir 250 mg · Aptivus 250 mg capsules · 120 capsule [PDS]
      - £441.00

### Maraviroc

**DRUG ACTION**

Maraviroc is an antagonist of the CCR5 chemokine receptor.

**INDICATIONS AND DOSE**

CCR5-tropic HIV infection in combination with other antiretrovirals in patients previously treated with antiretrovirals—

- **BY MOUTH**
  - Adult: 300 mg twice daily

**CAUTIONS**

Cardiovascular disease

**INTERACTIONS**

▶ Appendix 1: maraviroc

**SIDE-EFFECTS**

- Common or very common · Abdominal pain · anaemia · appetite decreased · asthenia · depression · diarrhoea · flatulence · headache · insomnia · nausea · rash
- Uncommon · Hyperbilirubinaemia · increased risk of infection · myopathy · postural hypotension · proteinuria · renal failure · seizure
- Rare or very rare · Angina pectoris · granulocytopenia · hepatic disorders · metastases · neoplasms · pancytopenia · severe cutaneous adverse reactions (SCARs)
**Influenza 661**

### Influenza

**Management**

Oseltamivir p. 662 and zanamivir p. 663 are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; they are licensed for use within 48 hours of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. Oseltamivir or zanamivir can reduce the risk of complications from influenza in the elderly and in patients with chronic disease.

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza. However, in patients with severe influenza or in those who are immunocompromised, antivirals may still be effective after this time if viral shedding continues [unlicensed use]. Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

There is evidence that some strains of influenza A virus have reduced susceptibility to oseltamivir, but may retain susceptibility to zanamivir. Resistance to oseltamivir may be greater in severely immunocompromised patients.

Zanamivir should be reserved for patients who are severely immunocompromised, or when oseltamivir cannot be used, or when resistance to oseltamivir is suspected. For those unable to use the dry powder for inhalation, zanamivir is available as a solution that can be administered by nebuliser or intravenously [unlicensed]. Amantadine hydrochloride p. 418 is licensed for prophylaxis and treatment of influenza A but it is no longer recommended.

Information on pandemic influenza, avian influenza, and swine influenza may be found at [www.gov.uk/phe](http://www.gov.uk/phe).

Immunisation against influenza is recommended for persons at high risk, and to reduce transmission of infection.

**Oseltamivir in children under 1 year of age**

Data on the use of oseltamivir in children under 1 year of age is limited. Furthermore, oseltamivir may be ineffective in neonates because they may not be able to metabolise oseltamivir to its active form. However, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that during a pandemic, treatment with oseltamivir can be overseen by healthcare professionals experienced in assessing children.

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**5 Infection**

**CBICOSTAT**

30-Jun-2018

**INDICATIONS AND DOSE**

Pharmacokinetic enhancer used to increase the effect of atazanavir or darunavir

*BY MOUTH*

- Adults: 150 mg once daily

**INTERACTIONS**

- Appendix 1: cobicistat

**PREGNANCY**

Manufacturer advises avoid unless essential. For use with darunavir, see darunavir with cobicistat p. 657 or darunavir with cobicistat, emtricitabine and tenofovir alafenamide p. 658. For use with elvitegravir, see elvitegravir with cobicistat, emtricitabine and tenofovir disoproxil p. 650 or elvitegravir with cobicistat, emtricitabine and tenofovir alafenamide p. 649.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in severe impairment—no information available.

**RENAL IMPAIRMENT**

No dose adjustment required; inhibits tubular secretion of creatinine; when any co-administered drug requires dose adjustment based on renal function, avoid initiating cobicistat if eGFR less than 70 mL/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

Dispense in original container (contains desiccant).

**PATIENT AND CARER ADVICE**

Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**MEDICAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

*Tybost* (Gilead Sciences International Ltd)

- Cobicistat 150 mg Tybost 150 mg tablets | 30 tablet [UPL] £21.38

Infection

Breast feeding

In adults Avoid for treatment and prevention if eGFR less than 10 mL/minute/1.73 m².

In children Avoid for treatment and prevention if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

Dose adjustments - in adults For treatment, use 30 mg twice daily if eGFR 30–60 mL/minute/1.73 m² (30 mg once daily if eGFR 10–30 mL/minute/1.73 m²). For prevention, use 30 mg once daily if eGFR 30–60 mL/minute/1.73 m² (30 mg every 48 hours if eGFR 10–30 mL/minute/1.73 m²).

In children For treatment, use 40% of normal dose twice daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose once daily if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²). For prevention, use 40% of normal dose once daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose every 48 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²).

Directions for administration If suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as sugar water or chocolate syrup, just before administration.

Prescribing and dispensing information Flavours of oral liquid formulations may include tutti-frutti.

Patient and carer advice Medicines for Children leaflet: Oseltamivir for influenza (flu) www.medicinesforchildren.org.uk/oseltamivir-influenza-flu

National funding/access decisions

NICE decisions

Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158

Oseltamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

Oseltamivir is not recommended for seasonal prophylaxis against influenza.

When influenza is circulating in the community, oseltamivir is an option recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)

During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, oseltamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At risk patients include those aged 65 years or older or those who have one or more of the following conditions:

- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

www.getintopharma.com
This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/guidance/ta158

▶ Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) NICE TA168

Oseltamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

▲ When influenza is circulating in the community, oseltamivir is an option recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours of the onset of symptoms. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.)

▲ During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, oseltamivir may be used for treatment in at-risk patients living in long-term residential or nursing homes. At risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/guidance/ta168

NHS restrictions Tamiflu® is not prescribable in NHS primary care except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

▲ MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Oral suspension

CAUTIONARY AND ADVISORY LABELS 9

EXCIPIENTS: May contain sorbitol

▶ Tamiflu® (Roche Products Ltd) Oseltamivir (as Oseltamivir phosphate) 6 mg per 1 ml Tamiflu 6mg/ml oral suspension sugar-free | 65 ml £10.27 DT = £10.27

Capsule

CAUTIONARY AND ADVISORY LABELS 9

▶ Tamiflu® (Roche Products Ltd) Oseltamivir (as Oseltamivir phosphate) 30 mg Tamiflu 30mg capsules | 10 capsule £7.17

Oseltamivir (as Oseltamivir phosphate) 45 mg Tamiflu 45mg capsules | 10 capsule £15.41

Oseltamivir (as Oseltamivir phosphate) 75 mg Tamiflu 75mg capsules | 10 capsule £15.41

Zanamivir

▲ DRUG ACTION Reduces replication of influenza A and B viruses by inhibiting viral neuraminidase.

▲ INDICATIONS AND DOSE

Post-exposure prophylaxis of influenza

▲ BY INHALATION OF POWDER

Child 5-17 years: 10 mg once daily for 10 days

Adult: 10 mg once daily for 10 days

Prevention of influenza during an epidemic

▲ BY INHALATION OF POWDER

Child 5-17 years: 10 mg once daily for up to 28 days

Adult: 10 mg once daily for up to 28 days

Treatment of influenza

▲ BY INHALATION OF POWDER

Child 5-17 years: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)

Adult: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)

▲ UNLICENSED USE Use of zanamivir for up to 10 days if resistance to oseltamivir suspected is an unlicensed duration.

▲ CAUTIONS Asthma • chronic pulmonary disease • uncontrolled chronic illness

CAUTIONS, FURTHER INFORMATION

Asthma and chronic pulmonary disease Risk of bronchospasm—short-acting bronchodilator should be available.

Avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm.

▲ SIDE-EFFECTS

▶ Common or very common Skin reactions

▶ Uncommon Bronchospasm • dehydration • dyspnoea • oropharyngeal oedema • presyncope • severe cutaneous adverse reactions (SCARs) • throat tightness

▶ Rare or very rare Face oedema

▶ Frequency not known Behaviour abnormal • delirium • hallucination • level of consciousness decreased • psychiatric disorder • seizure

SIDE-EFFECTS, FURTHER INFORMATION Neurological and psychiatric disorders occur more commonly in children and adolescents.

▲ PREGNANCY Although safety data are limited, zanamivir can be used in women who are pregnant when the potential benefit outweighs the risk (e.g. during a pandemic). Use only if potential benefit outweighs risk (e.g. during a pandemic).

▲ BREAST FEEDING Although safety data are limited, zanamivir can be used in women who are breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic).

▲ DIRECTIONS FOR ADMINISTRATION Other inhaled drugs should be administered before zanamivir.

▲ PRESCRIBING AND DISPENSING INFORMATION Except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

▲ NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

▶ Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158

Zanamivir is not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

▲ Zanamivir is not recommended for seasonal prophylaxis against influenza.

www.getintopharma.com
When influenza is circulating in the community, zanamivir is an option recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Zanamivir should be given within 36 hours of exposure to influenza. (National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community).

During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, zanamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant. This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/guidance/TA168

Drugs for Respiratory Diseases

Respiratory syncytial virus

Management in children

Ribavirin p. 626 is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis.

Palivizumab below is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation.

Palivizumab is recommended for:
- children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm;
- children under 6 months of age with haemodynamically significant, acyanotic congenital heart disease who were born preterm.

Palivizumab should be considered for:
- children under 2 years of age with severe combined immunodeficiency syndrome;
- children under 1 year of age who require long-term ventilation;
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

For details of the preterm age groups included in the recommendations, see Immunisation against Infectious Disease (2006), available at www.gov.uk/dh.

Palivizumab

Indications and dose

Prevention of serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease (under expert supervision)
- By intramuscular injection
  - Child 1–23 months: 15 mg/kg once a month, preferably injected in the anterolateral thigh, to be administered during season of RSV risk, injection volume over 1 mL should be divided between 2 or more sites

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/guidance/TA168
Prevention of serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease and undergoing cardiac bypass surgery (under expert supervision)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-23 months: Initially 15 mg/kg, to be administered as soon as stable after surgery, preferably in the anterolateral thigh, then 15 mg/kg once a month, preferably injected in the anterolateral thigh, to be administered during season of RSV risk, injection volume over 1 mL should be divided between 2 or more sites.

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**UNLICENSED USE** Licensed for the prevention of serious lower respiratory-tract disease caused by respiratory syncytial virus (RSV) in children under 6 months of age (at the start of the RSV season) and born at less than 35 weeks corrected gestational age, or in children under 2 years of age who have received treatment for bronchopulmonary dysplasia in the last 6 months, or in children under 2 years of age with haemodynamically significant congenital heart disease.

**CAUTIONS** Moderate to severe acute infection · moderate to severe febrile illness · serum-palivizumab concentration may be reduced after cardiac surgery · thrombocytopenia

**SIDE-EFFECTS**
- Common or very common Apnoea
- Uncommon Seizure · thrombocytopenia · urticaria
- Frequency not known Hypersensitivity

**ALLERGY AND CROSS-SENSITIVITY** Hypersensitivity to humanised monoclonal antibodies.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Synagis** (AbbVie Ltd)
  - Palivizumab 100 mg per 1 ml Synagis 100mg/1ml solution for injection vials | 1 vial £563.64
  - Synagis 50mg/0.5ml solution for injection vials | 1 vial £306.34

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www.getintopharma.com
1 Antidiuretic hormone disorders

Posterior pituitary hormones and antagonists

Posterior pituitary hormones

Diabetes insipidus

Vasopressin p. 669 (antidiuretic hormone, ADH) is used in the treatment of pituitary (‘cranial’) diabetes insipidus as is its analogue desmopressin p. 667. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose intramuscularly or intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides.

Carbamazepine p. 311 is sometimes useful in partial pituitary diabetes insipidus [unlicensed]; it may act by sensitising the renal tubules to the action of remaining endogenous vasopressin.

Other uses

Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand’s disease; it is also used to test fibrinolytic response. Desmopressin may also have a role in nocturnal enuresis.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. Terlipressin acetate, a derivative of vasopressin with reportedly less pressor and antidiuretic activity, is used similarly.

Oxytocin p. 823, another posterior pituitary hormone, is indicated in obstetrics.

Antidiuretic hormone antagonists

Demeclocycline hydrochloride p. 564 can be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable. Demeclocycline hydrochloride is thought to act by directly blocking the renal tubular effect of antidiuretic hormone.

Tolvaptan p. 669 is a vasopressin V2-receptor antagonist licensed for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion; treatment duration with tolvaptan is determined by the underlying disease and its treatment. Rapid correction of hyponatraemia during tolvaptan therapy can cause osmotic demyelination, leading to serious neurological events; close monitoring of serum sodium concentration and fluid balance is essential.

1.1 Diabetes insipidus

Other drugs used for Diabetes insipidus Chlortalidone, p. 230
**Desmopressin**

- **DRUG ACTION** Desmopressin is an analogue of vasopressin.

- **INDICATIONS AND DOSE**

  **Diabetes insipidus, treatment**
  - **BY MOUTH**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: 200 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 5–17 years: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY ORAL SUSPENSION**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 2–11 years: 5 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Child 1 year or less: 2 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Primary nocturnal enuresis**

  - **BY MOUTH**
  - Child 5–17 years: 200 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Adult 18–65 years: 200 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - **BY SUBLINGUAL ADMINISTRATION**
  - Child 5–17 years: 120 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted
  - Adult 18–65 years: 120 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Postoperative polyuria or polydipsia**

  - **BY MOUTH**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Polyuria or polydipsia after hypophysectomy**

  - **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 20 micrograms once daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Idiopathic nocturnal polyuria in females**

  - **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 25 micrograms daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Idiopathic nocturnal polyuria in males**

  - **BY SUBLINGUAL ADMINISTRATION**
  - Adult: 50 micrograms daily, dose to be decreased according to urine osmolality; oral fluid intake to be restricted

- **Diabetes insipidus, diagnosis (water deprivation test)**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 20 micrograms, dose to be increased according to response; usual dose 200 micrograms daily
  - Child 2–11 years: 5 micrograms, dose to be increased according to response; usual dose 100–200 micrograms daily
  - Child 1 year or less: 2 micrograms, dose to be increased according to response; usual dose 2–10 micrograms daily

- **Nocturia associated with multiple sclerosis (when other treatments have failed)**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult 18–65 years: 10–20 micrograms daily, dose to be increased according to response; usual dose 200 micrograms daily

- **Renal function testing**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 40 micrograms, dose to be increased according to response; usual dose 200 micrograms daily

- **Mild to moderate haemophilia and von Willebrand’s disease**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 300 micrograms every 12 hours if required, dose to be increased according to response; usual dose 300 micrograms/kg for 1 dose
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 300 micrograms/kg for 1 dose, dose to be increased according to response; usual dose 200 micrograms/kg for 1 dose

- **Fibrinolytic response testing**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 300 micrograms/kg for 1 dose, dose to be increased according to response; usual dose 200 micrograms/kg for 1 dose
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 300 micrograms/kg for 1 dose, dose to be increased according to response; usual dose 200 micrograms/kg for 1 dose

- **Lumbar-puncture-associated headache**

  - **BY INTRANASAL ADMINISTRATION**
  - Adult: 200 micrograms/kg for 1 dose, dose to be increased according to response; usual dose 200 micrograms/kg for 1 dose

- **Diabetes insipidus**

  - **20-Feb-2019**

  - **Desmopressin**
  - www.getintopharma.com
UNLICENSED USE Consult product literature for individual preparations. Oral use of DDAVP intravenous injection is not licensed.

CONTRA-INDICATIONS Cardiac insufficiency - conditions treated with diuretics - history of hyponatraemia - polydipsia in alcohol dependence - psychogenic polydipsia - syndrome of inappropriate ADH secretion (in adults)

CAUTIONS

GENERAL CAUTIONS Asthma - avoid fluid overload - cardiovascular disease (not indicated for nocturnal enuresis or nocturia) - conditions which might be aggravated by water retention - cystic fibrosis - elderly (avoid for primary nocturnal enuresis and nocturia associated with multiple sclerosis in those over 65 years) - epilepsy - heart failure - hypertension (not indicated for nocturnal enuresis or nocturia) - migraine - nocturia — limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards - nocturnal enuresis — limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards

SPECIFIC CAUTIONS

With intranasal use should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects

CAUTIONS, FURTHER INFORMATION Elderly patients are at increased risk of hyponatraemia and renal impairment — manufacturer advises measure baseline serum sodium concentration, then monitor regularly during treatment; discontinue treatment if levels fall below the normal range. Review treatment if no therapeutic benefit after 3 months.

INTERACTIONS ➔ Appendix 1: desmopressin

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

• Common or very common Hyponatraemia (on administration without restricting fluid intake) - nausea

• Frequency not known Abdominal pain - aggression (in children) - allergic dermatitis - emotional disorder - fluid retention - headache - hyponatraemic seizure - vomiting - weight increased

SPECIFIC SIDE-EFFECTS

• With intranasal use Epistaxis - nasal congestion - rhinitis

• With intravenous or subcutaneous use Vasodilation

• With sublingual use Epistaxis - nasal congestion

SIDE-EFFECTS, FURTHER INFORMATION Manufacturer advises avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants) — increases risk of hyponatraemia.

PREGNANCY Small oxytocic effect in third trimester; increased risk of pre-eclampsia.

BREAST FEEDING Amount too small to be harmful.

RENAL IMPAIRMENT Use with caution; antidiuretic effect may be reduced.

MONITORING REQUIREMENTS In nocturia, periodic blood pressure and weight checks are needed to monitor for fluid overload.

DIRECTIONS FOR ADMINISTRATION DDAVP® and Desmota® tablets may be crushed. DDAVP® intranasal solution may be diluted with Sodium Chloride 0.9% to a concentration of 10 micrograms/mL. DDAVP® injection may be administered orally. Desmopressin oral lyophilisates are for sublingual administration.

With intravenous use in adults For intravenous infusion (DDAVP®, Octim®), give intermittently in Sodium chloride 0.9%; dilute with 50 mL and give over 20 minutes.

PRESCRIBING AND DISPENSING INFORMATION Oral, intranasal, intravenous, subcutaneous and intramuscular doses are expressed as desmopressin acetate; sublingual doses are expressed as desmopressin base.

Children requiring an intranasal dose of less than 10 micrograms should be given DDAVP® intranasal solution.

PATIENT AND CARER ADVICE

Hyponatraemic convulsions Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal).

Medicines for Children leaflet: Desmopressin for bedwetting www.medicinesforchildren.org.uk/desmopressin-bedwetting-0

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions SMC No. 1218/17 The Scottish Medicines Consortium has advised (August 2017) that desmopressin oral lyophilisate (Noqdina®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in patients aged 65 years and over.

All Wales Medicines Strategy Group (AWMSG) decisions AWMSG No. 2382 The All Wales Medicines Strategy Group has advised (October 2017) that desmopressin acetate (Noqdina®) is recommended for restricted use within NHS Wales for idiopathic nocturnal polyuria in adults aged over 65 years, for whom treatment options are currently limited.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, spray, nasal drops

**Table**

<table>
<thead>
<tr>
<th><strong>Tablet</strong></th>
<th><strong>Desmopressin (Non-proprietary)</strong></th>
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<tbody>
<tr>
<td><strong>Desmopressin acetate 100 microgram</strong></td>
<td>Desmopressin 100microgram tablets</td>
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<td><strong>Desmopressin acetate 200 microgram</strong></td>
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<td><strong>DDAVP (Ferring Pharmaceuticals Ltd)</strong></td>
<td><strong>Desmopressin acetate 100 microgram DDAVP 0.1mg tablets</strong></td>
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<td><strong>DDAVP</strong></td>
<td><strong>Desmopressin acetate 200 microgram DDAVP 0.2mg tablets</strong></td>
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<td><strong>Desmotabs (Ferring Pharmaceuticals Ltd)</strong></td>
<td><strong>Desmopressin acetate 200 microgram Desmotabs 0.2mg tablets</strong></td>
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SOLUTION FOR INJECTION

| **DDAVP (Ferring Pharmaceuticals Ltd)** | **Desmopressin acetate 4 microgram per 1 ml DDAVP 4micrograms/1ml solution for injection ampoules** | 10 ampoule £13.16 |
| **Octim (Ferring Pharmaceuticals Ltd)** | **Desmopressin acetate 15 microgram per 1 ml Octim 15micrograms/1ml solution for injection ampoules** | 10 ampoule £132.20 |

**Spray**

| **Desmospray (Ferring Pharmaceuticals Ltd)** | **Desmospray 2.5 microgram/dose nasal spray** | 50 dose £53 |
| **Desmospray** | **Desmospray 10micrograms/dose nasal spray 2.5micrograms/dose nasal spray** | 60 dose £25.02 DT = £23.35 |
| **Octim (Ferring Pharmaceuticals Ltd)** | **Desmospray 150 microgram per 1 dose Octim 15micrograms/dose nasal spray** | 25 dose £57.60 DT = £57.60 |

**Oral lyophilisate**

CAUTIONARY AND ADVISORY LABELS: 26

| **DDAVP Melt (Ferring Pharmaceuticals Ltd)** | **Desmopressin (as Desmopressin acetate) 60 microgram DDAVP Melt 60microgram oral lyophilisates sugar-free** | 100 tablet £50.53 DT = £50.53 |
| **Desmopressin (as Desmopressin acetate) 120 microgram DDAVP Melt 120microgram oral lyophilisates sugar-free** | 100 tablet £101.07 DT = £101.07 |

www.getintopharma.com
1.2 Syndrome of inappropriate antidiuretic hormone secretion

Other drugs used for Syndrome of inappropriate antidiuretic hormone secretion: Demeclocycline hydrochloride, p. 564

www.getintopharma.com
6 Tolvaptan for treating autosomal dominant polycystic kidney disease

NATIONAL FUNDING/ACCESS DECISIONS

PATIENT AND CARER ADVICE

▶ When used for Hyponatraemia secondary to syndrome of nephrogenic diabetes insipidus, Manufacturer advises monitor serum-sodium concentration no later than 6 hours or 8 mmol/litre in the first 6–12 hours, frequency of monitoring should be increased; interrupt or discontinue treatment if serum-sodium increases by 12 mmol/litre or greater in 24 hours or 18 mmol/litre or greater in 48 hours.

▶ When potentially less harmful measures are ineffective corticosteroids are used topicaly for the treatment of inflammatory conditions of the skin. Corticosteroids should be avoided or used only under specialist supervision in pregnancy. Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn’s disease. They are also included in locally applied creams for haemorrhoids. Use can be made of the mineralocorticoid activity of fludrocortisone acetate p. 676 to treat postural hypotension in autonomic neuropathy.

High-dose corticosteroids should be avoided for the management of septic shock. However, there is evidence that administration of lower doses of hydrocortisone p. 676 and fludrocortisone acetate is of benefit in adrenocortical insufficiency resulting from septic shock.

Dexamethasone p. 675 and betamethasone p. 674 have little if any mineralocorticoid activity and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17-hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamic–pituitary–adrenal axis is greatest and most prolonged when they are given at night. In most individuals a single dose of dexamethasone at night, is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the ‘overnight dexamethasone suppression test’ for diagnosing Cushing’s syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

2 Corticosteroid responsive conditions

Corticosteroids, general use

Overview

Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topicaly for the treatment of inflammatory conditions of the skin. Corticosteroids should be avoided or used only under specialist supervision in pregnancy. Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn’s disease. They are also included in locally applied creams for haemorrhoids. Use can be made of the mineralocorticoid activity of fludrocortisone acetate p. 676 to treat postural hypotension in autonomic neuropathy.

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Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.
Corticosteroids, replacement therapy

Overview
The adrenal cortex normally secretes hydrocortisone p. 676 (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of hydrocortisone and the mineralocorticoid fludrocortisone acetate p. 676; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In Addison’s disease or following adrenalectomy, hydrocortisone by mouth is usually required. This is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone acetate.

In acute adrenocortical insufficiency, hydrocortisone is given intravenously (preferably as sodium succinate) every 6 to 8 hours in sodium chloride intravenous infusion 0.9% p. 1040.

In hypopituitarism, glucocorticoids should be given as in adrenocortical insufficiency, but since production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required. Additional replacement therapy with levothyroxine sodium p. 773 and sex hormones should be given as indicated by the pattern of hormone deficiency.
The relatively high mineralocorticoid activity of hydrocortisone p. 676, and the resulting fluid retention, makes it unsuitable for disease suppression on a long-term basis. However, hydrocortisone can be used for adrenal replacement therapy. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked. Prednisolone p. 678 and prednisone have predominantly glucocorticoid activity. Prednisolone is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone p. 674 and dexamethasone p. 675 have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage. Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia).

Some esters of betamethasone and of beclometasone dipropionate p. 45 (beclometasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations). Deflazacort p. 674 has a high glucocorticoid activity; it is derived from prednisolone.

Corticosteroids (systemic)

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes. The MHRA recommends that patients should be advised to report any blurred vision or other visual disturbances with corticosteroid treatment given by any route; consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems.

• CONTRA-INDICATIONS Avoid injections containing benzyl alcohol in neonates • avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished) • systemic infection (unless specific therapy given)

• CONTRA-INDICATIONS, FURTHER INFORMATION For further information on contra-indications associated with intra-articular, intradermal and intralesional preparations, consult product literature.

• CAUTIONS Congestive heart failure • diabetes mellitus (including a family history of) • diverticulitis • erythromelalgia • glaucoma (including a family history of or susceptibility to) • history of steroid myopathy • history of tuberculosis or X-ray changes (frequent monitoring required) • hypertension • hypothyroidism • infection (particularly untreated) • myasthenia gravis • ocular herpes simplex (risk of corneal perforation) • osteoporosis (in children) • osteoporosis (post-menopausal women and the elderly at special risk) (in adults) • peptic ulcer • psychiatric reactions • recent intestinal anastomoses • recent myocardial infarction (rupture reported) • severe affective disorders (particularly if history of steroid-induced psychosis) • should not be used long-term • thromboembolic disorders • ulcerative colitis

CAUTIONS, FURTHER INFORMATION For further information on cautions associated with intra-articular, intradermal and intralesional preparations, consult product literature.

• SIDE-EFFECTS
  • Common or very common Anxiety • behaviour abnormal • cataract • subcapsular • cognitive impairment • Cushing’s syndrome • electrolyte imbalance • fluid retention • gastrointestinal discomfort • headache • healing impaired • hirsutism • hypertension • increased risk of infection • menstrual cycle irregularities • mood altered • nausea • osteoporosis • peptic ulcer • psychotic disorder • skin reactions • sleep disorders • weight increased
  • Uncommon Adrenal suppression • alkalosis • hypokalaemia • appetite increased • bone fractures • diabetic control impaired • eye disorders • fatigue • glaucoma • haemorrhage • heart failure • hyperhidrosis • hypotension • leucocytosis • myopathy • osteonecrosis • pancreatitis • papilloedema • seizure • thromboembolism • tuberculosis reactivation • vertigo • vision blurred
  • Rare or very rare Malaise • tendon rupture
  • Frequency not known Chorioretinopathy • growth retardation (very common in children) • intracranial pressure increased with papilloedema (usually after withdrawal) • telangiectasia

SIDE-EFFECTS, FURTHER INFORMATION Adrenal suppression During prolonged therapy with corticosteroids, particularly with systemic use, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to
Acute adrenal insufficiency, hypotension, or death. To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary reintroduction of corticosteroid treatment. Patients on long-term corticosteroid treatment should carry a steroid treatment card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

**Infections** Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. septicaemia and tuberculosis may reach an advanced stage before being recognised, and amoeobiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

**Chickenpox** Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non–immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

**Measles** Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

**Psychiatric reactions** Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment. Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid–induced psychosis, or who have a personal or family history of psychiatric disorders.

**Pregnancy** The benefit of treatment with corticosteroids during pregnancy outweighs the risk. Corticosteroid cover is required during labour. Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) concluded that corticosteroids vary in their ability to cross the placenta but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip. When administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome). Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important.

**Monitoring** Pregnant women with fluid retention should be monitored closely when given systemic corticosteroids.

- **Breastfeeding** The benefit of treatment with corticosteroids during breast-feeding outweighs the risk.
- **Hepatic Impairment** In general, manufacturers advise caution (risk of increased exposure).
- **Renal Impairment** Use by oral and injectable routes should be undertaken with caution.
- **Monitoring Requirements**
  - in children The height and weight of children receiving prolonged treatment with corticosteroids should be monitored annually; if growth is slowed, referral to a paediatrician should be considered.
- **Effect on Laboratory Tests** May suppress skin test reactions.
- **Treatment Cessation**
  - in adults Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss. The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case–by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. Gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:
    - received more than 40 mg prednisolone (or equivalent) daily for more than 1 week;
    - been given repeat doses in the evening;
    - received more than 3 weeks’ treatment;
    - received more than 3 weeks’ treatment;
    - taken a short course within 1 year of stopping long-term therapy;
    - other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

- in children The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case–by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. Gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:
  - received more than 40 mg prednisolone (or equivalent) daily for more than 1 week or 2 mg/kg daily for 1 week or 1 mg/kg daily for 1 month;
  - been given repeat doses in the evening;
  - received more than 3 weeks’ treatment;
  - received more than 3 weeks’ treatment;
  - received more than 3 weeks’ treatment;
  - taken a short course within 1 year of stopping long-term therapy;
  - other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above. During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to
Betamethasone

**INDICATIONS AND DOSE** Suppression of inflammatory and allergic disorders | Congenital adrenal hyperplasia

- **BY MOUTH**
  - Adult: Usual dose 0.5–5 mg daily
  - Child 1 month–11 years: 0.25–1.5 mg/kg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations
  - Child 12–17 years: 3–18 mg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations

- **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: 4–20 mg, repeated up to 4 times in 24 hours

**INTERACTIONS** → Appendix 1: corticosteroids

**SIDE-EFFECTS** Hiccups, myocardial rupture (following recent myocardial infarction), oedema, Stevens-Johnson syndrome

**PREGNANCY** Readily crosses the placenta. Transient effect on fetal movements and heart rate.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (as sodium phosphate) (Betresol®), give continuously or intermittently or via drip tubing In Glucose 5% or Sodium chloride 0.9%.

**PATIENT AND CARER ADVICE**

- With oral use Patient counselling is advised for betamethasone soluble tablets (steroid card).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Soluble tablet**

| CAUTIONARY AND ADVISORY LABELS | 5, 13, 21 (not for use as mouthwash for oral ulceration) |
| Betamethasone (Non-proprietary) |  |
| Betamethasone (as Betamethasone sodium phosphate) |  |
| 500 microgram | Betamethasone 500 microgram soluble tablets sugar-free sugar-free | 100 tablet | £65.18 DT = £58.15

**Solution for injection**

| CAUTIONARY AND ADVISORY LABELS | 10 |
| Betamethasone (Non-proprietary) |  |
| Betamethasone (as Betamethasone sodium phosphate) |  |
| 4 mg per 1 ml | Betamethasone 4 mg/1 ml 5 ampoules | £33.93 DT = £32.61

**Deflazacort**

**DRUG ACTION** Deflazacort is derived from prednisolone; it has predominantly glucocorticoid activity.

**INDICATIONS AND DOSE**

**Suppression of inflammatory and allergic disorders**

- **BY MOUTH**
  - Adult: Maintenance 3–18 mg daily
  - Adult: Initially up to 120 mg daily

**Suppression of inflammatory and allergic disorders (acute disorders)**

- **BY MOUTH**
  - Adult: 60 mg per dose
  - Child 1 month–11 years: 0.25–1.5 mg/kg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations
  - Child 12–17 years: 3–18 mg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations

**INTERACTIONS** → Appendix 1: corticosteroids

**SIDE-EFFECTS**

- Uncommon: Oedema

**HEPATIC IMPAIRMENT**

- Dose adjustments Manufacturer advises adjust to the minimum effective dose.

**PATIENT AND CARER ADVICE** Patient counselling is advised for deflazacort tablets (steroid card).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 5, 10 |
| Deflazacort |  |
| 6 mg | Calcort 6mg tablets | 60 tablet | £15.82 DT = £15.82

www.getintopharma.com
Dexamethasone

**DRUG ACTION** Dexamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity.

**INDICATIONS AND DOSE**

- **Suppression of inflammatory and allergic disorders**
  - **By mouth**
  - **Adults:** 0.5–10 mg daily
  - **Children:** Initially 150 micrograms/kg for 1 dose

- **Mild croup**
  - **By mouth**
  - **Child:** 150 micrograms/kg for 1 dose

- **Severe croup (or mild croup that might cause complications)**
  - **Initial** by mouth
  - **Child:** Initially 150 micrograms/kg for 1 dose, to be given before transfer to hospital, then (by mouth or by intravenous injection) 150 micrograms/kg, then (by mouth or by intravenous injection) 150 micrograms/kg after 12 hours if required

- **Congenital adrenal hyperplasia (under expert supervision)**
  - **By mouth**
  - **Adults:** Consult specialist for advice on dosing
  - **Intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
  - **Adults:** Consult specialist for advice on dosing

- **Overnight dexamethasone suppression test**
  - **By mouth**
  - **Adults:** 1 mg for 1 dose, to be given at night

- **Adjunctive treatment of bacterial meningitis (starting before or with first dose of antibiotic)**
  - **By intravenous injection**
  - **Adults:** 8.3 mg every 6 hours for 4 days

- **Symptom control of anorexia in palliative care**
  - **Adults:** 2–4 mg daily

- **Dysphagia due to obstruction by tumour in palliative care**
  - **Adults:** 8 mg daily

- **Dyspnoea due to bronchospasm or partial obstruction in palliative care**
  - **Adults:** 4–8 mg daily

- **Adjunct in the treatment of nausea and vomiting in palliative care**
  - **By mouth**
  - **Adults:** 8–16 mg daily

- **Headaches due to raised intracranial pressure in palliative care**
  - **Adults:** 16 mg daily for 4–5 days, then reduced to 4–6 mg daily, reduce dose if possible. To be given before 6pm to reduce the risk of insomnia

- **Pain due to nerve compression in palliative care**
  - **Adults:** 8 mg daily

- **Cerebral oedema associated with malignancy**
  - **By mouth**
  - **Adults:** 0.5–10 mg daily

- **Cerebral oedema**
  - **Initially by intravenous injection**
  - **Adults:** Initially 8–16 mg for 1 dose, then (by intramuscular injection or by intravenous injection) 5 mg every 6 hours until adequate response achieved then taper-off gradually, use the 3.8 mg/mL injection preparation for this dose

- **Cerebral oedema associated with malignancy**
  - **Initially by intravenous injection**
  - **Adults:** Initially 8.3 mg for 1 dose, then (by intramuscular injection) 3.3 mg every 6 hours as required for 2–4 days, subsequently, reduce dose

**INTERACTIONS**

- **With oral use** Hiccups, hyperglycaemia, myocardial rupture (following recent myocardial infarction), protein catabolism

- **With parental use** Perineal irritation (may occur following the intravenous injection of large doses of the phosphate ester)

**PREGNANCY** Dexamethasone readily crosses the placenta.

**DIRECTIONS FOR ADMINISTRATION**

- **With systemic use in children** For further information on the dose of dexamethasone in palliative care, see www.medicinescomplete.com/#/content/palliative/systemic-corticosteroids.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Dexamethasone for croup www.medicinesforchildren.org.uk/dexamethasone-croup-0

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

**Soluble tablet**

- **Dexamethasone (Non-proprietary)**
  - **Dexamethasone**
  - **Dexamethasone (as Dexamethasone sodium phosphate)**
    - 2 mg Dexamethasone 2mg soluble tablets sugar-free sugar-free | 50 tablet (POM) £30.00–£30.01 DT + £30.01
    - 4 mg Dexamethasone 4mg soluble tablets sugar-free sugar-free | 50 tablet (POM) £60.00–£60.01 DT + £60.01
  - **Dexamethasone (as Dexamethasone sodium phosphate)**
    - 8 mg Dexamethasone 8mg soluble tablets sugar-free sugar-free | 50 tablet (POM) £120.00–£120.01 DT + £120.01
  - **Glensoludex** (Glenmark Pharmaceuticals Europe Ltd)
    - **Dexamethasone (as Dexamethasone sodium phosphate)**
      - 2 mg Glensoludex 2mg soluble tablets sugar-free | 50 tablet (POM) £10.00 DT + £30.01
      - 4 mg Glensoludex 4mg soluble tablets sugar-free | 50 tablet (POM) £20.00 DT + £60.01
    - **Dexamethasone (as Dexamethasone sodium phosphate)**
      - 8 mg Glensoludex 8mg soluble tablets sugar-free | 50 tablet (POM) £40.00 DT + £120.01

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **Dexamethasone (Non-proprietary)**
  - **Dexamethasone 500 microgram** Dexamethasone 500microgram tablets | 28 tablet (POM) £9.51–£54.24 DT + £10.27 | 30 tablet (POM) £11.00–£64.92
  - **Dexamethasone 2 mg** Dexamethasone 2mg tablets | 50 tablet (POM) £49.00 DT + £9.79 | 100 tablet (POM) £17.32–£38.00

Gradually and stop over 5–7 days, use the 3.3 mg/mL injection preparation for this dose
### Endocrine system

#### SIDE-EFFECTS

- **Conjunctivitis**
- **Idiopathic intracranial hypertension**
- **Muscle weakness**
- **Thrombophlebitis**

#### INTERACTIONS

- Not licensed for use in neuropathic postural hypotension.
- **Appendix 1**: corticosteroids

#### DRUG ACTION

**Hydrocortisone**

- **Drug action**: Hydrocortisone has equal glucocorticoid and mineralocorticoid activity.

- **Indications and dose**
  - **Thyrotoxic crisis (thyroid storm)**
    - **By intravenous injection**
    - Adult: 100 mg every 6 hours, to be administered as sodium succinate
  - **Adrenocortical insufficiency resulting from septic shock**
    - **By intravenous injection**
    - Adult: 50 mg every 6 hours, given in combination with fludrocortisone
  - **Acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylaxis (adjunct to adrenaline)**
    - **By intravenous injection**
    - Adult: 100–300 mg, to be administered as sodium succinate
  - **Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of minor surgery under general anaesthesia**
    - **By intravenous injection, or by intravenous infusion**
    - Adult: Initially 25–50 mg, to be administered at induction of surgery, the patient’s usual oral corticosteroid dose is recommenced after surgery
  - **Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of moderate or major surgery**
    - **Initially by intravenous injection, or by intravenous infusion**
    - Adult: Initially 25–50 mg, to be administered at induction of surgery (following usual oral corticosteroid dose on the morning of surgery), followed by (by intravenous injection) 25–50 mg 3 times a day for 24 hours after moderate surgery and for 48–72 hours after major surgery
  - **Adrenocortical insufficiency in Addison’s disease or following adrenalectomy**
    - **By mouth using immediate-release medicines**
    - Adult: 20–30 mg daily in 2 divided doses, the larger dose to be given in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion, the optimum daily dose is determined on the basis of clinical response
  - **Adrenocortical insufficiency**
    - **By intramuscular injection, or by slow intravenous injection, or by intravenous infusion**
    - Adult: 100–500 mg 3–4 times a day or when required

#### Unlicensed use

- Not licensed for use in neuropathic postural hypotension.

#### Hepatic impairment

- **Monitoring**: Monitor patient closely in hepatic impairment.

#### Medicinal forms

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension

#### Table

- **CAUTIONARY AND ADVISORY LABELS**
  - **10, 21**
  - **Oral solution**
  - **10**
  - **15**
  - **100**
  - **1000**
  - **5000**
  - **10000**
  - **20000**
  - **50000**
  - **100000**
  - **200000**

#### Medica...
Replacement in adrenocortical insufficiency

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 20–30 mg once daily, adjusted according to response, dose to be taken in the morning
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 20–30 mg daily in divided doses, adjusted according to response

**Ulcerative colitis / Proctitis / Proctosigmoiditis**

- **BY RECTUM USING RECTAL FOAM**
  - Adult: Initially 1 metered application 1–2 times a day for 2–3 weeks, then reduced to 1 metered application once daily on alternate days, to be inserted into the rectum

**Acute hypersensitivity reactions / Angioedema**

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION**
  - Child 1-5 months: Initially 25 mg 3 times a day, adjusted according to response
  - Child 6 months-5 years: Initially 50 mg 3 times a day, adjusted according to response
  - Child 6-11 years: Initially 100 mg 3 times a day, adjusted according to response
  - Child 12-17 years: Initially 200 mg 3 times a day, adjusted according to response

**Severe acute asthma / Life-threatening acute asthma**

- **BY INTRAVENOUS INJECTION**
  - Child 1 month-1 year: 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 25 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate
  - Child 2-4 years: 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 50 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate
  - Child 5-11 years: 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate
  - Child 12-17 years: 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate
  - Adult: 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate

**DOSE EQUIVALENCE AND CONVERSION**

- With oral use
- When switching from immediate-release hydrocortisone tablets to modified release Plenadren® use same total daily dose. Bioavailability of Plenadren® lower than immediate release tablets—monitor clinical response.

- **CONTRA-INDICATIONS**
  - With rectal use Bowel perforation · extensive fistulas · intestinal obstruction · recent intestinal anastomoses

- **CAUTIONS**
  - With rectal use Systemic absorption may occur

- **INTERACTIONS** → Appendix 1: corticosteroids

- **SIDE-EFFECTS**
  - With oral use Dyslipidaemia · myocardial rupture (following recent myocardial infarction) · oedema.
  - With parenteral use Hiccups · Kaposi’s sarcoma · lipomatosis · myocardial rupture (following recent myocardial infarction)

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children For intravenous administration, dilute with Glucose 5% or Sodium Chloride 0.9%. For intermittent infusion give over 20–30 minutes.

- With intravenous use in adults For intravenous infusion (SoluCortef®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.

- **PATIENT AND CARER ADVICE**
  - Patient counselling is advised for hydrocortisone tablets and injections (steroid card).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions

  - **CONTRA-INDICATIONS**
    - With intravenous use Hydrocortisone as the sodium phosphate is less suitable for prescribing as paraesthesia and pain (particularly in the perineal region) may follow intravenous injection.

  - **EXCEPTIONS TO LEGAL CATEGORY**
    - With intramuscular use or intravenous use Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

  - **Modified-release tablet**
    - Hydrocortisone (as Hydrocortisone sodium phosphate) 10 mg, Hydrocortisone 10 mg soluble tablets sugar free sugar-free | 30 tablet £13.50

  - **Tablet**
    - Hydrocortisone 10 mg, Hydrocortisone 10 mg tablets | 30 tablet £0.84 £0.20 £0.19
    - Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.147 £0.26 £0.17

  - **Solu-Cortef** (Pfizer Ltd)
    - Hydrocortisone as Hydrocortisone sodium succinate 100 mg Solu-Cortef 100 mg powder for solution for injection vials | 10 vial £0.17

  - **Suspension for injection**
    - Hydrocortisone acetate 25 mg per 1 ml Hydrocortisone acetate 25 mg/1 ml suspension for injection ampoules | 10 ampoule £0.68 £0.72

  - **Powder for solution for injection**
    - Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg Telokortel 100 mg powder for solution for injection vials | 10 vial £0.59 £0.59

  - **Solution for injection**
    - Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg Solu-Cortef 100 mg powder for solution for injection vials | 1 vial £0.16 £0.16

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg per 1 ml Hydrocortisone sodium phosphate 100 mg/1 ml solution for injection ampoules | 5 ampoule £0.10 £0.60

  - **Hydrocortisone (Non-proprietary)**
    - Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14
    - Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14

  - **Plenadren** (Shire Pharmaceuticals Ltd)
    - Hydrocortisone 5 mg Plenadren 5 mg modified-release tablets | 50 tablet £0.26 £0.20 £0.22
    - Hydrocortisone 10 mg Plenadren 10 mg modified-release tablets | 50 tablet £0.30 £0.25 £0.27

  - **Hydventia** (Pfizer Ltd)
    - Hydrocortisone 10 mg, Hydrocortisone 10 mg tablets | 30 tablet £0.15 £0.50 £0.14
    - Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 10 mg Solu-Cortef 10 mg powder for solution for injection vials | 10 vial £0.17

  - **Hydrocortisone acetate 25 mg per 1 ml Hydrocortisone acetate 25 mg/1 ml suspension for injection ampoules | 10 ampoule £0.68 £0.72

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg Solu-Cortef 100 mg powder for solution for injection vials | 10 vial £0.17

  - **Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14

  - **Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 10 mg Telokortel 100 mg powder for solution for injection vials | 10 vial £0.17

  - **Hydrocortisone acetate 25 mg per 1 ml Hydrocortisone acetate 25 mg/1 ml suspension for injection ampoules | 10 ampoule £0.68 £0.72

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg Solu-Cortef 100 mg powder for solution for injection vials | 10 vial £0.17

  - **Hydrocortisone 20 mg Hydrocortisone 20 mg tablets | 30 tablet £0.15 £0.50 £0.14

  - **Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg Solu-Cortef 100 mg powder for solution for injection vials | 10 vial £0.17


Methylprednisolone

- **DRUG ACTION** Methylprednisolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects.

- **INDICATIONS AND DOSE** Suppression of inflammatory and allergic disorders
  - By mouth
    - Adult: Initially 2–40 mg daily
    - By intramuscular injection, or by slow intravenous injection, or by intravenous infusion
    - Adult: Initially 10–500 mg
  - Treatment of graft rejection reactions
    - By intravenous infusion
    - Adult: Up to 1 g daily for up to 3 days
  - Treatment of relapse in multiple sclerosis
    - By mouth
    - Adult: 500 mg once daily for 5 days
  - Treatment of relapse in multiple sclerosis (when oral steroids have failed or have not been tolerated, or in those who require hospital admission)
    - By intravenous infusion
    - Adult: 1 g once daily for 3–5 days

**DEPO-MEDRONE ®**

- **Suppression of inflammatory and allergic disorders**
  - By deep intramuscular injection
  - Adult: 40–120 mg, then 40–120 mg after 2–3 weeks if required, to be injected into the gluteal muscle

- **UNLICENSED USE**
  - With intravenous use or oral use. Not licensed for use by mouth for the treatment of multiple sclerosis relapse. Not licensed for use by intravenous infusion for the treatment of multiple sclerosis relapse for durations longer than 3 days. Methylprednisolone doses in the BNF may differ from those in product literature.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE:** Methylprednisolone injectable medicine containing lactose (Solu-Medrone ® 40 mg): Do not use in patients with cows’ milk allergy (October 2017)

- With intramuscular use or intravenous use
  - An EU-wide review has concluded that Solu-Medrone ® 40 mg may contain trace amounts of milk proteins and should not be used in patients with a known or suspected allergy to cows’ milk. Serious allergic reactions, including bronchospasm and anaphylaxis, have been reported in patients allergic to cows’ milk proteins. If a patient’s symptoms worsen or new allergic symptoms occur, administration should be stopped and the patient treated accordingly.

**CAUTIONS**

- With intravenous use Rapid intravenous administration of large doses associated with cardiovascular collapse

**INTERACTIONS** Appendix 1: corticosteroids

**SIDE-EFFECTS**

- Common or very common
  - With oral use Depressed mood
  - Frequency not known
  - With oral use Confusion, delusions, diarrhea, dizziness, dyslipidaemia, hallucination, hiccups, Kaposi’s sarcoma, lipomatosis, myocardial rupture (following recent myocardial infarction), oedema, schizophrenia, suicidal ideation, withdrawal syndrome
  - With parenteral use Confusion, delusions, depressed mood, diarrhea, dizziness, dyslipidaemia, hallucination, hiccups, Kaposi’s sarcoma, lipomatosis, oedema, schizophrenia, suicidal thoughts, vomiting, withdrawal syndrome

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (as sodium succinate) (Solu-Medrone ®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially with water for injections; doses up to 250 mg should be given over at least 5 minutes, high doses over at least 30 minutes.

**PATIENT AND CARER ADVICE** Patient counselling is advised for methylprednisolone tablets and injections (steroid card).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Formulations available from special-order manufacturers include: oral suspension

**Powder and solvent for solution for injection**

**CAUTIONARY AND ADVISORY LABELS 10**

- **Solu-Medrone (Pfizer Ltd)**
  - Methylprednisolone (as Methylprednisolone sodium succinate) 40 mg Solu-Medrone 40 mg powder and solvent for solution for injection vials | 1 vial £1.58
  - Methylprednisolone (as Methylprednisolone sodium succinate) 125 mg Solu-Medrone 125 mg powder and solvent for solution for injection vials | 1 vial £4.75
  - Methylprednisolone (as Methylprednisolone sodium succinate) 500 mg Solu-Medrone 500 mg powder and solvent for solution for injection vials | 1 vial £9.60

- **Methylprednisolone (as Methylprednisolone sodium succinate) 1 gram** Solu-Medrone 1 g powder and solvent for solution for injection vials | 1 vial £17.30

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 10, 21**

- **Medrone (Pfizer Ltd)**
  - Methylprednisolone 2 mg Medrone 2 mg tablets | 30 tablet £3.88
  - Methylprednisolone 4 mg Medrone 4 mg tablets | 30 tablet £6.19
  - Methylprednisolone 16 mg Medrone 16 mg tablets | 30 tablet £11.17
  - Methylprednisolone 100 mg Medrone 100 mg tablets | 20 tablet £46.32 DT = £46.32

**Suspension for injection**

**CAUTIONARY AND ADVISORY LABELS 10**

- **Depo-Medrone (Pfizer Ltd)**
  - Methylprednisolone acetate 40 mg per 1 ml Depo-Medrone 40 mg/1 ml suspension for injection vials | 1 vial £3.44 10 vial £34.04
  - Depo-Medrone 80 mg/2 ml suspension for injection vials | 1 vial £6.18 10 vial £61.39
  - Depo-Medrone 120 mg/3 ml suspension for injection vials | 1 vial £8.96 10 vial £88.81

**Prednisolone**

- **DRUG ACTION** Prednisolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects.

- **INDICATIONS AND DOSE**
  - Acute exacerbation of chronic obstructive pulmonary disease (if increased breathlessness interferes with daily activities)
    - By mouth
    - Adult: 30 mg daily for 7–14 days
Severe myasthenia gravis (before transfer to hospital) / Mild myasthenia that might cause complications (before transfer to hospital)
- BY MOUTH
  - Adult: 1–2 mg/kg
  - Child: 1–2 mg/kg

Mild to moderate acute asthma (when oral corticosteroid taken for more than a few days) / Severe or life-threatening acute asthma (oral corticosteroid taken for more than a few days)
- BY MOUTH
  - Adult: Initial dose 40–50 mg daily for at least 5 days
  - Child 10–18 years: 10–20 mg/kg daily for up to 3 days, longer if necessary

Mild to moderate acute asthma / Severe or life-threatening acute asthma
- BY MOUTH
  - Adult: 25–100 mg 1–2 times a day, as prednisolone acetate

Suppression of inflammatory and allergic disorders (initial dose in severe disease)
- BY MOUTH
  - Adult: Initially 60 mg daily, dose preferably taken in the morning after breakfast, can often be reduced within a few days but may need to be continued for several weeks or months

Idiopathic thrombocytopenic purpura
- BY MOUTH
  - Adult: 1 mg/kg daily, gradually reduce dose over several weeks

Ulcerative colitis / Crohn’s disease
- BY MOUTH
  - Adult: Initially 20–40 mg daily until remission occurs, followed by reducing doses, up to 60 mg daily, may be used in some cases, doses preferably taken in the morning after breakfast

Neuritic pain or weakness heralding rapid onset of permanent nerve damage (during reversal reactions of multibacillary leprosy)
- BY MOUTH
  - Adult: Initially 40–60 mg daily, dose to be instituted at once

Generalised myasthenia gravis (when given on alternate days)
- BY MOUTH
  - Adult: Initially 10 mg once daily on alternate days, then increased in steps of 10 mg once daily on alternate days; increased to 1–1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

Generalised myasthenia gravis in ventilated patients (when given on alternate days)
- BY MOUTH
  - Adult: Initially 1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

Generalised myasthenia gravis (when giving daily)
- BY MOUTH
  - Adult: Initially 5 mg daily, increased in steps of 5 mg daily, maintenance 60–80 mg daily, alternatively maintenance 0.75–1 mg/kg daily, ventilated patients may be started on 1.5 mg/kg (max. 100 mg) on alternate days

Ocular myasthenia
- BY MOUTH
  - Adult: Usual dose 10–40 mg once daily on alternate days, reduce to minimum effective dose

Reduction in rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years’ duration
- BY MOUTH
  - Adult: 7.5 mg daily

Polymyalgia rheumatica
- BY MOUTH
  - Adult: 10–15 mg daily until remission of disease activity; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

Giant cell (temporal) arteritis
- BY MOUTH
  - Adult: 60–80 mg daily until remission of disease activity, the higher dose being used if visual symptoms occur; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

Polyarteritis nodosa / Polymyositis / Systemic lupus erythematosus
- BY MOUTH
  - Child: 5–10 mg/kg once daily on alternate days, increased to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

Pneumocystis pneumonia in moderate to severe infections associated with HIV infection
- BY MOUTH
  - Adult: 50–80 mg daily for 5 days, the dose is then reduced to complete 21 days of treatment, corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete

Short-term prophylaxis of episodic cluster headache as monotherapy or in combination with verapamil during verapamil titration
- BY MOUTH
  - Adult: 60–100 mg once daily for 2–5 days, then reduced in steps of 10 mg every 2–3 days until prednisolone is discontinued

Proctitis
- BY RECTUM USING RECTAL FOAM
  - Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone

Distal ulcerative colitis
- BY RECTUM USING RECTAL FOAM
  - Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone
Rectal complications of Crohn's disease
- **BY RECTUM USING SUPPOSITORIES**
- Adult: 5 mg twice daily, to be inserted in to the rectum morning and night, after a bowel movement.

Rectal and rectosigmoidal ulcerative colitis | Rectal and rectosigmoidal Crohn's disease
- **BY RECTUM USING ENEMA**
- Adult: 20 mg daily for 2–4 weeks, continued if response good, to be used at bedtime.

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**
- With systemic use Prednisolone has been confused with propranolol; care must be taken to ensure the correct drug is prescribed and dispensed.

**CONTRA-INDICATIONS**
- With rectal use Bowel perforation • extensive fistulas • intestinal obstruction • recent intestinal anastomoses

**CAUTIONS**
- With rectal use systemic absorption may occur with rectal preparations
- With systemic use Duchenne's muscular dystrophy (possible transient rhabdomyolysis and myoglobinuria following strenuous physical activity) • systemic sclerosis (increased incidence of scleroderma renal crisis with a daily dose of 15 mg or more)

**INTERACTIONS**
- Appendix 1: corticosteroids

**SIDE-EFFECTS**
- With intramuscular use Diarrhoea • dizziness • hiccups • Kaposis's sarcoma • myocardial infarction (following recent myocardial infarction) • scleroderma renal crisis • vomiting
- With oral use Diarrhoea • dizziness • dyslipidaemia • lipomatosis • protein catabolism • scleroderma renal crisis

**PREGNANCY**
- As it crosses the placenta 88% of prednisolone is inactivated.

**Monitoring**
- With systemic use Pregnant women with fluid retention should be monitored closely.

**BREAST FEEDING**
- Prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant.

**Monitoring**
- With systemic use Infant should be monitored for adrenal suppression if mother is taking a dose higher than 40 mg.

**MONITORING REQUIREMENTS**
- With systemic use Manufacturer advises monitor blood pressure and renal function (S-creatinine) routinely in patients with systemic sclerosis—increased incidence of scleroderma renal crisis.

**PRESCRIBING AND DISPENSING INFORMATION**
- Palliative care
  - With oral use in adults For further information on the use of prednisolone in palliative care, see www.medicinescomplete.com/#/content/palliative/systemic-corticosteroids.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Prednisolone for asthma
  - With oral use www.medicinesforchildren.org.uk/prednisolone-asthma

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, enema

**Foam**
- Prednisolone (Non-proprietary) Prednisolone (as Prednisolone sodium metasulfobenzoate) 20 mg per 1 application Prednisolone 20mg/application foam enema | 14 dose (PSTM) £187.00 DT = £187.00

**Gastro-resistant tablet**
- **CAUTIONARY AND ADVISORY LABELS 5, 10, 25**
- Prednisolone (Non-proprietary) Prednisolone 1 mg Prednisolone 1mg gastro-resistant tablets | 30 tablet (PSTM) £1.60–£1.92 DT = £1.92
- Prednisolone 2.5 mg Prednisolone 2.5mg gastro-resistant tablets | 28 tablet (PSTM) £0.93 DT = £0.93 | 30 tablet (PSTM) £0.98–£1.15
- Prednisolone 5 mg Prednisolone 5mg gastro-resistant tablets | 28 tablet (PSTM) £2.34 DT = £0.94 | 30 tablet (PSTM) £0.96–£6.29

- DeltaCortril Enteric (Alliance Pharmaceuticals Ltd) Prednisolone 2.5 mg DeltaCortril 2.5mg gastro-resistant tablets | 30 tablet (PSTM) £1.16
- Dilacort (Crescent Pharma Ltd, Teva UK Ltd) Prednisolone 2.5 mg Dilacort 2.5mg gastro-resistant tablets | 28 tablet (PSTM) £1.14–£1.85 DT = £0.93
- Prednisolone 5 mg Dilacort 5mg gastro-resistant tablets | 28 tablet (PSTM) £1.45–£1.85 DT = £0.94

**Soluble tablet**
- **CAUTIONARY AND ADVISORY LABELS 10, 13, 21**
- Prednisolone (Non-proprietary) Prednisolone (as Prednisolone sodium phosphate) 5 mg Prednisolone 5mg soluble tablets | 30 tablet (PSTM) £53.48 DT = £17.27

**Tablet**
- **CAUTIONARY AND ADVISORY LABELS 10, 21**
- Prednisolone (Non-proprietary) Prednisolone 1 mg Prednisolone 1mg tablets | 28 tablet (PSTM) £4.00 DT = £0.63
- Prednisolone 2.5 mg Prednisolone 2.5mg tablets | 28 tablet (PSTM) £1.35
- Prednisolone 5 mg Prednisolone 5mg tablets | 28 tablet (PSTM) £3.86 DT = £0.74
- Prednisolone 10 mg Prednisolone 10mg tablets | 28 tablet (PSTM) £1.77
- Prednisolone 20 mg Prednisolone 20mg tablets | 28 tablet (PSTM) £3.55
- Prednisolone 25 mg Prednisolone 25mg tablets | 56 tablet (PSTM) £78.38 DT = £77.23
- Prednisolone 30 mg Prednisolone 30mg tablets | 28 tablet (PSTM) £6.15 DT = £8.15
- Pevanti (Advanz Pharma) Prednisolone 2.5 mg Pevanti 2.5mg tablets | 30 tablet (PSTM) £1.42 DT = £1.42
- Prednisolone 5 mg Pevanti 5mg tablets | 30 tablet (PSTM) £0.95
- Prednisolone 10 mg Pevanti 10mg tablets | 30 tablet (PSTM) £1.90 DT = £1.90
- Prednisolone 20 mg Pevanti 20mg tablets | 30 tablet (PSTM) £3.80 DT = £3.80
- Prednisolone 25 mg Pevanti 25mg tablets | 56 tablet (PSTM) £40.00 DT = £77.23

**Suppository**
- Prednisolone (Non-proprietary) Prednisolone (as Prednisolone sodium phosphate) 5 mg Prednisolone sodium phosphate 5mg suppositories | 10 suppository (PSTM) £70.73 DT = £69.79

**Suspension for injection**
- DeltaTast (Advanz Pharma) Prednisolone acetate 25 mg per 1 ml DeltaTast 25mg/1ml suspension for injection ampoules | 10 ampoule (PSTM) £68.72

**Oral solution**
- **CAUTIONARY AND ADVISORY LABELS 10**
- Prednisolone (Non-proprietary) Prednisolone 1 mg per 1 ml Prednisolone 5mg/5ml oral solution unit dose | 10 unit dose (PSTM) £11.41 DT = £11.41
- Prednisolone 10 mg per 1 ml Prednisolone 10mg/1ml oral solution sugar free sugar-free | 30 ml (PSTM) £55.50 DT = £55.50

**Enema**
- Prednisolone (Non-proprietary) Prednisolone sodium phosphate 200 microgram per 1 ml Prednisolone 20mg/100ml rectal solution | 7 enema (PSTM) £14.95 DT = £15.00
Triamcinolone acetonide

**DRUG ACTION** Triamcinolone exerts predominantly glucocorticoid effects with minimal mineralcorticoid effect.

**INDICATIONS AND DOSE**

**Suppression of inflammatory and allergic disorders**

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adults: 40 mg (max. per dose 100 mg), repeated if necessary, dose given for depot effect, to be administered into gluteal muscle; repeated at intervals according to patient’s response.

**CAUTIONS** High dosage (may cause proximal myopathy), avoid in chronic therapy.

**INTERACTIONS**

- **Uncommon** Dizziness, flushing, hyperglycaemia.

**PATIENT AND CARER ADVICE** Patient counselling is advised for triamcinolone acetonide injection (steroid card).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Injection for suspension**

**CAUTIONARY AND ADVISORY LABELS** 10

**EXCIPIENTS** May contain Benzyl alcohol.

- **Adcortyl Intra-articular / Intradermal** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - **Triamcinolone acetonide 10 mg per 1 ml** Adcortyl Intra-articular / Intradermal 50mg/5ml suspension for injection vials | 1 vial (POM) £3.63
  - **Adcortyl Intra-articular / Intradermal 10mg/1ml suspension for injection ampoules** | 5 ampoule (POM) £4.47 DT = £4.47
  - **Kenalog** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - **Triamcinolone acetonide 40 mg per 1 ml** Kenalog Intra-articular / Intramuscular 40mg/1ml suspension for injection vials | 5 vial (POM) £7.45 DT = £7.45

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2.1 Cushing’s syndrome and disease

**Cushing’s Syndrome**

**Management**

Most types of Cushing’s syndrome are treated surgically, that which occasionally accompanies carcinoma of the bronchus is not usually amenable to surgery. Metyrapone p. 682 has been found helpful in controlling the symptoms of the disease; it is also used in other forms of Cushing’s syndrome to prepare the patient for surgery.

The dosages of metyrapone used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

Ketoconazole below may have a direct effect on corticotropic tumour cells in patients with Cushing’s disease. It is used under specialist supervision for treatment of endogenous Cushing’s syndrome.

**Other drugs used for Cushing’s syndrome and disease**

Pasireotide, p. 951

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**ENZYME INHIBITORS**

**Ketoconazole**

**DRUG ACTION** An imidazole derivative which acts as a potent inhibitor of cortisol and aldosterone synthesis by inhibiting the activity of 17α-hydroxylase, 11-hydroxylation steps and at higher doses the cholesterol side-chain cleavage enzyme. It also inhibits the activity of adrenal C17-20 lyase enzymes resulting in androgen synthesis inhibition, and may have a direct effect on corticotropic tumour cells in patients with Cushing’s disease.

**INDICATIONS AND DOSE**

**Endogenous Cushing’s syndrome (specialist use only)**

- **BY MOUTH**
  - Adult: Initially 400–600 mg daily in 2–3 divided doses, increased to 800–1200 mg daily; maintenance 400–800 mg daily in 2–3 divided doses, for dose titrations in patients with established dose, adjustments in adrenal insufficiency, or concomitant corticosteroid replacement therapy, consult product literature; maximum 1200 mg per day

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises max. dose 200 mg daily with concurrent use of cobicistat.

**IMPORTANT SAFETY INFORMATION**

**CHMP ADVICE: KETOCONAZOLE (JULY 2013)**

The CHMP has recommended that the marketing authorisation for oral ketoconazole to treat fungal infections should be suspended. The CHMP concluded that the risk of hepatotoxicity associated with oral ketoconazole is greater than the benefit in treating fungal infections. Doctors should review patients who are being treated with oral ketoconazole for fungal infections, with a view to stopping treatment or choosing an alternative treatment. Patients with a prescription of oral ketoconazole for fungal infections should be referred back to their doctors.

Oral ketoconazole for Cushing’s syndrome and topical products containing ketoconazole are not affected by this advice.

**CONTRA-INDICATIONS** Acquired QTc prolongation - Acute porphyrias p. 1058 - Avoid concomitant use of hepatotoxic drugs - Congenital QTc prolongation

**CAUTIONS** Pre-treatment liver enzymes should not exceed 2 times the normal upper limit - Risk of adrenal insufficiency

**INTERACTIONS**

- **Appendix 1: antifungals, azoles**

**SIDE-EFFECTS**

- **Common or very common** Adrenal insufficiency - diarrhoea - gastrointestinal discomfort - nausea - skin reactions - vomiting

- **Uncommon** Allergic conditions - alopecia - angioedema - asthenia - dizziness - drowsiness - headache - thrombocytopenia

- **Rare or very rare** Fever - hepatic disorders - taste altered

- **Frequency not known** Alcohol intolerance - appetite abnormal - arthralgia - azospermia - dry mouth - epistaxis - flatulence - fontanelle bulging - gynaecomastia - hot flush - insomnia - intracranial pressure increased - malaise - menstrual disorder - myalgia - nervousness - papilloedema - paraesthesia - peripheral oedema - photophobia - photosensitivity reaction - tongue discoloration

**SIDE-EFFECTS, FURTHER INFORMATION** Potentially life-threatening hepatotoxicity reported rarely with oral use.

www.getintopharma.com
Diabetes mellitus and hypoglycaemia

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used in women of child-bearing potential.

**PREGNANCY** Manufacturer advises avoid—teratogenic in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in breast milk.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid.

**MONITORING REQUIREMENTS**
- **Adrenal insufficiency** Monitor adrenal function within one week of initiation, then monthly for 6 months. When cortisol levels are normalised or close to target and effective dose established, monitor every 3–6 months as there is a risk of autoimmune disease development or exacerbation after normalisation of cortisol levels. If symptoms suggestive of adrenal insufficiency such as fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia, hyperkalaemia, and/or hypoglycaemia occur, measure cortisol levels and discontinue treatment temporarily (can be resumed thereafter at lower dose) or reduce dose if necessary.
- **Hepatotoxicity** Monitor liver function before initiation of treatment, then weekly for 1 month after initiation, then monthly for 6 months—more frequently if dose adjusted or abnormal lower limit detected. Reduce dose if liver enzymes increase less than 3 times the normal upper limit. If liver enzymes are raised to 3 times or greater the normal upper limit, discontinue treatment permanently.

**PATIENT AND CARER ADVICE** Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, or dark urine develop. Patients or their carers should also be told how to recognise signs of adrenal insufficiency.

**Driving and skilled tasks** Dizziness and somnolence may affect the performance of skilled tasks (e.g. driving).

**CONTRA-INDICATIONS** Adrenocortical insufficiency

**CAUTIONS** Avoid in Acute porphyrias p. 1058 · gross hypopituitarism (risk of precipitating acute adrenal failure) · hypertension on long-term administration · hypothyroidism (delayed response)

**INTERACTIONS** → Appendix 1: metyrapone

**SIDE-EFFECTS**
- **Common or very common** Dizziness · headache · hypotension · nausea · sedation · vomiting
- **Rare or very rare** Abdominal pain · adrenal insufficiency · allergic dermatitis · hirsutism
- **Frequency not known** Alopecia · bone marrow failure · hypertension

**PREGNANCY** Avoid (may impair biosynthesis of fetal-placental steroids).

**HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of delayed response).

**PATIENT AND CARER ADVICE**
- **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>2, 5, 21</th>
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<tr>
<td>Metopirone (non-proprietary)</td>
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<td>Metopirone 200 mg</td>
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<td>60 tablet ▼ £480.00 DT – £480.00</td>
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**Drug Action** Metyrapone is a competitive inhibitor of 11β-hydroxylase in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. Metyrapone may be used as a test of anterior pituitary function.

**Indications and Dose**

**Differential diagnosis of ACTH-dependent Cushing’s syndrome (specialist supervision in hospital)**
- **By Mouth**
  - Adult: 750 mg every 4 hours for 6 doses

**Management of Cushing’s syndrome (specialist supervision in hospital)**
- **By Mouth**
  - Adult: Usual dose 0.25–6 g daily, dose to be tailored to cortisol production, dose is either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed

**Resistant oedema due to increased aldosterone secretion in cirrhosis, nephrotic syndrome, and congestive heart failure (with glucocorticoid replacement therapy)** (specialist supervision in hospital)
- **By Mouth**
  - Adult: 3 g daily in divided doses

**Contra-Indications** Adrenocortical insufficiency

**Cautions** Avoid in Acute porphyrias p. 1058 · gross hypopituitarism (risk of precipitating acute adrenal failure) · hypertension on long-term administration · hypothyroidism (delayed response)

**Interactions** → Appendix 1: metyrapone

**Side-Effects**
- **Common or very common** Dizziness · headache · hypotension · nausea · sedation · vomiting
- **Rare or very rare** Abdominal pain · adrenal insufficiency · allergic dermatitis · hirsutism
- **Frequency not known** Alopecia · bone marrow failure · hypertension

**Pregnancy** Avoid (may impair biosynthesis of fetal-placental steroids).

**Hepatic Impairment** Manufacturer advises caution (risk of delayed response).

**Patient and Carer Advice**
- **Driving and skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving).

**Medicinal Forms** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

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<tr>
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<tr>
<td>Metopirone 250 mg</td>
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<td>Metopirone 250 mg capsules</td>
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<td>100 capsule ▼ £363.66 DT – £363.66</td>
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## 3 Diabetes mellitus and hypoglycaemia

### 3.1 Diabetes mellitus

**Diabetes**

**Description of condition**

Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia is caused by deficient insulin secretion or by resistance to the action of insulin. This leads to the abnormalities of carbohydrate, fat, and protein metabolism that are characteristic of diabetes mellitus.

Type 1 diabetes mellitus p. 684 and Type 2 diabetes mellitus p. 686 are the two most common classifications of diabetes. Other common types of diabetes are gestational diabetes (develops during pregnancy and resolves after delivery) and secondary diabetes (may be caused by pancreatic damage, hepatic cirrhosis, or endocrine disease). Treatment with endocrine, antiviral, or antipsychotic drugs may also cause secondary diabetes.

**Driving**

Drivers with diabetes may be required to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition depending on their treatment, the type of licence they hold, and whether they have diabetic complications (including episodes of hypoglycaemia). All drivers who are treated with insulin must inform the DVLA, with some exceptions for
temporary treatment. Detailed guidance on notification requirements, eligibility to drive, and precautions required, is available from the DVLA at www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive.

Advice from the DVLA
The DVLA recommends (2018) that drivers with diabetes need to be particularly careful to avoid hypoglycaemia and should be informed of the warning signs and actions to take. Drivers treated with insulin should always carry a glucose meter and blood-glucose strips when driving, and check their blood-glucose concentration no more than 2 hours before driving and every 2 hours while driving. More frequent self-monitoring may be required if, for any reason, there is a greater risk of hypoglycaemia, such as after physical activity or altered meal routine.

Blood-glucose should always be above 5 mmol/litre while driving. If blood-glucose falls to 5 mmol/litre or below, a snack should be taken. Drivers treated with insulin should ensure that a supply of fast-acting carbohydrate is always available in the vehicle. If blood-glucose is less than 4 mmol/litre, or warning signs of hypoglycaemia develop, the driver should not drive. If already driving, the driver should:

- stop the vehicle in a safe place;
- switch off the engine, remove keys from the ignition, and move from the driver’s seat;
- eat or drink a suitable source of sugar;
- wait until blood-glucose has returned to normal, before continuing journey.

Drivers must not drive if hypoglycaemia awareness has been lost and the DVLA must be notified; driving may resume if a medical report confirms that awareness has been regained.

Depending on the type of licence, notification and monitoring may also be necessary for drivers taking oral antidiabetic drugs, particularly those which carry a risk of hypoglycaemia (e.g. sulfonylureas, nateglinide p. 701, repaglinide p. 702).

Note: additional criteria apply for drivers of large goods or passenger carrying vehicles—consult DVLA guidance.

Alcohol
Alcohol can make the signs of hypoglycaemia less clear, and can cause delayed hypoglycaemia; specialist sources recommend that patients with diabetes should drink alcohol only in moderation, and when accompanied by food.

Oral glucose tolerance tests
The oral glucose tolerance test is used mainly for diagnosis of impaired glucose tolerance; it is not recommended or necessary for routine diagnostic use when severe symptoms of hyperglycaemia are present. In patients who have less severe symptoms and a blood-glucose concentration that does not establish or exclude diabetes (e.g. impaired fasting glycaemia), an oral glucose tolerance test may be required. It is also used to establish the presence of gestational diabetes.

An oral glucose tolerance test involves measuring the blood-glucose concentration after fasting, and then 2 hours after drinking a standard anhydrous glucose drink. Anhydrous glucose may alternatively be given as the appropriate amount of Polycal® or as Rapilose® OGTT oral solution.

HbA1c measurement
Glycated haemoglobin (HbA1c) forms when red blood cells are exposed to glucose in the plasma. The HbA1c test reflects average plasma glucose over the previous 2 to 3 months and provides a good indicator of glycaemic control. Unlike the oral glucose tolerance test, an HbA1c test can be performed at any time of the day and does not require any special preparation such as fasting.

HbA1c values are expressed in mmol of glycated haemoglobin per mol of haemoglobin (mmol/mol), a standardised unit specific for HbA1c created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). HbA1c values were previously aligned to the assay used in the Diabetes Control and Complications Trial (DCCT) and expressed as a percentage.

| Equivalent values |
|-------------------|------------------|
| IFCC-HbA1c (mmol/mol) | DCCT-HbA1c (%) |
| 42 | 6.0 |
| 48 | 6.5 |
| 53 | 7.0 |
| 59 | 7.5 |
| 64 | 8.0 |
| 69 | 8.5 |
| 75 | 9.0 |

Diagnosis
The HbA1c test is used for monitoring glycaemic control in both Type 1 diabetes p. 684 and Type 2 diabetes p. 685 and is now also used for diagnosis of type 2 diabetes. HbA1c should not be used for diagnosis in those with suspected type 1 diabetes, in children, during pregnancy, or in women who are up to two months postpartum. It should also not be used for patients who have:

- had symptoms of diabetes for less than 2 months;
- a high diabetes risk and are acutely ill;
- treatment with medication that may cause hypoglycaemia;
- Acute pancreatic damage;
- end-stage chronic kidney disease;
- HIV infection.

HbA1c used for diagnosis of diabetes should be interpreted with caution in patients with abnormal haemoglobin, anaemia, altered red cell lifespan, or who have had a recent blood transfusion.

Monitoring
HbA1c is also a reliable predictor of microvascular and macrovascular complications and mortality. Lower HbA1c is associated with a lower risk of long term vascular complications and patients should be supported to aim for an individualised HbA1c target (see Type 1 diabetes p. 684 and Type 2 diabetes p. 686).

HbA1c should usually be measured in patients with type 1 diabetes every 3 to 6 months, and more frequently if blood-glucose control is thought to be changing rapidly. Patients with type 2 diabetes should be monitored every 3 to 6 months until HbA1c and medication are stable when monitoring can be reduced to every 6 months.

HbA1c monitoring is invalid for patients with disturbed erythrocyte turnover or for patients with a lack of, or abnormal haemoglobin. In these cases, quality-controlled plasma glucose profiles, total glycated haemoglobin estimation (if there is abnormal haemoglobin), or fructosamine estimation can be used. Laboratory measurement of fructosamine concentration measures the glycated fraction of all plasma proteins over the previous 14 to 21 days but is a less accurate measure of glycaemic control than HbA1c.

Advanced Pharmacy Services
Patients with diabetes may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.
Type 1 diabetes

Description of condition
Type 1 diabetes describes an absolute insulin deficiency in which there is little or no endogenous insulin secretory capacity due to destruction of insulin-producing beta-cells in the pancreatic islets of Langerhans. This form of the disease has an auto-immune basis in most cases, and it can occur at any age, but most commonly before adulthood. Loss of insulin secretion results in hyperglycaemia and other metabolic abnormalities. If poorly managed, the resulting tissue damage has both short-term and long-term adverse effects on health; this can result in retinopathy, nephropathy, neuropathy, premature cardiovascular disease, and peripheral arterial disease.

Typical features in adult patients presenting with type 1 diabetes are hyperglycaemia (random plasma-glucose concentration above 11 mmol/litre), ketosis, rapid weight loss, a body mass index below 25 kg/m², age younger than 50 years, and a personal/family history of autoimmune disease (though not all features may be present).

Aims of treatment
Treatment is aimed at using insulin regimens to achieve as optimal a level of blood-glucose control as is feasible, while avoiding or reducing the frequency of hypoglycaemic episodes, in order to minimise the risk of long-term microvascular and macrovascular complications.

Disability from complications can often be prevented by early detection and active management of the disease (see Diabetic complications p. 688). The target for glycaemic control should be individualised for each patient, considering factors such as daily activities, aspirations, likelihood of complications, adherence to treatment, comorbidities, occupation and history of hyperglycaemia.

A target HbA1c concentration of 48 mmol/mol (6.5%) or lower is recommended in patients with type 1 diabetes. Blood-glucose concentration should be monitored at least four times a day, including before each meal and before bed. Patients should aim for:

- a fasting blood-glucose concentration of 5–7 mmol/litre on waking;
- a blood-glucose concentration of 4–7 mmol/litre before meals at other times of the day;
- a blood-glucose concentration of 5–9 mmol/litre at least 90 minutes after eating;
- a blood-glucose concentration of at least 5 mmol/litre when driving.

Overview
Type 1 diabetes requires insulin replacement, supported by active management of other cardiovascular risk factors, such as hypertension and high circulating lipids (see Diabetic complications p. 688). Insulin replacement therapy aims to recreate normal fluctuations in circulating insulin concentrations while supporting a flexible lifestyle with minimal restrictions. Flexible insulin therapy usually involves self-injecting multiple daily doses of insulin, with doses adjusted according to planned exercise, intended food intake and other factors, including current blood-glucose, which the patient needs to test on a regular basis.

Patients who have a BMI of 25 kg/m² or above (23 kg/m² or above for patients of South Asian or related ethnicity) who wish to improve their blood-glucose control while minimising their effective insulin dose, may benefit from metformin hydrochloride p. 692 [unlicensed indication] as an addition to insulin therapy.

Dietary control is important in both type 1 and type 2 diabetes and patients should receive advice from a diettian. Dietary advice should include information on weight control, cardiovascular risk, hyperglycaemic effects of different foods and appropriate changes in insulin doses according to food intake. Healthy eating can reduce cardiovascular risk and dietary modifications may be recommended to account for various associated features of diabetes such as excess weight and obesity, low body-weight, eating disorders, hypertension and renal failure. Patients with type 1 diabetes should be offered carbohydrate-counting training as part of a structured education programme.

Insulin therapy in type 1 diabetes
All patients with type 1 diabetes require insulin therapy (see also Insulin p. 685). Treatment should be initiated and managed by clinicians with relevant expertise; there are several different types of regimens.

Multiple daily injection basal–bolus insulin regimens
One or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue as the basal insulin; alongside multiple bolus injections of short-acting insulin before meals. This regimen offers flexibility to tailor insulin therapy with the carbohydrate load of each meal.

Mixed (biphasic) regimen
One, two, or three insulin injections per day of short-acting insulin with intermediate-acting insulin. The insulin preparations may be mixed by the patient at the time of injection, or a premixed product can be used.

Continuous subcutaneous insulin infusion (insulin pump)
A regular or continuous amount of insulin (usually in the form of a rapid-acting insulin analogue or soluble insulin), delivered by a programmable pump and insulin storage reservoir via a subcutaneous needle or cannula.

Recommended insulin regimens
Patients with type 1 diabetes should be offered multiple daily injection basal–bolus insulin regimens as the first-line choice. Twice-daily insulin detemir p. 717 should be offered as the long-acting basal insulin therapy. Once-daily insulin glargine p. 718 may be prescribed if insulin detemir is not tolerated, or if a twice–daily regimen is not acceptable to the patient. Insulin detemir may also be offered as an alternative once-daily regimen.

Patients who are using alternative basal regimens may continue if agreed targets are being achieved; other basal insulin regimens should be considered only if the recommended regimens do not deliver agreed targets. Non-basal–bolus insulin regimens (e.g. twice-daily mixed [biphasic], basal-only, or bolus-only regimens) are not recommended for adults with newly diagnosed type 1 diabetes.

A rapid-acting insulin analogue is recommended as the bolus or mealtime insulin replacement, rather than soluble human insulin or animal insulin (rarely used). The rapid-acting insulin analogue should be injected before meals—routine use after meals should be discouraged. Patients who have a strong preference for an alternative mealtime insulin should be offered their preferred insulin.

Alternatively, if a multiple daily injection basal–bolus regimen is not possible, a twice-daily mixed insulin regimen should be considered if it is preferred.

In patients who are using a twice-daily human insulin mixed regimen and have hypoglycaemia that affects their quality of life, a trial of a twice–daily analogue mixed insulin regimen should be considered.

Continuous subcutaneous insulin infusion (insulin pump) therapy, should only be offered to adults who suffer disabling hypoglycaemia, or, who have high HbA1c concentrations (69 mmol/mol [8.5%] or above) with multiple daily injection therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care. Insulin pump therapy should be initiated by a specialist team.
Insulin requirements

The dosage of insulin must be determined individually for each patient and should be adjusted as necessary according to the results of regular monitoring of blood-glucose concentrations. Persistent poor glucose control, leading to erratic insulin requirements or episodes of hypoglycaemia, may be due to many factors, including adherence, injection technique, injection site problems, blood-glucose monitoring skills, lifestyle issues (including diet, exercise and alcohol intake), psychological issues, and organic causes such as renal disease, thyroid disorders, coeliac disease, Addison’s disease or gastroparesis.

Injection, stress, accidental or surgical trauma can all increase the required insulin dose. Insulin requirements may be decreased (and therefore susceptibility to hypoglycaemia increased) by physical activity, intercurrent illness, reduced food intake, impaired renal function, and in certain endocrine disorders.

Risks of hypoglycaemia with insulin

Hypoglycaemia is an inevitable adverse effect of insulin treatment, and patients should be advised of the warning signs and actions to take (for guidance on management, see Hypoglycaemia p. 724).

Impaired awareness of hypoglycaemia can occur when the ability to recognise usual symptoms is lost, or when the symptoms are blunted or no longer present. Patients’ awareness of hypoglycaemia should be assessed annually using the Gold score or the Clarke score.

An increase in the frequency of hypoglycaemic episodes may reduce the warning symptoms experienced by the patient. Impaired awareness of symptoms below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia. Beta-blockers can also blunt hypoglycaemic awareness, by reducing warning signs such as tremor.

Loss of warning of hypoglycaemia among insulin-treated patients can be a serious hazard, especially for drivers and those in dangerous occupations. Advice should be given in line with the Driver and Vehicle Licensing Agency (DVLA) guidance (see Driving under Diabetes p. 682).

To restore the warning signs, episodes of hypoglycaemia must be minimised. Insulin regimens, doses and blood-glucose targets should be reviewed and continuous subcutaneous insulin infusion therapy and real-time continuous blood-glucose monitoring should be considered. Patients should receive structured education to ensure they are following the principles of a flexible insulin regimen correctly, with additional education regarding avoiding and treating hypoglycaemia for those who continue to have impaired awareness. Relaxation of individualised blood-glucose targets should be avoided as a strategy to improve impaired awareness of symptoms. If recurrent severe episodes of hypoglycaemia continue despite appropriate interventions, the patient should be referred to a specialist centre.

There is conflicting evidence regarding reports that some patients may experience loss of awareness of hypoglycaemia after transfer from animal to human insulin; clinical studies do not confirm that human insulin decreases hypoglycaemia awareness.

Manufacturers advise any switch between brands or formulation of insulin (including switching from animal to human insulin) should be done under strict supervision; a change in dose may be required.

Hypodermic equipment

Patients should be advised on the safe disposal of lancets, single-use syringes, and needles, and should be provided with suitable disposal containers. Arrangements should be made for the suitable disposal of these containers.

Lancets, needles, syringes, and accessories are listed under Hypodermic Equipment in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 of the Scottish Drug Tariff). The drug Tariffs can be access online at:

- Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusiness.hscni.net/services/2034.htm
- Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff

Advanced Pharmacy Services

Patients with type 1 diabetes may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Useful Resources


www.nice.org.uk/guidance/ng17

Insulin

Overview

For recommended insulin regimens see Type 1 diabetes p. 684 and Type 2 diabetes p. 686.

Insulin is a polypeptide hormone secreted by pancreatic beta-cells. Insulin increases glucose uptake by adipose tissue and muscles, and suppresses hepatic glucose release. The role of insulin is to lower blood-glucose concentrations in order to prevent hyperglycaemia and its associated microvascular, macrovascular and metabolic complications.

The natural profile of insulin secretion in the body consists of basal insulin (a low and steady secretion of background insulin that controls the glucose continuously released from the liver) and meal-time bolus insulin (secreted in response to glucose absorbed from food and drink).

Sources of insulin

Three types of insulin are available in the UK: human insulin, human insulin analogues, and animal insulin. Animal insulins are extracted and purified from animal sources (bovine or porcine insulin). Although widely used in the past, animal insulins are no longer initiated in people with diabetes but may still be used by some adult patients who cannot, or do not wish to, change to human insulins. Human insulins are produced by recombinant DNA technology and have the same amino acid sequence as endogenous human insulin. Human insulin analogues are produced in the same way as human insulins, but the insulin is modified to produce a desired kinetic characteristic, such as an extended duration of action or faster absorption and onset of action.

Immunological resistance to insulin is uncommon and true insulin allergy is rare. Human insulin and insulin analogues are less immunogenic than animal insulins.

Administration of insulin

Insulin is inactivated by gastro-intestinal enzymes and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin should be injected into a body area with plenty of subcutaneous fat—usually the abdomen (fastest absorption rate) or outer thighs/buttocks (slower absorption compared with the abdomen or inner thighs).
Absorption from a limb site can vary considerably (by as much as 20–40%) day-to-day, particularly in children. Local tissue reactions, changes in insulin sensitivity, injection site, blood flow, depth of injection, and the amount of insulin injected can all affect the rate of absorption. Increased blood flow around the injection site due to exercise can also increase insulin absorption.

Lipohypertrophy can occur due to repeatedly injecting into the same small area, and can cause erratic absorption of insulin, and contribute to poor glycaemic control. Patients should be advised not to use affected areas for further injection until the skin has recovered.

Lipohypertrophy can be minimised by using different injection sites in rotation. Injection sites should be checked for signs of infection, swelling, bruising, and lipohypertrophy before administration.

**Insulin preparations**

Insulin preparations can be broadly categorised into three groups based on their time-action profiles: short-acting insulins (including soluble insulin and rapid-acting insulins), intermediate-acting insulins and long-acting insulins. The duration of action of each particular type of insulin varies considerably from one patient to another, and needs to be assessed individually.

**Short-acting insulins**

Short-acting insulins have a short duration and a relatively rapid onset of action, to replicate the insulin normally produced by the body in response to glucose absorbed from a meal. These are available as soluble Insulin p. 685 (human and, bovine or porcine—both rarely used), and the rapid-acting insulin analogues (insulin aspart p. 713, insulin glulisine p. 714 and insulin lispro p. 714).

**Soluble insulin**

Soluble insulin is usually given subcutaneously but some preparations can be given intravenously and intramuscularly. For maintenance regimens, it is usual to inject the insulin 15 to 30 minutes before meals, depending on the insulin preparation used.

When injected intravenously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 1 and 4 hours, and a duration of action of up to 9 hours. When injected intramuscularly, soluble insulin has a short half-life of only a few minutes and its onset of action is instantaneous.

Soluble insulin administered intravenously is the most appropriate form of insulin for use in diabetic emergencies e.g. Diabetic ketoacidosis p. 689 and peri-operatively.

**Rapid-acting insulin**

Insulin aspart, insulin glulisine, and insulin lispro have a faster onset of action (within 15 minutes) and shorter duration of action (approximately 2–5 hours) than soluble insulin, and are usually given by subcutaneous injection.

For maintenance regimens, these insulins should ideally be injected immediately before meals. Rapid-acting insulin, administered before meals, has an advantage over short-acting soluble insulin in terms of improved glucose control, reduction of HbA1c, and reduction in the incidence of severe hypoglycaemia, including nocturnal hypoglycaemia.

The routine use of post-meal injections of rapid-acting insulin should be avoided—when given during or after meals, they are associated with poorer glucose control, an increased risk of high postprandial glucose concentration, and subsequent hypoglycaemia.

**Intermediate-acting insulin**

Intermediate-acting insulins (isophane insulin p. 716) have an intermediate duration of action, designed to mimic the effect of endogenous basal insulin. When given by subcutaneous injection, they have an onset of action of approximately 1–2 hours, a maximal effect at 3–12 hours, and a duration of action of 11–24 hours.

Isophane insulin is a suspension of insulin with protamine; it may be given as one or more daily injections alongside separate meal-time short-acting insulin injections, or mixed with a short-acting (soluble or rapid-acting) insulin in the same syringe—for recommended insulin regimens see Type 1 diabetes p. 684 and Type 2 diabetes below. Isophane insulin may be mixed with a short-acting insulin by the patient, or a pre-mixed biphasic insulin can be supplied (biphasic isophane insulin p. 715, biphasic insulin aspart p. 716 and biphasic insulin lispro p. 716).

Biphasic insulins (biphasic isophane insulin, biphasic insulin aspart, biphasic insulin lispro) are pre-mixed insulin preparations containing various combinations of short-acting insulin (soluble insulin or rapid-acting analogue insulin) and an intermediate-acting insulin.

The percentage of short-acting insulin varies from 15% to 50%. These preparations should be administered by subcutaneous injection immediately before a meal.

**Long-acting insulin**

Like intermediate-acting insulins, the long-acting insulins (protamine zinc insulin p. 719, insulin zinc suspension p. 718, insulin detemir p. 717, insulin glargine p. 718, insulin degludec p. 717) mimic endogenous basal insulin secretion, but their duration of action may last up to 36 hours. They achieve a steady-state level after 2–4 days to produce a constant level of insulin.

Insulin glargine and insulin degludec are given once daily and insulin detemir is given once or twice daily according to individual requirements. The older long-acting insulins, (insulin zinc suspension and protamine zinc insulin) are now rarely prescribed.

**Type 2 diabetes**

**Description of condition**

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance. Insufficient pancreatic insulin production also occurs progressively over time, resulting in hyperglycaemia. It is commonly associated with obesity, physical inactivity, raised blood pressure, dyslipidaemia and a tendency to develop thrombosis; therefore it increases cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

Type 2 diabetes typically develops later in life but is increasingly diagnosed in children, despite previously being considered a disease of adulthood.

**Aims of treatment**

Treatment is aimed at minimising the risk of long-term microvascular and macrovascular complications by effective blood-glucose control and maintenance of HbA1c at or below the target value set for each individual patient.

**Overview**

Weight loss, smoking cessation and regular exercise can help to reduce hyperglycaemia and reduce cardiovascular risk, and should be encouraged (with input from a dietician where appropriate). For guidance on reducing cardiovascular risk, see Cardiovascular disease risk assessment and prevention p. 189. Antidiabetic drugs should be prescribed to augment lifestyle interventions, when these changes are not adequate to control blood-glucose alone.
Antidiabetic drugs

There are several classes of non-insulin antidiabetic drugs available for the treatment of type 2 diabetes. The choice of drug should be based on effectiveness, safety, tolerability and should also take into consideration the patient’s comorbidities and concomitant medication. For recommended treatment regimens and the place in therapy of each drug, see Drug treatment, antidiabetic drugs (below).

Metformin hydrochloride p. 692 has an anti-hyperglycaemic effect, lowering both basal and postprandial blood-glucose concentrations. It does not stimulate insulin secretion and therefore, when given alone, does not cause hypoglycaemia. The dose of standard-release metformin hydrochloride should be increased gradually to minimise the risk of gastro-intestinal side effects. Modified-release metformin hydrochloride should be offered if standard treatment is not tolerated.

The sulfonylureas (glibenclamide p. 709, glyburide p. 709, glimepiride p. 710, tolbutamide p. 710) may cause hypoglycaemia; it is more likely with long-acting sulfonylureas such as glibenclamide, which have been associated with severe, prolonged and sometimes fatal cases of hypoglycaemia. Sulfonylureas are also associated with modest weight gain, probably due to increased plasma-insulin concentrations.

Acarbose p. 692 has a poorer anti-hyperglycaemic effect than many other antidiabetic drugs, including the sulfonylureas, metformin hydrochloride, and pioglitazone p. 710.

The meglitinides, nateglinide p. 701 and repaglinide p. 702, have a rapid onset of action and short duration of activity. These drugs can be used flexibly around mealtimes and adjusted to fit around individual eating habits which may be beneficial for some patients, but generally are a less preferred option than the sulfonylureas.

The thiazolidinedione, pioglitazone, is associated with several long-term risks and its ongoing benefit to the patient should be reviewed regularly and treatment stopped if response is insufficient (see Important safety information under pioglitazone).

The dipeptidylpeptidase-4 inhibitors (gliptins), alogliptin p. 694, linagliptin p. 694, sitagliptin p. 694, saxagliptin p. 695, and vildagliptin p. 697, do not appear to be associated with weight gain and have less incidence of hypoglycaemia than the sulfonylureas.

The sodium glucose co-transporter 2 inhibitors, canagliflozin p. 702, dapagliflozin p. 704, and empagliflozin p. 706, may be suitable for some patients when first-line options are not appropriate. Canagliflozin and empagliflozin can be beneficial in patients with type 2 diabetes and established cardiovascular disease.

Sodium glucose co-transporter 2 inhibitors are associated with a risk of diabetic ketoacidosis.

The glucagon-like peptide-1 receptor agonists, dulaglutide p. 698, exenatide p. 698, liraglutide p. 695 and lixisenatide p. 700, should be reserved for combination therapy when other treatment options have failed.

Polycystic ovary syndrome

Metformin hydrochloride (initiated by a specialist) is prescribed as an insulin sensitising drug in women with polycystic ovary syndrome who are not planning pregnancy (unlicensed indication). Long-term benefit or superiority over other treatment options has not been confirmed by good quality evidence. Metformin hydrochloride may improve short-term insulin sensitivity and reduce androgen concentrations, but there is insufficient supporting evidence that metformin improves weight gain, hirsutism, acne or regulation of the menstrual cycle. Treatment should only be initiated by a specialist. Metformin hydrochloride does not exert a hypoglycaemic action in non-diabetic patients except in overdose.

Drug treatment, antidiabetic drugs

Type 2 diabetes should initially be treated with a single oral antidiabetic drug. A target HbA1c concentration of 48 mmol/mol (6.5%) is generally recommended when type 2 diabetes is managed by diet and lifestyle alone or when combined with a single antidiabetic drug not associated with hypoglycaemia (such as metformin hydrochloride). Adults prescribed a single drug associated with hypoglycaemia (such as a sulphonylurea), or two or more antidiabetic drugs in combination, should usually aim for an HbA1c concentration of 53 mmol/mol (7.0%). Targets may differ and should be individualised and agreed with each patient.

Note: Consider relaxing the target HbA1c level on a case-by-case basis, with particular consideration for people who are older, frail, or where tight blood-glucose control is not appropriate or poses a high risk of the consequences of hypoglycaemia.

If HbA1c concentrations are poorly controlled despite treatment with a single drug (usually considered to be a rise of HbA1c to 58 mmol/mol (7.5%) or higher), the drug treatment should be intensified, alongside reinforcement of advice regarding diet, lifestyle, and adherence to drug treatment.

When two or more antidiabetic drugs are prescribed, an HbA1c concentration target of 53 mmol/mol (7.0%) is recommended for patients in which it is appropriate, but a relaxation of the target may be more appropriate in some individual cases (for example, those at high risk of the consequences of hypoglycaemia, poor life expectancy, or significant comorbidities).

Initial treatment

Metformin hydrochloride is recommended as the first choice for initial treatment for all patients, due to its positive effect on weight loss, reduced risk of hypoglycaemic events and the additional long-term cardiovascular benefits associated with its use.

If metformin is contra-indicated or not tolerated, see Alternative non-metformin regimens below.

First intensification of treatment

If metformin hydrochloride (alongside modification to diet) does not control HbA1c to below the agreed threshold, treatment should be intensified, and metformin hydrochloride combined with one of the following:

- a sulfonylurea (glibenclamide, glimepiride, glipizide, tolbutamide);
- Pioglitazone;
- a dipeptidylpeptidase-4 inhibitor (lixisenatide, sitagliptin, vildagliptin);
- a sodium glucose co-transporter 2 inhibitor (canagliflozin, dapagliflozin or empagliflozin) only when sulfonylureas are contra-indicated or not tolerated, or if the patient is at significant risk of hypoglycaemia or its consequences.

Elderly patients or those with renal impairment are at particular risk of hypoglycaemia; if a sulfonylurea is indicated, a shorter-acting sulfonylurea, such as glimepiride p. 709 or tolbutamide p. 710 should be prescribed. The place in therapy of alogliptin p. 694 (a dipeptidylpeptidase-4 inhibitor) is not yet known.

Second intensification of treatment

If dual therapy is unsuccessful, treatment should be intensified again, and one of the following triple therapy regimens prescribed:

- Metformin hydrochloride p. 692 and a dipeptidylpeptidase-4 inhibitor and a sulfonylurea;
- Metformin hydrochloride and pioglitazone p. 710 and a sulfonylurea;
Diabetes mellitus and hypoglycaemia

- Metformin hydrochloride and a sulfonylurea and one of the sodium glucose co-transporter 2 inhibitors;
- Metformin hydrochloride and pioglitazone and a sodium glucose co-transporter 2 inhibitor (canagliflozin p. 702 or empagliflozin p. 706; note that dapagliflozin is not recommended in a triple therapy regimen with pioglitazone).

Alternatively, it may be appropriate to start insulin-based treatment at this stage—see Drug treatment, insulin.

**Glucagon-like peptide-1 receptor agonists**

If triple therapy with metformin hydrochloride and two other oral drugs is tried and is not effective, not tolerated or contra-indicated, a glucagon-like peptide-1 receptor agonist may be prescribed as part of a triple combination regimen with metformin hydrochloride and a sulfonylurea.

These should only be prescribed for patients who have a BMI of 35 kg/m² or above (adjusted for ethnicity) and who also have specific psychological or medical problems associated with obesity; or for those who have a BMI lower than 35 kg/m² but for whom insulin therapy would have significant occupational implications or if the weight loss associated with glucagon-like peptide-1 receptor agonists would benefit other significant obesity-related comorbidities.

After 6 months, the drug should be reviewed and only continued if there has been a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body-weight).

Insulin should only be prescribed in combination with a glucagon-like peptide-1 receptor agonist under specialist care advice and with ongoing support from a consultant-led multidisciplinary team.

**Alternative non-metformin regimens**

If metformin is contra-indicated or not tolerated, initial treatment should be single therapy with:

- a sulfonylurea (glibenclamide p. 709, gliclazide, glimepiride p. 709, glipizide p. 710, or tolbutamide) (first choice) or
- a dipeptidyl peptidase-4 inhibitor (linagliptin p. 694, saxagliptin p. 695, sitagliptin p. 696, or vildagliptin p. 697), or
- Pioglitazone.

The sodium glucose co-transporter 2 inhibitors canagliflozin, dapagliflozin p. 704, or empagliflozin are also options for monotherapy when metformin is contra-indicated or not tolerated, only if a dipeptidylpeptidase-4 inhibitor would otherwise be prescribed and neither a sulfonylurea nor pioglitazone is appropriate.

Repaglinide p. 702 is also an effective alternative option for single therapy, but it has a limited role in treatment because, should an intensification of treatment be required, it is not licensed to be used in any combination other than with metformin hydrochloride; it would therefore require a complete change of treatment in those patients who have started it due to intolerance or contra-indication to metformin.

**Intensification**

If the initial single drug does not control HbA1c to below the agreed threshold, treatment should be intensified and one of the following dual combinations prescribed:

- a dipeptidylpeptidase-4 inhibitor and pioglitazone;
- a dipeptidylpeptidase-4 inhibitor and a sulfonylurea; or
- Pioglitazone and a sulfonylurea.

If dual therapy does not provide adequate glucose control, insulin-based treatment should be considered—see Drug treatment, insulin.

**Drug treatment, insulin**

When indicated for intensification, insulin (see also, Insulin p. 685) should be started with a structured support programme covering insulin dose titration, injection technique, self-monitoring, and knowledge of dietary effects and glucose control. Metformin hydrochloride should be continued unless it is contra-indicated or not tolerated. Other antidiabetic drugs should be reviewed and stopped if necessary.

Recommended insulin regimens include:

- human isophane insulin p. 716 injected once or twice daily, according to requirements;
- a human isophane insulin in combination with a short-acting insulin, administered either separately or as a pre-mixed (biphasic) human insulin preparation (this may be particularly appropriate if HbA1c is 75 mmol/mol (9.0%) or higher);
- Insulin detemir p. 717 or insulin glargine p. 718 as an alternative to human isophane insulin. This can be preferable if a once daily injection would be beneficial (for example if assistance is required to inject insulin), or if recurrent symptomatic hypoglycaemic episodes are problematic, or if the patient would otherwise need twice-daily human isophane insulin injections in combination with oral glucose-lowering drugs. Also consider switching to insulin detemir or insulin glargine from human isophane insulin if significant hypoglycaemia is problematic, or in patients who cannot use the device needed to inject human isophane insulin;
- biphasic preparations (pre-mixed) that include a short-acting human analogue insulin (rather than short-acting human soluble insulin) can be preferable for patients who prefer injecting insulin immediately before a meal, or if hypoglycaemia is a problem, or if blood-glucose concentrations rise markedly after meals.

When starting insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (fasting) glucose. Patients who are prescribed a basal insulin regimen (human isophane insulin, insulin detemir or insulin glargine) should be monitored for the need for short-acting insulin before meals (or a biphasic insulin preparation).

Patients who are prescribed a biphasic insulin should be monitored for the need for a further injection of short-acting insulin before meals or for a change to a basal-bolus regimen with human isophane insulin or insulin detemir or insulin glargine if blood-glucose control remains inadequate.

**Advanced Pharmacy Services**

Patients with type 2 diabetes may be eligible for the New Medicines Service / Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

**Useful Resources**


**Diabetic complications**

10-May-2018

**See also**

Diabetes p. 682
Type 1 diabetes p. 684
Type 2 diabetes p. 686

**Diabetes and cardiovascular disease**

Diabetes is a strong risk factor for cardiovascular disease.

Other risk factors for cardiovascular disease that should
also be addressed are: smoking, hypertension, obesity, and dyslipidaemia. Cardiovascular risk in patients with diabetes can be further reduced by the use of an ACE inhibitor (or an angiotensin-II receptor antagonist) and lipid‐regulating drugs. For full guidance on the assessment and prevention of cardiovascular disease, see Cardiovascular disease risk assessment and prevention p. 189.

Diabetic nephropathy

In diabetic patients with nephropathy, blood pressure should be reduced to the lowest achievable level to slow the rate of decline of glomerular filtration rate and reduce proteinuria. Provided there are no contra-indications, all diabetic patients with nephropathy causing proteinuria or with established microalbuminuria should be treated with an ACE inhibitor or an angiotensin-II receptor antagonist, even if the blood pressure is normal. ACE inhibitors or angiotensin-II receptor antagonists should also be given as monotherapy, or combined therapy, in patients with chronic kidney disease and proteinuria, to reduce the rate of progression of chronic kidney disease. ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in patients with renal impairment.

See also treatment of hypertension in diabetes in Hypertension p. 140.

Diabetic neuropathy

Optimal diabetic control is beneficial for the management of painful neuropathy. Monotherapy with antidepressant drugs, including tricyclics (such as amitriptyline hydrochloride p. 372 and imipramine hydrochloride p. 376 [unlicensed use]), duloxetine p. 367, and venlafaxine p. 368 [unlicensed use] should be considered in patients for the treatment of painful diabetic peripheral neuropathy. Antiepileptic drugs, such as pregabalin p. 324 and gabapentin p. 315, can also be considered. Opioid analgesics in combination with gabapentin can be considered if pain is not controlled with monotherapy.

In autonomic neuropathy, diabetic diarrhoea can often be managed by antidiarrhoeal preparations such as loperamide p. 299 [unlicensed use], or codeine phosphate p. 454 as the best alternative; other antidiarrhoeal preparations can also be tried. Erythromycin (especially when given intravenously) may be useful in postural hypotension.

In diabetic autonomic neuropathy, diabetic diarrhoea can often be managed by antidiarrhoeal preparations [both unlicensed use], or codeine phosphate p. 454 as the best alternative; other antidiarrhoeal preparations can also be tried. Erythromycin p. 539 (especially when given intravenously) may be beneficial for gastroparesis [unlicensed use]. In neuropathic postural hypotension, increased salt intake and the use of the mineralocorticoid fludrocortisone acetate p. 576 [unlicensed use] may help by increasing plasma volume, but uncomfortable oedema is a common side-effect. Fludrocortisone can also be combined with flurbiprofen p. 1140 and ephedrine hydrochloride p. 272 [both unlicensed]. Midodrine [unlicensed], an alpha agonist, may also be useful in postural hypotension.

Gustatory sweating can be treated with an antimuscarinic such as propantheline bromide p. 86; side-effects are common. See also, the management of hyperhidrosis (Hyperhidrosis p. 1264).

In some patients with neuropathic oedema, ephedrine hydrochloride [unlicensed use] offers effective relief. See also the management of Erectile dysfunction p. 812.

Visual impairment

Optimal diabetic control (HbA1c ideally around 7% or 53 mmol/mol) and blood pressure control (<130/80 mmHg) should be maintained to prevent onset and progression of diabetic eye disease.

Diabetic ketoacidosis

Management


To restore circulating volume if systolic blood pressure is below 90 mmHg (adjusted for age, sex, and medication as appropriate), give 500 mL sodium chloride 0.9% by intravenous infusion over 10–15 minutes; repeat if blood pressure remains below 90 mmHg and seek senior medical advice.

When blood pressure is over 90 mmHg, sodium chloride 0.9% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance; see guideline or suggested regimen.

Include potassium chloride in the fluids unless anuria is suspected; adjust according to plasma-potassium concentration (measure at 60 minutes, 2 hours, and 2 hourly thereafter; measure hourly if outside the normal range).

Start an intravenous insulin infusion: soluble insulin should be diluted (and mixed thoroughly) with sodium chloride 0.9% intravenous infusion to a concentration of 1 unit/mL; infuse at a fixed rate of 0.1 units/kg/hour.

Established subcutaneous therapy with long-acting insulin analogues (insulin detemir p. 717 or insulin glargine p. 718) should be continued during treatment of diabetic ketoacidosis.

Monitor blood-ketone and blood-glucose concentrations hourly and adjust the insulin infusion rate accordingly. Blood-ketone concentration should fall by at least 0.5 mmol/litre/hour and blood-glucose concentration should fall by at least 3 mmol/litre/hour.

Once blood-glucose concentration falls below 14 mmol/litre, glucose 10% should be given by intravenous infusion (into a large vein through a large-gauge needle) at a rate of 125 mL/hour, in addition to the sodium chloride 0.9% infusion.

Continue insulin infusion until blood-ketone concentration is below 0.3 mmol/litre, blood pH is above 7.3 and the patient is able to eat and drink; ideally give subcutaneous fast-acting insulin and a meal, and stop the insulin infusion 1 hour later.

The management of hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion are usually necessary and slower rehydration may be required.

Diabetes, surgery and medical illness

Management of diabetes during surgery

Peri-operative management of blood-glucose concentrations depends on factors including the required duration of fasting, timing of surgery (morning or afternoon), usual treatment regimen (insulin, antidiabetic drugs or diet), prior glycaemic control, other co-morbidities, and the likelihood that the patient will be capable of self-managing their diabetes in the immediate post-operative period. All patients should have emergency treatment for hypoglycaemia written on their drug chart on admission.
Note: The following recommendations provide general guidance for the management of diabetes during surgery. Local protocols and guidelines should be followed where they exist.

Use of insulin during surgery

Elective surgery—minor procedures in patients with good glycaemic control

Patients usually treated with insulin who have good glycaemic control (HbA1c less than 69 mmol/mol or 8.5%) and are undergoing minor procedures, can be managed during the operative period by adjustment of their usual insulin regimen, which should be adjusted depending on the type of insulin usually prescribed, following detailed local protocols (which should also include intravenous fluid management, monitoring and control of electrolytes and avoidance of hyperchloremic metabolic acidosis). On the day before the surgery, the patient’s usual insulin should be given as normal, other than once daily long-acting insulin analogues, which should be given at a dose reduced by 20%.

Elective surgery—major procedures or poor glycaemic control

Patients usually treated with insulin, who are either undergoing major procedures (surgery requiring a long fasting period of more than one missed meal) or whose diabetes is poorly controlled, will usually require a variable rate intravenous insulin infusion (continued until the patient is eating/drinking and stabilised on their previous glucose-lowering medication).

The aim is to achieve and maintain glucose concentration within the usual target range (6–10 mmol/litre; but up to 12 mmol/litre is acceptable) by infusing a constant rate of glucose-containing fluid as a substrate, while also infusing insulin at a variable rate. Detailed local protocols should be consulted. In general, the following steps should be followed:

- on the day before surgery, once daily long-acting insulin analogues should be given at 80% of the usual dose; otherwise the patient’s usual insulin should be given as normal;
- on the day of surgery and throughout the intra-operative period, once daily long-acting insulin analogues should be continued at 80% of the usual dose; all other insulin should be stopped until the patient is eating and drinking again after surgery;
- on the day of surgery, start an intravenous substrate infusion of potassium chloride with glucose and sodium chloride. p. 1039 (based on serum electrolytes which must be measured frequently), and infuse at a rate appropriate to the patient’s fluid requirements. To prevent hypoglycaemia, this infusion must not be stopped while the insulin infusion is running;
- a variable rate intravenous insulin infusion of soluble human insulin p. 712 in sodium chloride 0.9% p. 1040 (made either according to locally agreed protocols or using prefilled syringes) should be given via a syringe pump at an initial infusion rate determined by bedside capillary blood-glucose measurement. Hourly blood-glucose measurement should be undertaken to ensure that the intravenous insulin infusion rate is correct for at least the first 12 hours; the insulin infusion rate should be adjusted according to local protocol to maintain blood-glucose concentrations within the usual target range (6–10 mmol/litre; up to 12 mmol/litre is acceptable);
- intravenous glucose 20% p. 1041 should be given if blood-glucose drops below 6 mmol/litre, and blood-glucose checked every hour, to prevent a drop below 4 mmol/litre. If blood-glucose drops below 4 mmol/litre, intravenous glucose 20% should be adjusted and blood-glucose checked every 15 minutes, until blood-glucose is above 6 mmol/litre (testing can then revert to hourly). If blood-glucose rises above 12 mmol/litre, check ketones and consider other signs of diabetic ketoacidosis (see Diabetic ketoacidosis p. 689).

Conversion back to a subcutaneous insulin should not begin until the patient can eat and drink without nausea or vomiting. Once the patient’s previous insulin regimen is restarted, the usual insulin dose may require adjustment, as insulin requirements can change due to post-operative stress, infection or altered food intake.

Previous subcutaneous basal-bolus regimens, should be restarted when the first postoperative meal-time insulin dose is due (e.g. with breakfast or lunch); doses may need adjustment due to postoperative stress, infection or altered food intake. The variable rate intravenous insulin infusion and intravenous fluids should be continued until 30–60 minutes after the first meal-time short-acting insulin dose. If the patient was previously on a long-acting insulin analogue, this should have been continued throughout the operative period at 80% of the normal dose, and should now just continue at that same dose until the patient leaves hospital; only the short-acting insulin needs to be restarted as above.

Previous subcutaneous twice-daily mixed insulin regimens, should be restarted before breakfast or an evening meal (not at any other time). The variable rate intravenous insulin infusion should be maintained for 30–60 minutes after the first subcutaneous insulin dose has been given.

Patients who were previously managed with a continuous subcutaneous insulin infusion should be referred to a specialist team. The subcutaneous infusion should be restarted at the normal basal rate, not at bedtime, and the insulin infusion continued until the next meal bolus has been given.

Patients not previously prescribed insulin, who are to start a subcutaneous insulin regimen post-surgery, should have an insulin dose calculated with advice from a specialist diabetes team, considering the patient’s sensitivity to insulin, degree of glycaemic control, weight, age, and the average hourly insulin dose used in the peri-operative period.

Emergency surgery

Patients with diabetes (type 1 and 2) requiring emergency surgery, should always have their blood-glucose, blood or urinary ketone concentration, serum electrolytes and serum bicarbonate checked before surgery. If ketones are high or bicarbonate is low, blood gases should also be checked. If ketoadiposis is present, recommendations for Diabetic ketoacidosis p. 689 should be followed immediately, and surgery delayed if possible. If there is no acidosis, intravenous fluids and an insulin infusion should be started and managed as for major elective surgery (above).

Use of antidiabetic drugs during surgery

Manipulation of antidiabetic drug may not be appropriate for all surgery or for all patients; particularly when fasting time is more than one missed meal, in patients with poor glycaemic control, and when there is risk of renal injury. In these cases, a variable rate intravenous insulin p. 712 infusion should be used as for major elective surgery (above), and usual antidiabetic medication adjusted in the peri-operative period. Insulin is almost always required in medical and surgical emergencies.

When insulin is required and given during surgery, acarbose p. 692, meglitinides, sulfonylureas, pioglitazone p. 710, dipeptidyl peptidase-4 inhibitors (gliptins) and sodium glucose co-transporter 2 inhibitors should be stopped once the insulin infusion is commenced and not restarted until the patient is eating and drinking normally. Glucagon-like peptide-1 receptor agonists can be continued as normal during the insulin infusion.

If elective minor surgical procedures only require a short-fasting period (just one missed meal), it may be possible to adjust antidiabetic drugs to avoid a switch to a variable rate intravenous insulin infusion; normal drug treatment can continue.
In suitable cases, acarbose, nateglinide p. 701 and repaglinide p. 702 can be continued with just the dose omitted on the morning of surgery if fasting (the morning dose may be given if the patient is not fasting and surgery is in the afternoon).

Pioglitazone, dipeptidylpeptidase-4 inhibitors (gliptins) and glucagon-like peptide-1 receptor agonists can be taken as normal during the whole peri-operative period.

Sodium glucose co-transporter 2 inhibitors should be omitted on the day of surgery and not restarted until the patient is stable; their use during periods of dehydration and acute illness is associated with an increased risk of developing diabetic ketoacidosis.

Sulfonylureas are associated with hypoglycaemia in the fasted state and therefore should always be omitted on the day of surgery until the patient is eating and drinking again. Capillary blood-glucose should be checked hourly. If hyperglycaemia occurs, an appropriate dose of subcutaneous rapid-acting insulin may be given. A second dose may be given 2 hours later, and a variable rate intravenous insulin infusion considered if hyperglycaemia persists.

Metformin hydrochloride p. 692 is renally excreted; renal impairment may lead to accumulation and lactic acidosis during surgery. If only one meal will be missed during surgery, and the patient has an eGFR greater than 60 mL/minute/1.73m² and a low risk of acute kidney injury (and the procedure does not involve administration of contrast media), it may be possible to continue metformin hydrochloride throughout the peri-operative period—just the lunchtime dose should be omitted if the usual dose is prescribed three times a day.

If the patient will miss more than one meal or there is significant risk of the patient developing acute kidney injury, metformin hydrochloride should be stopped when the pre-operative fast begins. A variable rate intravenous insulin infusion should be started if the metformin hydrochloride dose is more than once daily. Otherwise insulin should only be started if blood-glucose concentration is greater than 12 mmol/litre on two consecutive occasions. Metformin should not be recommenced until the patient is eating and drinking again, and renal function has been assessed. There is no need to stop metformin hydrochloride after contrast medium in patients missing only one meal or who have an eGFR greater than 60 mL/minute/1.73m². If contrast medium is to be used, and eGFR is less than 60 mL/minute/1.73m², metformin should be omitted on the day of the procedure and for the following 48 hours.

Use of antidiabetic drugs during medical illness
Manufacturers of some antidiabetic drugs recommend that they may need to be replaced temporarily with insulin during intercurrent illness when the drug is unlikely to control hyperglycaemia (such as myocardial infarction, coma, severe infection, trauma and other medical emergencies). Consult individual product literature.

Sodium glucose co-transport 2 inhibitors are associated with increased risk of developing diabetic ketoacidosis during periods of dehydration, stress, surgery, trauma, acute medical illness or any other catabolic state, and should be used with caution during these times. The MHRA has advised (2016) that these drugs should be temporarily stopped in patients who are hospitalised for acute serious illness until the patient is medically stable.

Diabetes mellitus

Management of pre-existing diabetes

Women with pre-existing diabetes who are planning on becoming pregnant should aim to keep their HbA1c concentration below 48 mmol/mol (6.5%) if possible without causing problematic hypoglycaemia. Any reduction towards this target is likely to reduce the risk of congenital malformations in the newborn.

Women with pre-existing diabetes who are planning to become pregnant should be advised to take folic acid at the dose for women who are at high-risk of conceiving a child with a neural tube defect, see folic acid p. 1025.

Overview

Oral antidiabetic drugs

All oral antidiabetic drugs, except metformin hydrochloride p. 692, should be discontinued before pregnancy (or as soon as an unplanned pregnancy is identified) and substituted with insulin therapy. Women with diabetes may be treated with metformin hydrochloride p. 692 [unlicensed in type 1 diabetes] as an adjunct or alternative to insulin in the preconception period and during pregnancy, when the likely benefits from improved blood-glucose control outweigh the potential for harm. Metformin hydrochloride p. 692 can be continued, or glibenclamide p. 709 resumed, immediately after birth and during breastfeeding for those with pre-existing Type 2 diabetes p. 686. All other antidiabetic drugs should be avoided while breastfeeding.

Insulin

Limited evidence suggests that the rapid-acting insulin analogues (insulin aspart p. 713 and insulin lispro p. 714) can be associated with fewer episodes of hypoglycaemia, a reduction in postprandial glucose excursions and an improvement in overall glycaemic control compared with regular human insulin.

Glargine p. 716 is the first-choice for long-acting insulin during pregnancy, however in women who have good blood-glucose control before pregnancy with the long-acting insulin analogues (insulin detemir p. 717 or insulin glargine p. 718), it may be appropriate to continue using them throughout pregnancy.

Continuous subcutaneous insulin infusion p. 712 (insulin pump therapy) may be appropriate for pregnant women who have difficulty achieving glycaemic control with multiple daily injections of insulin p. 712 without significant disabling hypoglycaemia.

All women treated with insulin p. 712 during pregnancy should be aware of the risks of hypoglycaemia, particularly in the first trimester, and should be advised to always carry a fast-acting form of glucose, such as dextrose tablets or a glucose-containing drink. Pregnant women with Type 1 diabetes p. 684 should also be prescribed glucagon p. 724 for use if needed.

Women with pre-existing diabetes treated with insulin p. 712 during pregnancy are at increased risk of hypoglycaemia in the postnatal period and should reduce their insulin immediately after birth. Blood-glucose levels should be monitored carefully to establish the appropriate dose.

Medication for diabetic complications

Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists should be discontinued and replaced with an alternative antihypertensive suitable for use in pregnancy before conception or as soon as pregnancy is confirmed (see Hypertension in pregnancy under Endocrine system).
Hypertension p. 140). Statins should not be prescribed during pregnancy and should be discontinued before a planned pregnancy.

**Gestational diabetes**

Women with gestational diabetes who have a fasting plasma glucose below 7 mmol/litre at diagnosis, should first attempt a change in diet and exercise alone in order to reduce blood-glucose. If blood-glucose targets are not met within 1 to 2 weeks, metformin hydrochloride below may be prescribed [unlicensed use]. Insulin p. 712 may be prescribed if metformin is contra-indicated or not acceptable, and may also be added to treatment if metformin is not effective alone.

Women who have a fasting plasma glucose above 7 mmol/litre at diagnosis should be treated with insulin in 712 immediately, with or without metformin hydrochloride below, in addition to a change in diet and exercise.

Women who have a fasting plasma glucose between 6 and 6.9 mmol/litre alongside complications such as macrosomia or hydramnios should be considered for immediate insulin p. 712 treatment, with or without metformin hydrochloride below.

Glibenclamide p. 709 [unlicensed use] may be considered for women from 11 weeks gestation (after organogenesis) who cannot tolerate metformin, or for those in whom metformin is not effective and do not wish to have insulin therapy.

Women with gestational diabetes should discontinue hypoglycaemic treatment immediately after giving birth.

**Useful Resources**


www.sign.ac.uk/assets/sign116.pdf


www.nice.org.uk/guidance/ng3

**BLOOD GLUCOSE LOWERING DRUGS > ALPHA GLUCOSIDASE INHIBITORS**

**Acarbose**

**Drug action** Acarbose, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose.

**Indications and dose**

Diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs

- **By mouth**
  - Adult: Initially 50 mg daily, then increased to 50 mg 3 times a day for 6–8 weeks, then increased if necessary to 100 mg 3 times a day (max. per dose 200 mg 3 times a day)

**Contra-Indications** Hernia - inflammatory bowel disease - predisposition to partial intestinal obstruction - previous abdominal surgery

**Caution** May enhance hypoglycaemic effects of insulin and sulfonylureas (hypoglycaemic episodes may be treated with oral glucose but not with sucrose)

**Interactions** → Appendix 1: acarbose

**Side-effects**

- Common or very common Diarrhoea (may need to reduce dose) - gastrointestinal discomfort - gastrointestinal disorders

- Uncommon Nausea - vomiting

- Rare or very rare Hepatic disorders - oedema

- Frequency not known Acute generalised exanthematous pustulosis (AGEP) - thrombocytopenia

**Side-effects, further information**

Antacids containing magnesium and aluminium salts unlikely to be beneficial for treating side effects.

- **Pregnancy** Avoid.

- **Breast feeding** Avoid.

- **Hepatic impairment** Manufacturer advises avoid in severe impairment.

- **Renal impairment** Avoid if eGFR less than 25 mL/minute/1.73 m².

- **Monitoring requirements** Monitor liver function.

- **Directions for administration** Tablets should be chewed with first mouthful of food or swallowed whole with a little liquid immediately before food.

- **Patient and carer advice** Antacids unlikely to be beneficial for treating side-effects. To counteract possible hypoglycaemia, patients receiving insulin or a sulfonylurea as well as acarbose need to carry glucose (not sucrose—acarbose interferes with sucrose absorption). Patients should be given advice on how to administer acarbose tablets.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Acarbose (Non-proprietary)
  - Acarbose 50 mg Acarbose 50mg tablets | 90 tablet POM £15.00 DT + £11.51
  - Acarbose 100 mg Acarbose 100mg tablets | 90 tablet POM £27.00 DT + £13.03

**Blood glucose lowering drugs > Biguanides**

**Metformin hydrochloride**

**Drug action** Metformin exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose; since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

**Indications and dose**

Type 2 diabetes mellitus [monotherapy or in combination with other antidiabetic drugs (including insulin)]

- **By mouth using immediate-release medicines**
  - Child 10–17 years (specialist use only): Initially 500 mg once daily, dose to be adjusted according to response at intervals of at least 1 week, maximum daily dose to be given in 2–3 divided doses; maximum 2 g per day
  - Adult: Initially 500 mg once daily for at least 1 week, dose to be taken with breakfast, then 500 mg twice daily for at least 1 week, dose to be taken with breakfast and evening meal, then 500 mg 3 times a day, dose to be taken with breakfast, lunch and evening meal; maximum 2 g per day

- **By mouth using modified-release medicines**
  - Adult: Initially 500 mg once daily, then increased if necessary up to 2 g once daily, dose increased gradually, every 10–15 days, dose to be taken with evening meal, alternatively increased to 1 g twice daily, dose to be taken with meals, alternative dose only to be used if control not achieved with once daily dose regimen. If control still not achieved then change to standard release tablets
Type 2 diabetes mellitus [reduction in risk or delay of onset]

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult 18-74 years: Initially 500 mg once daily, then increased if necessary up to 2 g once daily, dose increased gradually, every 10–15 days, dose to be taken with evening meal, for further information on risk factors—consult product literature

### Polycystic ovary syndrome

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: Initially 500 mg once daily for 1 week, dose to be taken with breakfast, then 500 mg twice daily for 1 week, dose to be taken with breakfast and evening meal, then 1.5–1.7 g daily in 2–3 divided doses

### Hepatic impairment

- Rare or very rare

### Interactions

- **CAUTIONS** Risk factors for lactic acidosis
  - **CAUTIONS, FURTHER INFORMATION**
    - Risk factors for lactic acidosis: Manufacturer advises caution in chronic stable heart failure (monitor cardiac function), and concomitant use of drugs that can acutely impair renal function; interrupt treatment if dehydration occurs, and avoid in conditions that can acutely worsen renal function, or cause tissue hypoxia.

### Side-effects

- Common or very common: Abdominal pain - appetite decreased, diarrhoea (usually transient), gastrointestinal disorder - nausea - taste altered - vomiting
- Rare or very rare: Hepatitis - lactic acidosis (discontinue), skin reactions - vitamin B12 absorption decreased

### Side-effects, further information

- Gastro-intestinal side-effects are initially common with metformin, and may persist in some patients, particularly when very high doses are given. A slow increase in dose may improve tolerability.

### Pregnancy

- Can be used in pregnancy for both pre-existing and gestational diabetes. Women with gestational diabetes should discontinue treatment after giving birth.

### Breastfeeding

- May be used during breast-feeding in women with pre-existing diabetes.

### Renal impairment

- In adults: Manufacturer advises avoid if eGFR is less than 30 mL/minute/1.73 m².
- In children: Manufacturer advises avoid if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m².

#### Dose adjustments

- In children: Manufacturer advises consider dose reduction in moderate impairment.
- In adults: Manufacturer advises reduce dose in moderate impairment—consult product literature.

### Monitoring requirements

- Determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected).

### Prescribing and dispensing information

- In adults: Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of metformin modified release; not suitable if dose of standard-release tablets more than 2 g daily.

### Patient and carer advice

- Manufacturer advises that patients and their carers should be informed of the risk of lactic acidosis and told to seek immediate medical attention if symptoms such as dyspnoea, muscle cramps, abdominal pain, hypothermia, or asthenia occur.

### Medicines for Children

- Metformin is accepted for restricted use in patients for whom a once daily preparation is not licensed.

### National funding/access decisions

- Glucophage® SR

- Scottish Medicines Consortium (SMC) decisions

- The Scottish Medicines Consortium has advised (September 2009) that Glucophage® SR is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in adult patients who are intolerant of standard-release metformin, and in whom the prolonged-release tablet allows the use of a dose of metformin not previously tolerated, or in patients for whom a once daily preparation offers a clinically significant benefit.

### Medicinal forms

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.

#### Modified-release tablet

- **CAUTIONARY AND ADVISORY LABELS 21, 25**

- **Metformin hydrochloride (Non-proprietary)**
  - Metformin hydrochloride 500 mg: Metformin 500 mg modified-release tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £4.00
  - Bolamyn SR (Teva UK Ltd)
    - Metformin hydrochloride 500 mg: Bolamyn SR 500mg tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £4.00
    - Metformin hydrochloride 1 gram: Bolamyn SR 1000mg tablets | 28 tablet (30) £5.06 | 56 tablet (60) £10.13 DT = £6.40
  - Gluciant SR (Consilient Health Ltd)
    - Metformin hydrochloride 500 mg: Gluciant SR 500mg tablets | 28 tablet (30) £2.51 | 56 tablet (60) £5.03 DT = £4.00
    - Metformin hydrochloride 750 mg: Gluciant SR 750mg tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £6.40
    - Metformin hydrochloride 1 gram: Gluciant SR 1000mg tablets | 28 tablet (30) £4.26 | 56 tablet (60) £8.52 DT = £6.40
  - Glucophage SR (Merck Serono Ltd)
    - Metformin hydrochloride 500 mg: Glucophage SR 500mg tablets | 28 tablet (30) £1.99 | 56 tablet (60) £4.00 DT = £4.00
    - Metformin hydrochloride 750 mg: Glucophage SR 750mg tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £6.40
    - Metformin hydrochloride 1 gram: Glucophage SR 1000mg tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £6.40
  - Meijumet (Medreich Plc)
    - Metformin hydrochloride 500 mg: Meijumet 500mg modified-release tablets | 28 tablet (30) £2.66 | 56 tablet (60) £5.32 DT = £4.00
    - Metformin hydrochloride 750 mg: Meijumet 750mg modified-release tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £6.40
    - Metformin hydrochloride 1 gram: Meijumet 1000mg modified-release tablets | 28 tablet (30) £4.26 | 56 tablet (60) £8.52 DT = £6.40
  - Metabet SR (Actavis UK Ltd, Morningside Healthcare Ltd)
    - Metformin hydrochloride 500 mg: Metabet SR 500mg tablets | 28 tablet (30) £1.99-2.61 | 56 tablet (60) £3.22-5.32 DT = £4.00
    - Metformin hydrochloride 750 mg: Metabet SR 750mg tablets | 28 tablet (30) £3.20 | 56 tablet (60) £6.40 DT = £6.40
    - Metformin hydrochloride 1 gram: Metabet SR 1000mg tablets | 28 tablet (30) £4.53 | 56 tablet (60) £9.06 DT = £6.40
  - Metuxtran SR (Accord Healthcare Ltd)
    - Metformin hydrochloride 500 mg: Metuxtran SR 500mg tablets | 28 tablet (30) £1.99 | 56 tablet (60) £3.22 DT = £4.00
    - Metformin hydrochloride 750 mg: Metuxtran SR 750mg tablets | 28 tablet (30) £2.38 DT = £4.00
    - Metformin hydrochloride 1 gram: Metuxtran SR 1000mg tablets | 28 tablet (30) £3.82 DT = £6.40
  - Sukkarto SR (Morningside Healthcare Ltd)
    - Metformin hydrochloride 500 mg: Sukkarto SR 500mg tablets | 28 tablet (30) £1.44 | 56 tablet (60) £2.88 DT = £6.40
    - Metformin hydrochloride 750 mg: Sukkarto SR 750mg tablets | 28 tablet (30) £1.92 | 56 tablet (60) £3.83 DT = £6.40

- Yaltormin SR (Wockhardt UK Ltd)
  - Metformin hydrochloride 500 mg: Yaltormin SR 500mg tablets | 28 tablet (30) £1.99 | 56 tablet (60) £3.22 DT = £4.00
  - Metformin hydrochloride 750 mg: Yaltormin SR 750mg tablets | 28 tablet (30) £2.38 DT = £4.00
  - Metformin hydrochloride 1 gram: Yaltormin SR 1000mg tablets | 28 tablet (30) £3.82 DT = £6.40
Alogliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, alogliptin above, metformin hydrochloride p. 692.

INDICATIONS AND DOSE
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with other pioglitazone or insulin

INTERACTIONS → Appendix 1: alogliptin · metformin

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Vipidia (Takeda UK Ltd)
  Alogliptin (as Alogliptin benzoate) 6.25 mg  Vipidia 6.25mg tablets
  28 tablet (P413) £61.90 DT + £5.93 30 tablet (P413) £74.98 DT + £6.36
  Alogliptin (as Alogliptin benzoate) 12.5 mg  Vipidia 12.5mg tablets
  28 tablet (P413) £113.80 DT + £10.44
  Alogliptin (as Alogliptin benzoate) 25 mg  Vipidia 25mg tablets
  28 tablet (P413) £186.75 DT + £17.81

Linagliptin

DRUG ACTION
Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

INDICATIONS AND DOSE
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control

INTERACTIONS → Appendix 1: linagliptin

MEDICINAL FORMS
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with other pioglitazone or insulin if existing treatment fails to achieve adequate glycaemic control

SIDE-EFFECTS
- Cough
- Rare or very rare  Angioedema, skin reactions
- Frequency not known  Pancreatitis

Alogliptin

DRUG ACTION
Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

INDICATIONS AND DOSE
Type 2 diabetes mellitus in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control

INTERACTIONS → Appendix 1: alogliptin

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Vipidia (Takeda UK Ltd)
  Alogliptin (as Alogliptin benzoate) 6.25 mg  Vipidia 6.25mg tablets
  28 tablet (P413) £61.90 DT + £5.93 30 tablet (P413) £74.98 DT + £6.36
  Alogliptin (as Alogliptin benzoate) 12.5 mg  Vipidia 12.5mg tablets
  28 tablet (P413) £113.80 DT + £10.44
  Alogliptin (as Alogliptin benzoate) 25 mg  Vipidia 25mg tablets
  28 tablet (P413) £186.75 DT + £17.81

Note:
- Alogliptin is contraindicated in combination with metformin and pioglitazone.
- Alogliptin is not recommended in patients with moderate to severe hepatic impairment.
- Alogliptin is not recommended in patients with moderate to severe renal impairment.
- Alogliptin is not recommended in patients with severe renal impairment.
- Alogliptin is not recommended in patients with severe hepatic impairment.
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- Alogliptin is not recommended in patients with severe hepatic impairment.
Saxagliptin

**DRUG ACTION**
Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control.

- **BY MOUTH**
  - Adult: 5 mg once daily, for further information on use with other antidiabetic drugs—consult product literature.

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CAUTIONS**
Elderly—history of pancreatitis.

**INTERACTIONS**
Appendix 1: saxagliptin.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - dizziness - fatigue - headache - increased risk of infection - skin reactions - vomiting
- **Uncommon** Pancreatitis
- **Rare or very rare** Angioedema
- **Frequency not known** Constipation - nausea

**SIDE-EFFECTS, FURTHER INFORMATION**
Discontinue if symptoms of acute pancreatitis occur such as persistent, severe abdominal pain.

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated if patient has a history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

**PREGNANCY**
Avoid unless essential—toxicity in animal studies.

**BREAST FEEDING**
Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in moderate impairment; avoid in severe impairment (risk of increased exposure).

**RENAL IMPAIRMENT**
Use with caution in severe impairment.

**Dose adjustments**
Reduce dose to 2.5 mg once daily in moderate to severe impairment.

**MONITORING REQUIREMENTS**
Determine renal function before treatment and periodically thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**
The Scottish Medicines Consortium has advised that saxagliptin (Onglyza®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as triple therapy in combination with metformin and a sulfonylurea, as an alternative to existing dipeptidyl peptidase-4 inhibitors, when treatment with metformin and a sulfonylurea is inadequate (November 2013).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
| Onglyza (AstraZeneca UK Ltd) | Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg | £31.60 DT = £31.60 |
| Saxagliptin (as Saxagliptin hydrochloride) 5 mg | £31.60 DT = £31.60 |

Linagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, linagliptin p. 694, metformin hydrochloride p. 692.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin.

- **BY MOUTH**
  - Adult: 1 tablet twice daily, based on patient’s current metformin dose

**INTERACTIONS**
Appendix 1: linagliptin - metformin.

**NATIONAL FUNDING/ACCESS DECISIONS**
The Scottish Medicines Consortium has advised (May 2015) that linagliptin plus metformin combination tablets (Jentadueto®) are accepted for restricted use within NHS Scotland for the treatment of patients with type 2 diabetes mellitus in combination with insulin, as an adjunct to diet and exercise to improve glycaemic control when a combination of insulin and metformin alone is inadequate. It is restricted to use in the treatment of patients for whom a combination of linagliptin and metformin is an appropriate choice of therapy and the fixed doses are considered appropriate.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
| Jentadueto (Boehringer Ingelheim Ltd) |
| Linagliptin 2.5 mg, Metformin hydrochloride 850 mg | £33.26 DT + £33.26 |
| Linagliptin 2.5 mg, Metformin hydrochloride 1000 mg | £33.26 DT + £33.26 |

**INTERACTIONS**
Appendix 1: linagliptin - metformin.

**NATIONAL FUNDING/ACCESS DECISIONS**
The Scottish Medicines Consortium has advised that linagliptin (Trajenta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as monotherapy when both metformin and a sulfonylurea are inappropriate (January 2013), and in combination with metformin when addition of a sulfonylurea is inappropriate (December 2011).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
| Trajenta (Boehringer Ingelheim) |
| Linagliptin 5 mg Trajenta 5mg tablets | 28 tablet £33.26 DT + £33.26 |

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CAUTIONS**
Elderly—history of pancreatitis.

**INTERACTIONS**
Appendix 1: linagliptin - metformin.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - dizziness - fatigue - headache - increased risk of infection - skin reactions - vomiting
- **Uncommon** Pancreatitis
- **Rare or very rare** Angioedema
- **Frequency not known** Constipation - nausea

**SIDE-EFFECTS, FURTHER INFORMATION**
Discontinue if symptoms of acute pancreatitis occur such as persistent, severe abdominal pain.

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated if patient has a history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

**PREGNANCY**
Avoid unless essential—toxicity in animal studies.

**BREAST FEEDING**
Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in moderate impairment; avoid in severe impairment (risk of increased exposure).

**RENAL IMPAIRMENT**
Use with caution in severe impairment.

**Dose adjustments**
Reduce dose to 2.5 mg once daily in moderate to severe impairment.

**MONITORING REQUIREMENTS**
Determine renal function before treatment and periodically thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**
The Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised that linagliptin (Trajenta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as monotherapy when both metformin and a sulfonylurea are inappropriate (January 2013), and in combination with metformin when addition of a sulfonylurea is inappropriate (December 2011).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
| Trajenta (Boehringer Ingelheim) |
| Linagliptin 5 mg Trajenta 5mg tablets | 28 tablet £33.26 DT + £33.26 |
Saxagliptin with dapagliflozin

The properties listed below are those particular to the combination only. For the properties of the components please consider, saxagliptin p. 695, dapagliflozin p. 704.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus not controlled by metformin and/or a sulfonylurea with either saxagliptin or dapagliflozin

- **BY MOUTH**
  - Adult 18-74 years: 5/10 mg once daily
  - Adult 75 years and over: Initiation not recommended

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Dose of concomitant sulfonylurea may need to be reduced.

**DOSE EQUIVALENCE AND CONVERSION**
- Dose expressed as x/y mg saxagliptin/dapagliflozin.

**INTERACTIONS** → Appendix 1: dapagliflozin - saxagliptin

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT**
Dose adjustments Manufacturer advises avoid if eGFR less than 60 mL/minute/1.73 m² (ineffective).

**PATIENT AND CARER ADVICE**
Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (July 2017) that saxagliptin with dapagliflozin 5 mg/10 mg (Qtern®) is accepted for restricted use within NHS Scotland for the treatment of patients with type 2 diabetes mellitus in combination with metformin when the use of a sulfonylurea is inappropriate, only if:
- metformin and/or a sulfonylurea, in combination with dapagliflozin or saxagliptin, do not provide adequate glycaemic control; or
- the patient is already being treated with the free combination of dapagliflozin and saxagliptin.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Qtern (AstraZeneca UK Ltd)
  - Saxagliptin (as Saxagliptin hydrochloride) 5 mg, Dapagliflozin (as Dapagliflozin propanediol monohydrate) 10 mg
  - Tablets: 28 tablet (PFR) £40.56 DT + £40.56

Saxagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, saxagliptin p. 695, metformin hydrochloride p. 692.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin

- **BY MOUTH**
  - Adult: 1 tablet twice daily, based on patient’s current metformin dose

**INTERACTIONS** → Appendix 1: metformin - saxagliptin

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (May 2013) that Komboglyze® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone and when the addition of a sulfonylurea is inappropriate.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Komboglyze (AstraZeneca UK Ltd)
  - Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg, Metformin hydrochloride 850 mg
  - Tablets: 56 tablet (PFR) £31.60 DT + £31.60
  - Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg, Metformin hydrochloride 1 gram
  - Tablets: 56 tablet (PFR) £31.60 DT + £31.60

**Sitagliptin**

**DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control

- **BY MOUTH**
  - Adult: 100 mg once daily, for further information on use with other antidiabetic drugs—consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CONTRA-INDICATIONS** Ketoadicosis

**INTERACTIONS** → Appendix 1: sitagliptin

**SIDE-EFFECTS**
- Common or very common
  - Headache
- Uncommon
  - Constipation
  - Dizziness
  - Skin reactions
- Frequency not known
  - Angioedema
  - Back pain
  - Cutaneous vasculitis
  - Interstitial lung disease
  - Joint disorders
  - Myalgia
  - Pancreatitis acute
  - Renal impairment
  - Stevens-Johnson syndrome
  - Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION** Discontinue if symptoms of acute pancreatitis occur such as persistent, severe abdominal pain.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**RENAI IMPAIRMENT**
Dose adjustments Manufacturer advises reduce dose to 50 mg once daily if eGFR 30–45 mL/minute/1.73 m². Manufacturer advises reduce dose to 25 mg once daily if eGFR less than 30 mL/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
SMC No. 607/10
The Scottish Medicines Consortium has advised (July 2010) that sitagliptin (Januvia®) is accepted for restricted use within NHS Scotland as monotherapy, to improve glycaemic control in patients with type 2 diabetes mellitus, for whom both metformin and sulfonylureas are not appropriate.

SMC No. 1083/15
The Scottish Medicines Consortium has advised (September 2015) that sitagliptin (Januvia®) is accepted for use within NHS Scotland as an add-on to insulin (with or without metformin) to improve glycaemic control in adults with type 2 diabetes mellitus.
**Sitatgliptin with metformin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, sitagliptin p. 696, metformin hydrochloride p. 692.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or pioglitazone or insulin

- **BY MOUTH**
  - Adults: 1 tablet twice daily

**INTERACTIONS** → Appendix 1: metformin · sitagliptin

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (July 2008) that Janumet® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus when the addition of a sulfonylurea to metformin is not appropriate; it is also accepted for use in NHS Scotland in combination with a sulfonylurea in patients inadequately controlled on maximum tolerated doses of metformin and a sulfonylurea.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Januvia (Merck Sharp &amp; Dohme Ltd)</th>
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<tbody>
<tr>
<td>Sitagliptin (as Sitagliptin phosphate) 25 mg</td>
<td>Januvia 25 mg tablets</td>
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<tr>
<td>Sitagliptin (as Sitagliptin phosphate) 50 mg</td>
<td>Januvia 50 mg tablets</td>
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<td>Sitagliptin (as Sitagliptin phosphate) 100 mg</td>
<td>Januvia 100 mg tablets</td>
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**Vildagliptin**

27-Mar-2019

**DRUG ACTION**

Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs (including insulin) if existing treatment fails to achieve adequate glycaemic control

- **BY MOUTH**
  - Adults: 50 mg twice daily. Reduce dose to 50 mg once daily in the morning when used in dual combination with a sulfonylurea. For further information on use with other antidiabetic drugs—consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CONTRA-INDICATIONS**

Ketoacidosis

**CAUTIONS**

Manufacturer advises avoid in severe heart failure—no information available

**INTERACTIONS** → Appendix 1: vildagliptin

**SIDE-EFFECTS**

Common or very common: Dizziness

Common: Neuropathy

Uncommon: Arthralgia · constipation · headache · hypoglycaemia · peripheral oedema

Rare or very rare: Increased risk of infection

Frequency not known: Hepatitis · myalgia · pancreatitis · skin reactions

SIDE-EFFECTS, FURTHER INFORMATION

**Pancreatitis**

- **Discontinue if symptoms of acute pancreatitis occur, such as persistent severe abdominal pain.**
- **Liver toxicity**
  - Rare reports of liver dysfunction; discontinue if jaundice or other signs of liver dysfunction occur.
- **PREGNANCY**
  - Avoid—toxicity in animal studies.
- **BREAST FEEDING**
  - Avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 435/07

The Scottish Medicines Consortium has advised (April 2008) that vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with metformin when addition of a sulfonylurea is inappropriate.

SMC No. 57/09

The Scottish Medicines Consortium has advised (October 2009) that vildagliptin (Galvus®) is accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with a sulfonylurea for those patients where the maximal dose of a sulfonylurea as monotherapy is insufficient, or if metformin is inappropriate.

SMC No. 826/12

The Scottish Medicines Consortium has advised (January 2013) that vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of type 2 diabetes mellitus in adults when treatment with metformin or a sulfonylurea is inappropriate.

SMC No. 875/13

The Scottish Medicines Consortium has advised (December 2013) that vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in adults as triple therapy in combination with metformin and a sulfonylurea, as an alternative to existing dipeptidyl peptidase-4 inhibitors, when treatment with metformin and a sulfonylurea is inadequate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Galvus (Novartis Pharmaceuticals UK Ltd)</th>
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<tr>
<td>Vildagliptin 50 mg</td>
<td>Galvus 50 mg tablets</td>
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</table>
Vildagliptin with metformin  

The properties listed below are those particular to the combination only. For the properties of the components please consider, vildagliptin p. 697, metformin hydrochloride p. 692.

- **INTERACTIONS** → Appendix 1: metformin · vildagliptin

- **NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 477/08

The Scottish Medicines Consortium has advised (July 2008) that vildagliptin with metformin (Eucreas®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone or those already treated with vildagliptin and metformin as separate tablets.

- **MEDICAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 21

  - Eucreas (Novartis Pharmaceuticals UK Ltd)

Vildagliptin 50 mg, Metformin hydrochloride 850 mg  Eucreas 50mg/850mg tablets  | 60 tablet (PSt)  £35.68 DT + £35.68

Vildagliptin 50 mg, Metformin hydrochloride 1 gram  Eucreas 50mg/1000mg tablets  | 60 tablet (PSt)  £35.68 DT + £35.68

**BLOOD GLUCOSE LOWERING DRUGS**

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

**Dulaglutide**

- **DRUG ACTION** Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist that augments glucose-dependent insulin secretion, and slows gastric emptying.

- **INDICATIONS AND DOSE**

  - **Type 2 diabetes mellitus as monotherapy if metformin inappropriate**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 0.75 mg once weekly

  - **Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 1.5 mg once weekly

  - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
    - Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

- **CONTRA-INDICATIONS** Severe gastro-intestinal disease—no information available

- **CAUTIONS** Congestive heart failure—no information available

- **INTERACTIONS** → Appendix 1: dulaglutide

- **SIDE-EFFECTS**

  - Common or very common
    - Appetite decreased.
    - Atrioventricular block.
    - Constipation.
    - Diarrhoea.
    - Fatigue.
    - Gastrointestinal discomfort.
    - Gastrointestinal disorders.
    - Hypoglycaemia.
    - Nausea.
    - Sinus tachycardia.
    - Vomiting.

  - Rare or very rare
    - Anaphylactic reaction.
    - Angioedema.
    - Pancreatitis acute (discontinue)

  - **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

  - **BREAST FEEDING** Manufacturer advises avoid—no information available.

  - **RENAL IMPAIRMENT** Manufacturer advises avoid in severe impairment and end stage renal disease—no information available.

  - **HANDLING AND STORAGE** Refrigerated storage is usually necessary (2 °C – 8 °C). In use, may be stored unrefrigerated for up to 14 days at a temperature not above 30 °C.

  - **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer dulaglutide injection. Acute pancreatitis. Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek medical attention if symptoms such as persistent, severe abdominal pain develop.

  - **Missed doses** If a dose is missed, it should be administered as soon as possible only if there are at least 3 days until the next scheduled dose; if less than 3 days remain before the next scheduled dose, the missed dose should not be taken and the next dose should be taken at the normal time.

**Exenatide**

- **DRUG ACTION** Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

- **INDICATIONS AND DOSE**

  - **Type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination**
    - **BY SUBCUTANEOUS INJECTION USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 5 micrograms twice daily for at least 1 month, then increased if necessary up to 10 micrograms twice daily, dose to be taken within 1 hour before 2 main meals (at least 6 hours apart)
    - **BY SUBCUTANEOUS INJECTION USING MODIFIED-RELEASE MEDICINES**
      - Adult: 2 mg once weekly
**Type 2 diabetes mellitus in combination with basal insulin alone or with metformin or pioglitazone (or both)**

- **BY SUBCUTANEOUS INJECTION USING IMMEDIATE-RELEASE MEDICINES**
- **Adult:** Initially 5 micrograms twice daily for at least 1 month, then increased if necessary up to 10 micrograms twice daily, dose to be taken within 1 hour before 2 main meals (at least 6 hours apart)

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Dose of concomitant sulfonylurea may need to be reduced.

**SIDE-EFFECTS**

- **Common or very common**
  - Appetite decreased - asthenia - constipation - diarrhoea - dizziness - gastrointestinal discomfort - gastrointestinal disorders - headache - nausea - skin reactions - vomiting

- **Uncommon**
  - Alopecia - burping - drowsiness - hyperhidrosis - renal impairment - taste altered

- **Frequency not known**
  - Angioedema - pancreatitis acute

**CAUTIONS**

- Elderly: may cause weight loss greater than 1.5 kg weekly - pancreatitis

**INTERACTIONS**

- **Appendix 1: exenatide**

**CONTRA-INDICATIONS**

- Ketoacidosis - severe gastrointestinal disease

**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**CAUTIONARY AND ADVISORY LABELS**

- **Byetta (AstraZeneca UK Ltd)**
  - Exenatide 250 microgram per 1 ml Byetta 10 micrograms/0.04 ml solution for injection 2.4 ml pre-filled pen
  - 1 pre-filled disposable injection
  - £81.89 DT £81.89

- **Bydureon (AstraZeneca UK Ltd)**
  - Exenatide 2 mg Bydureon 2 mg powder and solvent for prolonged-release suspension for injection pre-filled pen
  - 4 pre-filled disposable injection
  - £73.36 DT £73.36

**Liraglutide**

- **14-Feb-2019**

**DRUG ACTION**

- Liraglutide binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

**INDICATIONS AND DOSE**

**SAXENDA®**

- **Adjunct in weight management [in conjunction with dietary measures and increased physical activity in individuals with a body mass index (BMI) of 30 kg/m² or more, or in individuals with a BMI of 27 kg/m² or more in the presence of at least one weight-related co-morbidity]**

  - **BY SUBCUTANEOUS INJECTION**
  - **Adult:** Initially 0.6 mg once daily, then increased in steps of 0.6 mg; dose to be increased at intervals of at least 1 week; consider discontinuation if escalation to the next dose is not tolerated for 2 consecutive weeks. Discontinue if at least 5% of initial body-weight has not been lost after 12 weeks at maximum dose; maximum 3 mg per day

**VICTOZA®**

- **Type 2 diabetes mellitus [monotherapy (if metformin inappropriate), or in combination with other antidiabetic drugs]**

  - **BY SUBCUTANEOUS INJECTION**
  - **Adult:** Initially 0.6 mg once daily for at least 1 week, then increased to 1.2 mg once daily for at least 1 week, then increased if necessary to 1.8 mg once daily, for information on use with other antidiabetic drugs—consult product literature
DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Dose of concomitant insulin or sulfonylurea may need to be reduced.

CONTRA-INDICATIONS
Diabetic gastroparesis - inflammatory bowel disease - severe congestive heart failure - no information available

SAXENDA®
Concomitant use with other products for weight management - elderly 75 years or over (limited information) - obesity secondary to endocrinological or eating disorders

VICTOZA®
Diabetic ketoacidosis

INTERACTIONS
Appendix 1: Liraglutide

SIDE-EFFECTS

Common or very common
- Appetite decreased - asthma - burping - constipation - diarrhea - dizziness - dry mouth - gallbladder disorders - gastrointestinal discomfort - gastrointestinal disorders - headache - increased risk of infection - insomnia - nausea - skin reactions - taste altered - toothache - vomiting

Uncommon
- Dehydration - malaise - pancreatitis - renal impairment - tachycardia

Frequency not known
- Angioedema - dyspnoea - hypotension - oedema - palpitations - pancreatitis acute (discontinue permanently) - thyroid disorder

SIDE-EFFECTS, FURTHER INFORMATION
Discontinue if symptoms of acute pancreatitis occur, such as persistent, severe abdominal pain.

PREGNANCY
Manufacturer advises avoid — toxicity in animal studies (recommendation also supported by tertiary sources).

BREAST FEEDING
Manufacturer advises avoid — no information available; animal studies suggest that transfer into milk is low, but excretion into human milk not known (a tertiary source confirms lack of information in human lactation, but also states that risk to infants appears to be negligible. [Eft] Blood glucose monitoring of the infant should be considered). [Eft]

HEPATIC IMPAIRMENT

SAXENDA®
Manufacturer advises use with caution in mild to moderate impairment; avoid in severe impairment (risk of decreased exposure).

VICTOZA®
Manufacturer advises avoid in severe impairment (risk of decreased exposure).

RENAL IMPAIRMENT

SAXENDA®
Manufacturer advises avoid if creatinine clearance less than 30 mL/minute.

VICTOZA®
Manufacturer advises avoid in end-stage renal disease.

HANDLING AND STORAGE
Manufacturer advises store in a refrigerator (2–8°C) — after first use can also be stored below 30°C and used within 1 month; keep cap on pen to protect from light.

PATIENT AND CARER ADVICE
Manufacturer advises patients and their carers should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek immediate medical attention if symptoms develop. Manufacturer advises patients and their carers should be informed of the potential risk of dehydration in relation to gastrointestinal side-effects and advised to take precautions to avoid fluid depletion; they should also be informed of the symptoms of cholelithiasis and cholecystitis, and of increased heart rate.

SAXENDA®
Missed doses
Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Saxenda (Novo Nordisk Ltd)
Liraglutide 6 mg per 1 ml Saxenda 6 mg/mL solution for injection 3 ml pre-filled disposable injection £196.20

Victoza (Novo Nordisk Ltd)
Liraglutide 6 mg per 1 ml Victoza 6 mg/mL solution for injection 3 ml pre-filled disposable injection £78.48 DT — £78.48 | 3 pre-filled disposable injection £117.72

Combinations available: Insulin degludec with liraglutide, p. 717

Lixisenatide
26-Mar-2019

DRUG ACTION
Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

INDICATIONS AND DOSE
Type 2 diabetes mellitus in combination with oral antidiabetic drugs (e.g. metformin, pioglitazone, or a sulfonylurea) or basal insulin, or both, when adequate glycaemic control has not been achieved with these drugs

BY SUBCUTANEOUS INJECTION

Adult: Initially 10 micrograms once daily for 14 days, then increased to 20 micrograms once daily, dose to be taken within 1 hour before the first meal of the day or the evening meal

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Dose of concomitant sulfonylurea or insulin may need to be reduced.

CONTRA-INDICATIONS
Ketoacidosis - severe gastrointestinal disease

CAUTIONS
History of pancreatitis

INTERACTIONS
Appendix 1: Lixisenatide

SIDE-EFFECTS

Common or very common
- Back pain - cystitis - diarrhea - dizziness - drowsiness - dyspepsia - headache - increased risk of infection - nausea - vomiting

Uncommon
- Urticaria

Frequency not known
- Pancreatitis acute

SIDE-EFFECTS, FURTHER INFORMATION
Manufacturer advises discontinue if symptoms of acute pancreatitis occur, such as persistent, severe abdominal pain.

CONCEPTION AND CONTRACEPTION
Women of childbearing age should use effective contraception.

PREGNANCY
Avoid — toxicity in animal studies.

BREAST FEEDING
Avoid — no information available.

RENAL IMPAIRMENT
Use with caution if eGFR less than 30 mL/minute; 1.73 m² — no information available.

PATIENT AND CARER ADVICE
Some oral medications should be taken at least 1 hour before or 4 hours after lixisenatide injection — consult product literature for details.

Missed doses
If a dose is missed, inject within 1 hour before the next meal — do not administer after a meal.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (August 2013) that lixisenatide (Lyxumia®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with oral antidiabetic drugs or basal insulin (or both), when adequate glycaemic control has not been achieved with these drugs; use is restricted to patients in whom a GLP-1 agonist is
appropriate, as an alternative to an existing GLP-1 agonist (exenatide or lixisenatide).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - **CAUTIONARY AND ADVISORY LABELS**
      - **10**
        - **Lyxumia** (Sanofi)
        - Lixisenatide 50 microgram per 1 ml Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen 1 pre-filled disposable injection £31.67 DT + £31.67
        - Lixisenatide 100 microgram per 1 ml Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen 2 pre-filled disposable injection £57.93 DT + £57.93
        - **Combinations available:** Insulin glargine with lixisenatide, p. 718

**Semaglutide**

- **DRUG ACTION** Semaglutide binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppress glucagon secretion, and slow gastric emptying.

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus [monotherapy (if metformin inappropriate) or in combination with other antidiabetic drugs]**
    - **BY SUBCUTANEOUS INJECTION**
    - **Adult:** Initially 0.25 mg once weekly for 4 weeks, then increased to 0.5 mg once weekly for at least 4 weeks, then increased if necessary to 1 mg once weekly, for information on use with other antidiabetic drugs—consult product literature.
    - **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
      - **Manufacturer advises dose of concomitant insulin or sulfonylurea may need to be reduced.**

- **CONTRA-INDICATIONS** Diabetic ketoacidosis • severe congestive heart failure (no information available)

- **CAUTIONS** Diabetic retinopathy (in patients treated with insulin) • history of pancreatitis

- **INTERACTIONS** → Appendix 1: semaglutide

- **SIDE-EFFECTS**
  - **Common or very common** Appetite decreased • burping • cholelithiasis • constipation • diarrhea • diziness • fatigue • gastrointestinal discomfort • gastrointestinal disorders • hypoglycaemia (in combination with insulin or sulfonylurea) • nausea • vomiting • weight decreased
  - **Uncommon** Taste altered

- **SIDE-EFFECTS, FURTHER INFORMATION** Discontinue if symptoms of acute pancreatitis occur, such as persistent, severe abdominal pain.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises women of childbearing potential should use effective contraception during and for at least two months after stopping treatment.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (limited information in severe impairment).

- **RENAL IMPAIRMENT** Manufacturer advises avoid in end-stage renal disease.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8°C) — after first use can also be stored below 30°C, keep cap on pen to protect from light.

- **PATIENT AND CARER ADVICE** Manufacturer advises patients and their carers should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek immediate medical attention if symptoms develop.

- **MISSED DOSES** Manufacturer advises if a dose is more than 5 days late, the missed dose should not be taken and the next dose should be administered at the normal time.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - **SME No. SMC2092**
      - The Scottish Medicines Consortium has advised (January 2019) that semaglutide (Ozempic®) is accepted for restricted use within NHS Scotland for the treatment of adults with insufficiently controlled type 2 diabetes mellitus in addition to other oral antidiabetic medicines, or as an add-on to basal insulin, as an alternative glucagon-like peptide-1 receptor agonist option.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - **Ozempic** (Novo Nordisk Ltd)
      - Semaglutide 1.34 mg per 1 ml Ozempic 1mg/0.74ml solution for injection 3ml pre-filled pen 1 pre-filled disposable injection £73.25
      - Ozempic 0.5mg/0.37ml solution for injection 1.5ml pre-filled pen 1 pre-filled disposable injection £73.25
      - Ozempic 0.25mg/0.19ml solution for injection 1.5ml pre-filled pen 1 pre-filled disposable injection £73.25

**BLOOD GLUCOSE LOWERING DRUGS**

- **MEGLITINIDES**

### Nateglinide

- **DRUG ACTION** Nateglinide stimulates insulin secretion.

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus in combination with metformin when metformin alone inadequate**
    - **BY MOUTH**
      - **Adult:** Initially 60 mg 3 times a day (max. per dose 180 mg), adjusted according to response, to be taken within 30 minutes before main meals

- **CONTRA-INDICATIONS** Ketoacidosis

- **CAUTIONS** Debilitated patients • elderly • malnourished patients

- **CAUTIONS, FURTHER INFORMATION** Substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit nateglinide on morning of surgery and recommence when eating and drinking normally).

- **INTERACTIONS** → Appendix 1: nateglinide

- **SIDE-EFFECTS**
  - **Common or very common** Diarrhoea • gastrointestinal discomfort • hypoglycaemia • nausea
  - **Uncommon** Vomiting
  - **Rare or very rare** Skin reactions
  - **Frequency not known** Appetite increased • diziness • fatigue • muscle weakness • palpitations • sweating • abnormal • tremor

- **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment; avoid in severe impairment (no information available).

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.
Repaglinide

- **DRUG ACTION** Repaglinide stimulates insulin secretion.

**INDICATIONS AND DOSE**

- **Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate)**
  - **BY MOUTH**
    - Adult 18-74 years: Initially 500 micrograms (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day.
    - Adult 75 years and over: Not recommended.

- **Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate), if transferring from another oral antidiabetic drug**
  - **BY MOUTH**
    - Adult 18-74 years: Initially 1 mg (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day.
    - Adult 75 years and over: Not recommended.

- **CONTRA-INDICATIONS** Ketoacidosis.

- **CAUTIONS** Debilitated patients • malnourished patients • severe liver disease • cardiovascular disease • severe renal impairment • history of hypoglycaemia • alcoholism • elderly patients.

**SIDE-EFFECTS**

- Common or very common Abdominal pain • diarrhoea • dyspepsia • hypoglycaemia
- Rare or very rare Cardiovascular disease • constipation • hepatic function abnormal • vasculitis • vision disorders • vomiting
- Frequency not known Acute coronary syndrome • hypoglycaemic coma • nausea • skin reactions

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment (risk of increased exposure).

- **RENAL IMPAIRMENT** Use with caution.

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.

**MEDICINAL FORMS**

-星形
- **Tablet**
  - **Repaglinide (Non-proprietary)**
    - Repaglinide 2 mg tablets | 90 tablet | £5.88
    - Repaglinide 1 mg tablets | 30 tablet | £3.33
    - Repaglinide 500 microgram tablets | 30 tablet | £2.86

**IMPORTANT SAFETY INFORMATION**

- **MHRA/CHM ADVICE (UPDATED APRIL 2016): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPAGLIFLOZIN)**

A review by the European Medicines Agency has concluded that serious, life-threatening, and fatal cases of diabetic ketoacidosis (DKA) have been reported rarely in patients taking an SGLT2 inhibitor. In several cases, the presentation of DKA was atypical with patients having only moderately elevated blood glucose levels, and some of them occurred during off-label use.

To minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- Inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these.
- Test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal.
- Use canagliflozin with caution in patients with risk factors for DKA, (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse), and discuss these risk factors with patients.
- Discontinue treatment if DKA is suspected or diagnosed.
● do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
● interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient’s condition has stabilised

MHRA/CHM ADVICE (UPDATED MARCH 2017): INCREASED RISK OF LOWER-LIMB AMPUTATION (MAINLY TOES)

Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Preventive foot care is important for all patients with diabetes. The MHRA has issued the following advice while clinical trials are ongoing:
● consider stopping canagliflozin if a patient develops a significant lower limb complication (e.g. skin ulcer, osteomyelitis, or gangrene)
● carefully monitor patients who have risk factors for amputation (e.g. previous amputations, existing peripheral vascular disease, or neuropathy)
● monitor all patients for signs and symptoms of water or salt loss; ensure patients stay sufficiently hydrated to prevent volume depletion in line with the manufacturer’s recommendations
● advise patients to stay well hydrated, carry out routine preventive foot care, and seek medical advice promptly if they develop skin ulceration, discoulouration, or new pain or tenderness
● start treatment for foot problems (e.g. ulceration, infection, or new pain or tenderness) as early as possible
● continue to follow standard treatment guidelines for routine preventive foot care for people with diabetes.

MHRA/CHM ADVICE: SGLT2 INHIBITORS: REPORTS OF FOURNIER’S GANGRENE (NECROTISING FASCIITIS OF THE GENITALIA OR PERINEUM) (FEBRUARY 2019)

Fournier’s gangrene, a rare but serious and potentially life-threatening infection, has been associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. If Fournier’s gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement). Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise—urgenital infection or perineal abscess may precede necrotising fasciitis.

● CONTRA-INDICATIONS  Ketaocidosis
● CAUTIONS  Cardiovascular disease (risk of hypertension) • elderly (risk of hypotension) • elevated haematocrit • history of hypotension

CAUTIONS, FURTHER INFORMATION
● Volume depletion  Correct hypovolaemia before starting treatment.

● INTERACTIONS  → Appendix 1: canagliflozin

● SIDE-EFFECTS
● Common or very common  Balanoposthitis • constipation • dyslipidaemia • hypoglycaemia (in combination with insulin or sulfonylurea) • increased risk of infection • nausea • thirst • urinary disorders • urosepsis
● Uncommon  Dehydration • dizziness postural • hypotension • lower limb amputations • renal failure • skin reactions • syncope
● Rare or very rare  Anaphylactic reaction • angioedema • diabetic ketoacidosis (discontinue immediately)
● Frequency not known  Fournier’s gangrene (discontinue and initiate treatment promptly)

SIDE-EFFECTS, FURTHER INFORMATION  Consider interrupting treatment if volume depletion occurs.

● PREGNANCY  Avoid—toxicity in animal studies.

● BREAST FEEDING  Avoid—present in milk in animal studies.

● HEPATIC IMPAIRMENT  Manufacturer advises avoid in severe impairment—no information available.

● RENAL IMPAIRMENT  Avoid initiation if eGFR less than 60 mL/minute/1.73 m². Avoid if eGFR less than 45 mL/minute/1.73 m².

Dose adjustments  Reduce dose to 100 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m² and existing canagliflozin treatment tolerated.

Monitoring  Monitor renal function at least twice a year in moderate impairment.

● MONITORING REQUIREMENTS  Determine renal function before treatment and at least annually thereafter, and before initiation of concomitant drugs that reduce renal function and periodically thereafter.

● PATIENT AND CARER ADVICE  Patients should be advised to report symptoms of volume depletion including postural hypotension and dizziness. Patients should be informed of the signs and symptoms of diabetic ketoacidosis, see MHRA advice.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

➤ Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016) NICE TA390

Canagliflozin (Invokana®) as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate.

Patients currently receiving canagliflozin whose disease does not meet the above criteria should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta390

➤ Canagliflozin in combination therapy for treating type 2 diabetes (June 2014) NICE TA315

Canagliflozin (Invokana®) in a dual therapy regimen in combination with metformin is recommended for the treatment of type 2 diabetes, only if a sulfonylurea is contra-indicated or not tolerated, or the patient has a significant risk of hypoglycaemia.

Canagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione.

Canagliflozin in combination with insulin (alone or with other antidiabetic drugs) is an option for the treatment of type 2 diabetes.

Patients currently receiving canagliflozin in a dual or triple therapy regimen that is not recommended according to the above criteria should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta315

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

➤ Invokana (Napp Pharmaceuticals Ltd)

Canagliflozin (as Canagliflozin hemihydrate) 100 mg Invokana 100mg tablets | 30 tablet £39.20 DT + £39.20
Canagliflozin (as Canagliflozin hemihydrate) 300 mg Invokana 300mg tablets | 30 tablet £39.20 DT + £39.20

www.getintopharma.com
Canagliflozin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, canagliflozin p. 702, metformin hydrochloride p. 692.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs

- **BY MOUTH**
  - Adult: 1 tablet twice daily, dose based on patient's current metformin dose, daily dose of metformin should not exceed 2 g

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**INTERACTIONS**  

- Appendix 1: canagliflozin - metformin

**RENAL IMPAIRMENT**

Avoid if eGFR less than 60 mL/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 1019/14

The Scottish Medicines Consortium has advised (January 2015) that canagliflozin with metformin (Vokanamet®) is accepted for restricted use within NHS Scotland in patients with type 2 diabetes mellitus for whom a combination of canagliflozin and metformin is an appropriate choice of therapy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>Cautionary and Advisory Labels</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (as Canagliflozin hemihydrate) 50 mg, Metformin hydrochloride 850 mg Vokanamet®</td>
<td>60 tablet</td>
</tr>
<tr>
<td>Canagliflozin (as Canagliflozin hemihydrate) 50 mg, Metformin hydrochloride 1 gram Vokanamet 50mg/1000mg tablets</td>
<td>60 tablet</td>
</tr>
</tbody>
</table>

Dapagliflozin

**DRUG ACTION**

Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus [as monotherapy if metformin inappropriate]  
Type 2 diabetes mellitus [in combination with insulin or other antidiabetic drugs]

- **BY MOUTH**
  - Adult 18-74 years: 10 mg once daily
  - Adult 75 years and over: Initiation not recommended

**Type 1 diabetes mellitus [as an adjunct to insulin in patients with a BMI greater than or equal to 27 kg/m², when insulin alone fails to achieve adequate glycaemic control] **

- **BY MOUTH**
  - Adult 18-74 years: 5 mg once daily
  - Adult 75 years and over: Initiation not recommended

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (UPDATED APRIL 2016): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPAGLIFLOZIN)

A review by the European Medicines Agency has concluded that serious, life-threatening, and fatal cases of diabetic ketoacidosis (DKA) have been reported rarely in patients taking an SGLT2 inhibitor. In several cases, the presentation of DKA was atypical with patients having only moderately elevated blood glucose levels, and some of them occurred during off-label use.

To minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these
- test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal
- use dapagliflozin with caution in patients with risk factors for DKA, (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse), and discuss these risk factors with patients
- discontinue treatment if DKA is suspected or diagnosed
- do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
- interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient’s condition has stabilised

MHRA/CHM ADVICE: SGLT2 INHIBITORS: REPORTS OF FOURNIER’S GANGRENE (NECROTISING FASCIITIS OF THE GENITALIA OR PERINEUM) (FEBRUARY 2019)

Fournier’s gangrene, a rare but serious and potentially life-threatening infection, has been associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. If Fournier’s gangrene is suspected, stop the SGLT2 inhibitor urgently and start treatment (including antibiotics and surgical debridement).

Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise—urogenital infection or perineal abscess may precede necrotising fasciitis.

**CONTRA-INDICATIONS**

- When used for type 1 diabetes mellitus high risk of diabetic ketoacidosis (consult product literature)

**CAUTIONS**

- Cardiovascular disease (risk of hypotension)  
- elderly (risk of hypotension)  
- electrolyte disturbances  
- hypotension  
- raised haematocrit

**CAUTIONS, FURTHER INFORMATION**

Volume depletion Correct hypovolaemia before starting treatment.

**INTERACTIONS**  

- Appendix 1: dapagliflozin
Canagliflozin, dapagliflozin and empagliflozin as
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▶ When used for Type 1 diabetes mellitus
RENAL IMPAIRMENT
BREAST FEEDING
Frequency not known
▶ Fournier’s gangrene (discontinue and initiate treatment promptly)
SIDE-EFFECTS, FURTHER INFORMATION
Interrupt treatment if volume depletion occurs.
▶ PREGNANCY
Avoid—toxicity in animal studies.
▶ BREAST FEEDING
Avoid—present in milk in animal studies.
▶ HEPATIC IMPAIRMENT
Manufacturer advises caution in severe impairment (risk of increased exposure, limited information available).
Dose adjustments
▶ When used for Type 2 diabetes mellitus Manufacturer advises initially 5 mg daily in severe impairment, increased if tolerated to 10 mg daily.
▶ RENAL IMPAIRMENT
Manufacturer advises avoid initiation if eGFR less than 60 mL/minute/1.73 m² (reduced efficacy). Manufacturer advises avoid if eGFR persistently less than 45 mL/minute/1.73 m² (reduced efficacy). If eGFR less than 60 mL/minute/1.73 m² manufacturer advises monitor renal function at least 2–4 times per year.
▶ MONITORING REQUIREMENTS
Manufacturer advises monitor renal function before treatment, and at least annually thereafter.
▶ When used for Type 1 diabetes mellitus Manufacturer advises patients should monitor ketone levels before starting and during treatment (blood ketone levels are preferred to urine)—consult product literature.
▶ PATIENT AND CARER ADVICE
Patients should be informed of the signs and symptoms of diabetic ketoacidosis, see MHRA advice.
▶ NATIONAL FUNDING/ACCESS DECISIONS
NICE FORMS
▶ Dapagliflozin in combination therapy for treating type 2 diabetes (updated November 2016) NICE TA288
Dapagliflozin (Forxiga®) in a dual therapy regimen in combination with metformin is recommended for the treatment of type 2 diabetes, only if the patient is at significant risk of hypoglycaemia or its consequences, or if a sulfonylurea is contra-indicated or not tolerated.
Dapagliflozin in combination with insulin (alone or with other antidiabetic drugs) is an option for the treatment of type 2 diabetes.
Patients currently receiving dapagliflozin in a dual therapy regimen that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop.
www.nice.org.uk/guidance/ta288
▶ Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016) NICE TA390
Dapagliflozin (Forxiga®) as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate.
Patients currently receiving dapagliflozin whose disease does not meet the above criteria should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
www.nice.org.uk/guidance/ta390

Diabetes mellitus 705

Dapagliflozin in triple therapy for treating type 2 diabetes (November 2016) NICE TA418
Dapagliflozin (Forxiga®) in a triple therapy regimen is recommended as an option for treating type 2 diabetes in adults, only in combination with metformin and a sulfonylurea.
Patients currently receiving dapagliflozin in other triple therapy regimens, whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
www.nice.org.uk/guidance/ta418

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
▶ Forxiga (AstraZeneca UK Ltd)
  Dapagliflozin (as Dapagliflozin propanediol monohydrate) 5 mg Forxiga 5mg tablets | 28 tablet | £36.59 DT + £36.59
  Dapagliflozin (as Dapagliflozin propanediol monohydrate) 10 mg Forxiga 10mg tablets | 28 tablet | £36.59 DT + £36.59
Combinations available: Saxagliptin with dapagliflozin, p. 696

Dapagliflozin with metformin 01-Mar-2019
The properties listed below are those particular to the combination only. For the properties of the components please consider, dapagliflozin p. 704, metformin hydrochloride p. 692.

INDICATIONS AND DOSE
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs
▶ BY MOUTH
  ▶ Adult 18–74 years: 1 tablet twice daily, based on patient’s current metformin dose
  ▶ Adult 75 years and over: Initiation not recommended

INTERACTIONS ➔ Appendix 1: dapagliflozin - metformin

HEPATIC IMPAIRMENT
Manufacturer advises avoid (increased risk of lactic acidosis).

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
SMC No. 983/14
The Scottish Medicines Consortium has advised (August 2014) that dapagliflozin plus metformin (Xigduo®) is accepted for restricted use within NHS Scotland in patients for whom a combination of dapagliflozin and metformin is an appropriate choice of therapy i.e when metformin alone does not provide adequate glycaemic control and a sulfonylurea is inappropriate, or in combination with insulin, when insulin and metformin does not provide adequate control, or in combination with a sulfonylurea, when a sulfonylurea and metformin does not provide adequate control.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS
  ▶ Xigduo (AstraZeneca UK Ltd)
  ▶ Dapagliflozin (as Dapagliflozin propanediol monohydrate) 5 mg, Metformin hydrochloride 850 mg Xigduo 5mg/850mg tablets | 56 tablet | £36.59 DT + £36.59
  ▶ Dapagliflozin (as Dapagliflozin propanediol monohydrate) 5 mg, Metformin hydrochloride 1 gram Xigduo 5mg/1000mg tablets | 56 tablet | £36.59 DT + £36.59

www.getintopharma.com
Empagliflozin

**DRUG ACTION** Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**INDICATIONS AND DOSE**

* Type 2 diabetes mellitus as monotherapy (if metformin inappropriate) * Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)

- **BY MOUTH**
  - Adult 18-84 years: 10 mg once daily, increased to 25 mg once daily if necessary and if tolerated
  - Adult 85 years and over: Initiation not recommended

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (UPDATED APRIL 2016): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS (CANAGLIFLOZIN, DAPAGLIFLOZIN OR EMPAGLIFLOZIN)**

A review by the European Medicines Agency has concluded that serious, life-threatening, and fatal cases of diabetic ketoacidosis (DKA) have been reported rarely in patients taking an SGLT2 inhibitor. In several cases, the presentation of DKA was atypical with patients having only moderately elevated blood glucose levels, and some of them occurred during off-label use.

To minimise the risk of such effects when treating patients with an SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

- Inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these
- Test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal
- Use empagliflozin with caution in patients with risk factors for DKA, (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse), and discuss these risk factors with patients
- Discontinue treatment if DKA is suspected or diagnosed
- Do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
- Interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient’s condition has stabilised

**MHRA/CHM ADVICE: SGLT2 INHIBITORS: REPORTS OF FOURNIER’S GANGRENE (NECTROTISING FASCITIS OF THE GENITALIA OR PERINEUM) (FEBRUARY 2019)**

Fournier’s gangrene, a rare but serious and potentially life-threatening infection, has been associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. If Fournier’s gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement). Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise—urogenital infection or perineal abscess may precede necrotising fasciitis.

**CONTRA-INDICATIONS** Diabetic ketoacidosis

**CAUTIONS** Cardiovascular disease (increased risk of volume depletion) - complicated urinary tract infections—consider temporarily interrupting treatment - concomitant antihypertensive therapy (increased risk of volume depletion) - elderly patients aged over 75 years (increased risk of volume depletion) - heart failure - history of hypotension (increased risk of volume depletion) - patients at increased risk of volume depletion - predisposition to fluid disturbances e.g. gastro-intestinal illness, concomitant use of diuretics (increased risk of volume depletion)

**CAUTIONS, FURTHER INFORMATION**

- Volume depletion Correct hypovolaemia before starting treatment. Consider interrupting treatment if volume depletion occurs.
- **INTERACTIONS** → Appendix 1: empagliflozin
- **SIDE-EFFECTS**
  - Common or very common: Balanoposthitis, hypoglycaemia (in combination with insulin or sulfonylurea) - increased risk of infection - pruritus generalised - thirst - urinary disorders
  - Uncommon: Hypovolaemia
  - Rare or very rare: Diabetic ketoacidosis (discontinue immediately)
  - Frequency not known: Fournier’s gangrene (discontinue and initiate treatment promptly)
- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.
- **RENAL IMPAIRMENT** Avoid initiation if eGFR below 60 mL/minute/1.73 m². Avoid if eGFR is persistently below 45 mL/minute/1.73 m².

**Dose adjustments** Reduce dose to 10 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Determine renal function before treatment and before initiation of concomitant drugs that may reduce renal function, then at least annually thereafter.

**PATIENT AND CARER ADVICE** Patients should be informed of the signs and symptoms of diabetic ketoacidosis, see MHRA advice.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016)
- NICE TA390

Empagliflozin (Jardiance®) as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate.

Patients currently receiving empagliflozin whose disease does not meet the above criteria should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta390
Empagliflozin in combination therapy for treating type 2 diabetes (March 2015) NICE TA336
Empagliflozin (Jardiance®) in a dual therapy regimen in combination with metformin is an option for the treatment of type 2 diabetes, only if:
• a sulfonylurea is contra-indicated or not tolerated, or
• the patient is at significant risk of hypoglycaemia or its consequences.

Empagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with:
• metformin and a sulfonylurea, or
• metformin and a thiazolidinedione.

Empagliflozin in combination with insulin with or without other antidiabetic drugs is an option for the treatment of type 2 diabetes.

Patients currently receiving empagliflozin whose disease does not meet the above criteria should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta336

Empagliflozin with metformin 01-Mar-2019

The properties listed below are those particular to the combination only. For the properties of the components please consider, empagliflozin p. 766, metformin hydrochloride p. 692.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet
> Jardiance (Boehringer Ingelheim Ltd)  
Empagliflozin 10 mg Jardiance 10mg tablets  |  28 tablet  
£36.59 DT + £36.59

Empagliflozin 25 mg Jardiance 25mg tablets  |  28 tablet  
£36.59 DT + £36.59

DOSAGE

INDICATIONS AND DOSE

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with other antidiabetic drugs or insulin

BY MOUTH

Adult 18-84 years: 5/850–5/1000 mg twice daily, based on patient’s current metformin dose, increased if necessary to 12.5/850–12.5/1000 mg twice daily

BY MOUTH

Adult 85 years and over: Initiation not recommended

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

DOSE EQUIVALENCE AND CONVERSION

The proportions are expressed in the form ‘x’/‘y’ where ‘x’ and ‘y’ are the strengths in milligrams of empagliflozin and metformin respectively.

INTERACTIONS  Appendix 1: empagliflozin - metformin

MEDICATIONS

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions
SMC No. 1092/15
The Scottish Medicines Consortium has advised (October 2015) that empagliflozin with metformin (Synjardy®) is accepted for restricted use within NHS Scotland in patients for whom a fixed dose combination of empagliflozin and metformin is an appropriate choice of therapy, or when use of a sulfonylurea is considered inappropriate.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (UPDATED APRIL 2016): RISK OF DIABETIC KETOACIDOSIS WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

A review by the European Medicines Agency has concluded that serious, life-threatening, and fatal cases of diabetic ketoacidosis (DKA) (DKA) have been reported rarely in patients taking an SGLT2 inhibitor. In several cases, the presentation of DKA was atypical with patients having only moderately elevated blood glucose levels, and some of them occurred during off-label use.

To minimise the risk of such effects when treating patients with a SGLT2 inhibitor, the European Medicines Agency has issued the following advice:

• inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these
• test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal
• use empagliflozin with caution in patients with risk factors for DKA, (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse), and discuss these risk factors with patients
• discontinue treatment if DKA is suspected or diagnosed
• do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
Diabetes mellitus and hypoglycaemia

- interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient’s condition has stabilised

MHRA/CHM ADVICE: SGLT2 INHIBITORS: REPORTS OF FOURNIER’S GANGRENE (NECROTISING FASCIITIS OF THE GENITALIA OR PERINEUM) (FEBRUARY 2019)

Fournier’s gangrene, a rare but serious and potentially life-threatening infection, has been associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. If Fournier’s gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement).

Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise—urogenital infection or perineal abscess may precede necrotising fasciitis.

- CONTRA-INDICATIONS Diabetic ketoacidosis
- CAUTIONS Dehydration - elderly (risk of volume depletion)
- HEPATIC IMPAIRMENT
- RARE or very RARE Diabetic ketoacidosis (discontinue immediately)
- FREQUENCY not known Fournier’s gangrene (discontinue and initiate treatment promptly) - lower limb amputations - phimosis

SIDE-EFFECTS, FURTHER INFORMATION

MANUFACTURER ADVICE: ERTUGLIFLOZIN

- For treatment of type 2 diabetes in adults for whom metformin is contra-indicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta572

Scottish Medicines Consortium (SMC) decisions

SMC No. SMC2102

The Scottish Medicines Consortium has advised (January 2019) that ertugliflozin (Steglatro®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes as monotherapy, in patients who would otherwise receive a dipeptidyl peptidase-4 inhibitor and in whom a sulphonylurea or pioglitazone is not appropriate, and as add-on therapy.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Steglatro (Merck Sharp & Dohme Ltd) £

Ertugliflozin (as Ertugliflozin L-pyroglutamic acid) 5 mg 
5mg tablets | 28 tablet | £29.40

Ertugliflozin (as Ertugliflozin L-pyroglutamic acid) 15 mg 
15mg tablets | 28 tablet | £29.40

BLOOD GLUCOSE LOWERING DRUGS > SULFONYLUREAS

Sulfonylureas

- DRUG ACTION The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action.

- CONTRA-INDICATIONS Presence of ketoacidosis

- CAUTIONS Can encourage weight gain (should be taken at the lowest dose that adequately controls blood glucose) - elderly - G6PD deficiency

- SIDE-EFFECTS

- COMMON or very common Abdominal pain - diarrhoea - hypoglycaemia - nausea

- UNCOMMON Hepatic disorders - vomiting

- RARE or very rare Agranulocytosis - erythropenia - granulocytopenia - haemolytic anaemia - leucopenia - pancytopenia - thrombocytopenia

- FREQUENCY not known Allergic dermatitis (usually in the first 6–8 weeks of therapy) - constipation - visual impairment

- HEPATIC IMPAIRMENT Jaundice may occur.

Dose adjustments Sulfonylureas should be avoided or a reduced dose should be used in severe hepatic impairment, because there is an increased risk of hypoglycaemia.

- RENAL IMPAIRMENT Sulfonylureas should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia. Care is required to use the lowest dose that adequately controls blood glucose. Avoid where possible in severe renal impairment.

- PATIENT AND CARER ADVICE The risk of hypoglycaemia associated with sulfonylureas should be discussed with the
Glibenclamide

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus**
    - **Adult:** Initially 5 mg daily, adjusted according to response, dose to be taken with or immediately after breakfast; maximum 15 mg per day


- **CONTRA-INDICATIONS** Avoid where possible in Acute porphyrias p. 1058

- **INTERACTIONS** → Appendix 1: sulfonylureas

- **SIDE-EFFECTS** Appetite decreased · gastrointestinal discomfort · SIADH · taste metallic

- **PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia; however, glibenclamide can be used during the second and third trimesters of pregnancy in women with gestational diabetes.

- **BREAST FEEDING** Glibenclamide can be used during breast-feeding in women with pre-existing diabetes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension Modified-release tablet

  **CAUTIONARY AND ADVISORY LABELS** 25

  - **Biloxna** (Actavis UK Ltd)
    - Glibenclamide 30 mg tablets | 28 tablet (POM) £4.21 DT + £2.81 | 56 tablet (POM) £3.27
  - **Gliclazide 60 mg**
    - Gliclazide 60 mg tablets | 28 tablet (POM) £3.27 DT + £4.77 | 56 tablet (POM) £6.55
  - **Dacalis MR** (Mylan)
    - Gliclazide 30 mg Dacalis MR 30mg tablets | 28 tablet (POM) £2.81 DT + £2.81 | 56 tablet (POM) £5.62
  - **Diamicron MR** (Servier Laboratories Ltd)
    - Gliclazide 30 mg Diamicron MR 30mg tablets | 28 tablet (POM) £2.81 DT + £2.81 | 56 tablet (POM) £5.62
  - **Edicil MR** (Teva UK Ltd)
    - Gliclazide 30 mg Edicil MR 30mg tablets | 28 tablet (POM) £2.62 DT = £2.81 | 56 tablet (POM) £5.24
  - **Laaglyda MR** (Consilient Health Ltd)
    - Gliclazide 60 mg Laaglyda MR 60mg tablets | 28 tablet (POM) £4.77 DT = £4.77
  - **Nazdol MR** (Consilient Health Ltd)
    - Gliclazide 30 mg Nazdol MR 30mg tablets | 28 tablet (POM) £2.35 DT = £2.81 | 56 tablet (POM) £4.92
  - **Vanaju** (Advanz Pharma)
    - Gliclazide 30 mg Vanju 30mg modified-release tablets | 28 tablet (POM) £1.64 DT + £2.81 | 56 tablet (POM) £3.28
  - **Gliclazide 60 mg**
    - Gliclazide 60 mg modified-release tablets | 28 tablet (POM) £3.28 DT = £4.77
  - **Ziclaseg** (Lupin Healthcare (UK) Ltd)
    - Gliclazide 30 mg Ziclaseg 30mg modified-release tablets | 28 tablet (POM) £2.38 DT + £2.81 | 56 tablet (POM) £4.77
  - **Zicron PR** (Bristol Laboratories Ltd)
    - Gliclazide 30 mg Zicron PR 30mg tablets | 28 tablet (POM) £1.95 DT = £2.81 | 56 tablet (POM) £3.90

- **Tablet**

  - **Glibenclamide (Non-proprietary)**
    - Glibenclamide 2.5 mg | Glibenclamide 2.5mg tablets | 28 tablet (POM) £1.13 DT + £1.376
    - Glibenclamide 5 mg | Glibenclamide 5mg tablets | 28 tablet (POM) £14.92 DT + £3.76

Gliclazide

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus**
    - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
      - Adult: Initially 40–80 mg daily, adjusted according to response, increased if necessary up to 160 mg once daily, dose to be taken with breakfast, doses higher than 160 mg to be given in divided doses; maximum 320 mg per day
    - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
      - Adult: Initially 30 mg daily, dose to be taken with breakfast, adjust dose according to response every 4 weeks (after 2 weeks if no decrease in blood glucose); maximum 120 mg per day

  **DOSE EQUIVALENT AND CONVERSION**

  - Gliclazide modified release 30 mg may be considered to be approximately equivalent in therapeutic effect to standard formulation gliclazide 80 mg.

- **CONTRA-INDICATIONS** Avoid where possible in Acute porphyrias p. 1058

- **INTERACTIONS** → Appendix 1: sulfonylureas

- **SIDE-EFFECTS** Anaemia · angioedema · dyspepsia · gastrointestinal disorder · hypersensitivity vasculitis · hyponatraemia · severe cutaneous adverse reactions (SCARs) · skin reactions

- **PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

- **BREAST FEEDING** Avoid—theroretical possibility of hypoglycaemia in the infant.

- **RENAL IMPAIRMENT** If necessary, gliclazide which is principally metabolised in the liver, can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Modified-release tablet**

  **CAUTIONARY AND ADVISORY LABELS** 25

  - **Biloxna** (Actavis UK Ltd)
    - Gliclazide 30 mg modified-release tablets | 28 tablet (POM) £1.63 DT + £2.81 | 56 tablet (POM) £3.27
  - **Gliclazide 60 mg**
    - Gliclazide 60 mg modified-release tablets | 28 tablet (POM) £3.27 DT + £4.77 | 56 tablet (POM) £6.55
  - **Dacalis MR** (Mylan)
    - Gliclazide 30 mg Dacalis MR 30mg tablets | 28 tablet (POM) £2.81 DT = £2.81 | 56 tablet (POM) £5.62
  - **Diamicron MR** (Servier Laboratories Ltd)
    - Gliclazide 30 mg Diamicron MR 30mg tablets | 28 tablet (POM) £2.81 DT + £2.81 | 56 tablet (POM) £5.62
  - **Edicil MR** (Teva UK Ltd)
    - Gliclazide 30 mg Edicil MR 30mg tablets | 28 tablet (POM) £2.62 DT = £2.81 | 56 tablet (POM) £5.24
  - **Laaglyda MR** (Consilient Health Ltd)
    - Gliclazide 60 mg Laaglyda MR 60mg tablets | 28 tablet (POM) £4.77 DT = £4.77
  - **Nazdol MR** (Consilient Health Ltd)
    - Gliclazide 30 mg Nazdol MR 30mg tablets | 28 tablet (POM) £2.35 DT = £2.81 | 56 tablet (POM) £4.92
  - **Vanaju** (Advanz Pharma)
    - Gliclazide 30 mg Vanju 30mg modified-release tablets | 28 tablet (POM) £1.64 DT + £2.81 | 56 tablet (POM) £3.28
  - **Gliclazide 60 mg**
    - Gliclazide 60 mg modified-release tablets | 28 tablet (POM) £3.28 DT = £4.77
  - **Ziclaseg** (Lupin Healthcare (UK) Ltd)
    - Gliclazide 30 mg Ziclaseg 30mg modified-release tablets | 28 tablet (POM) £2.38 DT + £2.81 | 56 tablet (POM) £4.77
  - **Zicron PR** (Bristol Laboratories Ltd)
    - Gliclazide 30 mg Zicron PR 30mg tablets | 28 tablet (POM) £1.95 DT = £2.81 | 56 tablet (POM) £3.90

- **Tablet**

  - **Gliclazide (Non-proprietary)**
    - Gliclazide 40 mg Gliclazide 40mg tablets | 28 tablet (POM) £0.75–£3.19 DT + £3.53
    - Gliclazide 80 mg Gliclazide 80mg tablets | 28 tablet (POM) £1.37 DT = £0.82 | 60 tablet (POM) £0.81–£1.80
    - **Diamicron** (Servier Laboratories Ltd)
      - Gliclazide 80 mg Diamicron 80mg tablets | 60 tablet (POM) £4.38
    - **Glydex** (Medreich Plc)
      - Gliclazide 160 mg Glydex 160mg tablets | 28 tablet (POM) £1.79
    - **Zicron** (Bristol Laboratories Ltd)
      - Gliclazide 40 mg Zicron 40mg tablets | 28 tablet (POM) £3.36 DT = £1.53

Glimepiride

- **INDICATIONS AND DOSE**
  - **Type 2 diabetes mellitus**
    - **BY MOUTH**
      - Adult: Initially 1 mg daily, adjusted according to response, then increased in steps of 1 mg every 1–2 weeks, increased to 4 mg daily, dose to be taken shortly before or with first main meal, the daily dose may be increased further, in exceptional circumstances; maximum 6 mg per day
Diabetes mellitus and hypoglycaemia

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

- Porphyria Sulfonylureas should be avoided where possible in Acute porphyrias p. 1058 but glimepiride is thought to be safe.

**INTERACTIONS** → Appendix 1: sulfonylureas

**SIDE-EFFECTS**

- Rare or very rare Gastrointestinal discomfort • Hypersensitivity vasculitis

**FREQUENCY not known** Drug cross-reactivity

**PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

**BREAST FEEDING** Avoid—theoretical possibility of hypoglycaemia in the infant.

**MONITORING REQUIREMENTS** Manufacturer recommends regular hepatic and haematological monitoring but limited evidence of clinical value.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

| Tablet | Glimperide (Non-proprietary) | Glimepiride 1 mg Glimperide 1mg tablets | 30 tablet | £5.00 DT = £1.63
| Glimepiride 2 mg Glimperide 2mg tablets | 30 tablet | £7.13 DT = £2.04
| Glimepiride 3 mg Glimepiride 3mg tablets | 30 tablet | £10.75 DT = £2.55
| Glimepiride 4 mg Glimepiride 4mg tablets | 30 tablet | £14.24 DT = £2.67
| Amaryl (Zeneca) | Glimepiride 3 mg Amaryl 3mg tablets | 30 tablet | £10.75 DT = £2.55

**Glipizide**

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

- BY MOUTH

  - Adult: Initially 2.5–5 mg daily, adjusted according to response, dose to be taken shortly before breakfast or lunch; doses up to 15 mg may be given as a single dose, higher doses to be given in divided doses; maximum 20 mg per day

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

- Porphyria Sulfonylureas should be avoided where possible in Acute porphyrias p. 1058 but glimepiride is thought to be safe.

**INTERACTIONS** → Appendix 1: sulfonylureas

**SIDE-EFFECTS**

- Common or very common Abdominal pain upper

- Uncommon Dizziness • drowsiness • skin reactions • tremor • vision disorders

- Frequency not known Confusion • headache • hyponatraemia • malaise • photosensitivity reaction

**PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

**BREAST FEEDING** Avoid—theoretical possibility of hypoglycaemia in the infant.

**HEPATIC IMPAIRMENT** Avoid if the patient has both renal and hepatic impairment.

**RENAI IMPAIRMENT** Avoid if the patient has both renal and hepatic impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

| Tablet | Glimperide (Non-proprietary) | Glimepiride 5 mg Glimepiride 5mg tablets | 28 tablet | £3.00 DT = £2.60
| Minodiol (Pfizer Ltd) | Glimepiride 5 mg Minodiol 5mg tablets | 28 tablet | £1.26 DT = £2.60

**Tolbutamide**

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

- BY MOUTH

  - Adult: 0.5–1.5 g daily in divided doses, dose to be taken with or immediately after meals, alternatively 0.5–1.5 g once daily, dose to be taken with or immediately after breakfast; maximum 2 g per day

**CONTRA-INDICATIONS** Avoid where possible in Acute porphyrias p. 1058

**INTERACTIONS** → Appendix 1: sulfonylureas

**SIDE-EFFECTS**

- Rare or very rare Aplastic anaemia • blood disorder

- Frequency not known Alcohol intolerance • appetite abnormal • erythema multiforme (usually in the first 6–8 weeks of therapy) • exfoliative dermatitis (usually in the first 6–8 weeks of therapy) • fever (usually in the first 6–8 weeks of therapy) • headache • hyponatraemia (usually in the first 6–8 weeks of therapy) • paraesthesia • photosensitivity reaction • tinnitus • weight increased

**PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

**BREAST FEEDING** The use of sulfonylureas in breastfeeding should be avoided because there is a theoretical possibility of hypoglycaemia in the infant.

**RENAI IMPAIRMENT** If necessary, the short-acting drug tolbutamide can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

| Tablet | Tolbutamide (Non-proprietary) | Tolbutamide 500 mg Tolbutamide 500mg tablets | 28 tablet | £34.88 DT = £13.74
| 112 tablet | £14.96

**BLOOD GLUCOSE LOWERING DRUGS**

**THIAZOLIDINEDIONES**

**Pioglitazone**

**DRUG ACTION** The thiazolidinedione, pioglitazone, reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

- BY MOUTH

  - Adult: Initially 15–30 mg once daily, adjusted according to response to 45 mg once daily, in elderly patients, initiate with lowest possible dose and increase gradually; review treatment after 3–6 months and regularly thereafter

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MONITORING REQUIREMENTS

- HEPATIC IMPAIRMENT
- BREAST FEEDING
- PREGNANCY

Frequency not known
- Uncommon
- Common or very common

CAUTIONS

- CONTRA-INDICATIONS History of heart failure - previous or active bladder cancer - uninvestigated macroscopic haematuria
- CAUTIONS Cardiovascular disease or in combination with insulin (risk of heart failure) - elderly (increased risk of heart failure, fractures, and bladder cancer) - increased risk of bone fractures, particularly in women - risk factors for bladder cancer

CAUTIONS, FURTHER INFORMATION Substitute insulin during peri-operative period.

INTERACTIONS Appendix 1: pioglitazone

SIDE-EFFECTS
- Common or very common Bone fracture - increased risk of infection - numbness - visual impairment - weight increased
- Uncommon Bladder cancer - insomnia
- Frequency not known Macular oedema

SIDE-EFFECTS, FURTHER INFORMATION Rare reports of liver dysfunction; discontinue if jaundice occurs.

PREGNANCY Avoid—toxicity in animal studies.

BREAST FEEDING Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises avoid.

MONITORING REQUIREMENTS Monitor liver function before treatment and periodically thereafter.

DOSE ADJUSTMENTS DUE TO INTERACTIONS
- Dose of concomitant sulfonylurea or insulin may need to be reduced.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: PIOGLITAZONE CARDIOVASCULAR SAFETY (DECEMBER 2007 AND JANUARY 2011)

Incidence of heart failure is increased when pioglitazone is combined with insulin especially in patients with predisposing factors e.g. previous myocardial infarction. Patients who take pioglitazone should be closely monitored for signs of heart failure; treatment should be discontinued if any deterioration in cardiac status occurs.

Pioglitazone should not be used in patients with heart failure or a history of heart failure.

PIOGLITAZONE: RISK OF BLADDER CANCER (JULY 2011)
The European Medicines Agency has advised that there is a small increased risk of bladder cancer associated with pioglitazone use. However, in patients who respond adequately to treatment, the benefits of pioglitazone continue to outweigh the risks.

Pioglitazone should not be used in patients with active bladder cancer or a past history of bladder cancer, or in those who have uninvestigated macroscopic haematuria. Pioglitazone should be used with caution in elderly patients as the risk of bladder cancer increases with age.

Before initiating treatment with pioglitazone, patients should be assessed for risk factors of bladder cancer (including age, smoking status, exposure to certain occupational or chemotherapy agents, or previous radiation therapy to the pelvic region) and any macroscopic haematuria should be investigated. The safety and efficacy of pioglitazone should be reviewed after 3–6 months and pioglitazone should be stopped in patients who do not respond adequately to treatment.

Patients already receiving treatment with pioglitazone should be assessed for risk factors of bladder cancer and treatment should be reviewed after 3–6 months, as above.

Patients should be advised to report promptly any haematuria, dysuria, or urinary urgency during treatment.

PATIENT AND CARER ADVICE

Liver toxicity Patients should be advised to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions The Scottish Medicines Consortium accepts use of pioglitazone (February 2007) with metformin and a sulfonylurea, for patients (especially if overweight) whose glycaemic control is inadequate despite the use of 2 oral hypoglycaemic drugs and who are unable or unwilling to take insulin; treatment should be initiated and monitored by an experienced diabetes physician.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
- Pioglitazone (Non-proprietary)
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg Pioglitazone 15mg tablets | 28 tablet (£89.30 DT = £1.55)
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg Pioglitazone 30mg tablets | 28 tablet (£15.89 DT = £2.20)
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg Pioglitazone 45mg tablets | 28 tablet (£39.55 DT = £2.15)
  - Actos (Takeda UK Ltd) Pioglitazone (as Pioglitazone hydrochloride) 15 mg Actos 15mg tablets | 28 tablet (£25.83 DT = £1.45)
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg Actos 30mg tablets | 28 tablet (£35.89 DT = £2.02)
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg Actos 45mg tablets | 28 tablet (£39.55 DT = £2.15)
  - Glidipion (Actavis UK Ltd) Pioglitazone (as Pioglitazone hydrochloride) 15 mg Glidipion 15mg tablets | 28 tablet (£25.83 DT = £1.45)
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg Glidipion 30mg tablets | 28 tablet (£35.89 DT = £2.02)
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg Glidipion 45mg tablets | 28 tablet (£39.55 DT = £2.15)

Pioglitazone with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, pioglitazone p. 710, metformin hydrochloride p. 692.

INDICATIONS AND DOSE

Type 2 diabetes not controlled by metformin alone
- BY MOUTH
  - Adult: 1 tablet twice daily, titration with the individual components (pioglitazone and metformin) desirable before initiation

INTERACTIONS Appendix 1: metformin - pioglitazone

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 21
- Pioglitazone with metformin (Non-proprietary)
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg, Metformin hydrochloride 850 mg Pioglitazone 15mg / Metformin 850mg tablets | 56 tablet (£54.10 DT = £3.19)
  - Competact (Takeda UK Ltd) Metformin hydrochloride 850 mg Competact 15mg/850mg tablets | 56 tablet (£35.89 DT = £31.94)

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Insulin

**INSULINS**

**INSULINS**

**Insulins**

**IMPORTANT SAFETY INFORMATION**

**NHS IMPROVEMENT PATIENT SAFETY ALERT: RISK OF SEVERE HARM AND DEATH DUE TO WITHDRAWING INSULIN FROM PEN DEVICES (NOVEMBER 2016)**

Insulin should not be extracted from insulin pen devices. The strength of insulin in pen devices can vary by multiples of 100 units/mL. Insulin syringes have graduations only suitable for calculating doses of standard 100 units/mL. If insulin extracted from a pen or cartridge is of a higher strength, and that is not considered in determining the volume required, it can lead to a significant and potentially fatal overdose.

**SIDE-EFFECTS**

- Common or very common Odema
- Uncommon Lipodystrophy

**SIDE-EFFECTS, FURTHER INFORMATION**

Overdose Overdose causes hypoglycaemia.

**PREGNANCY**

Dose adjustments During pregnancy, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician. The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy.

**BREAST FEEDING**

Dose adjustments During breast-feeding, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician.

**HEPATIC IMPAIRMENT**

Dose adjustments Insulin requirements may be decreased in patients with hepatic impairment.

**RENAL IMPAIRMENT**

The compensatory response to hypoglycaemia is impaired in renal impairment. Dose adjustments Insulin requirements may decrease in patients with renal impairment and therefore dose reduction may be necessary.

**MONITORING REQUIREMENTS**

- Many patients now monitor their own blood-glucose concentrations; all carers and children need to be trained to do this.
- Since blood-glucose concentration varies substantially throughout the day, ‘normoglycaemia’ cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia.
- In adults it is therefore best to recommend that patients should maintain a blood-glucose concentration of between 4 and 9 mmol/litre for most of the time (4–7 mmol/litre before meals and less than 9 mmol/litre after meals).
- In children it is therefore best to recommend that children should maintain a blood-glucose concentration of between 4 and 10 mmol/litre for most of the time (4–8 mmol/litre before meals and less than 10 mmol/litre after meals).

While accepting that on occasions, for brief periods, the blood-glucose concentration will be above these values, strenuous efforts should be made to prevent it from falling below 4 mmol/litre. Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen. The intake of energy and of simple and complex carbohydrates should be adequate to allow normal growth and development but obesity must be avoided.

**DIRECTIONS FOR ADMINISTRATION**

Insulin is generally given by subcutaneous injection; the injection site should be rotated to prevent lipodystrophy. Injection devices (‘pens’), which hold the insulin in a cartridge and meter the required dose, are convenient to use. Insulin syringes (for use with needles) are required for insulins not available in cartridge form, but are less popular with children and carers. For intensive insulin regimens multiple subcutaneous injections (3 or more times daily) are usually recommended.

**PRESCRIBING AND DISPENSING INFORMATION**

Show container to patient or carer and confirm the expected version is dispensed. Units The word ‘unit’ should not be abbreviated.

**PATIENT AND CARER ADVICE**

Hypoglycaemia Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Insulin Passport Insulin Passports and patient information booklets should be offered to patients receiving insulin. The Insulin Passport provides a record of the patient’s current insulin preparations and contains a section for emergency information. The patient information booklet provides advice on the safe use of insulin. They are available for purchase from:

3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham
OL9 QFH
Tel: 0845 610 1112
GP practices can obtain supplies through their Local Area Team stores.
NHS Trusts can order supplies from www.nhsforms.co.uk/ or by emailing nhsforms@mmd.com. Further information is available at www.npsa.nhs.uk.

**INSULINS**

**RAPID-ACTING**

**Insulin**

(Insulin Injection; Neutral Insulin; Soluble Insulin—short acting)

**INDICATIONS AND DOSE**

Diabetes mellitus

- By subcutaneous injection, or by intramuscular injection, or by intravenous injection, or by intravenous infusion
- Adult: According to requirements

Diabetic ketoacidosis | Diabetes during surgery

- By intravenous infusion
- Adult: (consult local protocol)

**INTERACTIONS**

Appendix 1: insulins

**SIDE-EFFECTS**

- Uncommon Skin reactions

**RARE OR VERY RARE**

Refraction disorder

**DIRECTIONS FOR ADMINISTRATION**

Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an expert training, advice and supervision from an
**Insulin aspart**

(Recombinant human insulin analogue—short acting)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIASP</strong></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
</tr>
<tr>
<td>▶ BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY CONTINUOUS SUBCUTANEOUS INFUSION</td>
</tr>
<tr>
<td>Adult: According to requirements</td>
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| **NOVORAPID** |
| **Diabetes mellitus** |
| ▶ BY SUBCUTANEOUS INJECTION |
| Child 2-17 years: Administer immediately before meals or when necessary shortly after meals, according to requirements |
| Adult: Administer immediately before meals or when necessary shortly after meals, according to requirements |
| ▶ BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INFUSION |
| Child 2-17 years: According to requirements |
| Adult: According to requirements |

| INTERACTIONS | Appendix 1: insulins |
| SIDE-EFFECTS | Uncommon Refraction disorder - skin reactions |
| PREGNANCY | Not known to be harmful—may be used during pregnancy |
| BREAST FEEDING | Not known to be harmful—may be used during lactation |

| DIRECTIONS FOR ADMINISTRATION | Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team. |
| With intravenous use in adults **For intravenous infusion**, give continuously in Glucose 5% or Sodium chloride 0.9%; dilute to 0.05–1 unit/mL with infusion fluid; adsorbed to some extent by plastics of infusion set. |
| With intravenous use in children **For intravenous infusion**, dilute to a concentration of 0.05–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin. |

| NATIONAL FUNDING/ACCESS DECISIONS |
| NICE decisions |
| Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151 |
| Continuous subcutaneous insulin infusion is recommended as an option for children over 12 years with type 1 diabetes: |
| who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or |
| whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens. Patient on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team. |

| MEDICINAL FORMS | There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion |
| Solution for injection |
| **Actrapid** (Novo Nordisk Ltd) |
| Insulin human (as Insulin soluble human) 100 unit per 1 ml Actrapid 100 units/mL solution for injection 10ml vials | 1 vial (POD) £7.48 DT = £15.68 |
| **Humulin R (Imported (United States))** |
| Insulin human 500 unit per 1 ml Humulin R 500 units/mL solution for injection 20ml vials | 1 vial (POD) £12.28 DT = £25.05 |
| Humulin R KwikPen 500 units/mL solution for injection 3ml pre-filled pen | 1 pre-filled disposable injection (POD) £7.60 |
| **Humulin S** (Eli Lilly and Company Ltd) |
| Insulin human (as Insulin soluble human) 100 unit per 1 ml Humulin S 100 units/mL solution for injection 10ml vials | 1 vial (POD) £15.68 DT = £31.35 |
| Humulin S 100 units/mL solution for injection 3ml cartridges | 5 cartridge (POD) £13.08 DT = £26.15 |
| **Hypurin Bovine Neutral** (Wockhardt UK Ltd) |
| Insulin bovine (as Insulin soluble bovine) 100 unit per 1 ml Hypurin Bovine Neutral 100 units/mL solution for injection 10ml vials | 1 vial (POD) £27.72 DT = £55.44 |
| Hypurin Bovine Neutral 100 units/mL solution for injection 3ml cartridges | 5 cartridge (POD) £41.58 DT = £83.16 |
| **Hypurin Porcine Neutral** (Wockhardt UK Ltd) |
| Insulin porcine (as Insulin soluble porcine) 100 unit per 1 ml Hypurin Porcine Neutral 100 units/mL solution for injection 10ml vials | 1 vial (POD) £33.80 DT = £67.60 |
| Hypurin Porcine Neutral 100 units/mL solution for injection 3ml cartridges | 5 cartridge (POD) £60.71 DT = £121.42 |
| **Insuman Insufast** (Sanofi) |
| Insulin human 100 unit per 1 ml Insuman Insufast 100 units/mL solution for injection 3.15ml cartridges | 5 cartridge (POD) £25.00 |
| Insuman Insufast 100 units/mL solution for injection 10ml vials | 3 vial (POD) £75.00 |
| **Insuman Rapid** (Sanofi) |
| Insulin human (as Insulin soluble human) 100 unit per 1 ml Insuman Rapid 100 units/mL solution for injection 3ml cartridges | 5 cartridge (POD) £17.50 DT = £35.00 |
| **Insuman Insufast** (Sanofi) |
| Insulin human (as Insulin soluble human) 100 unit per 1 ml Insuman Rapid 100 units/mL solution for injection 3ml cartridges | 5 cartridge (POD) £17.50 DT = £35.00 |

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Diabetes mellitus and hypoglycaemia

[BNF 78]

with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

Scottish Medicines Consortium (SMC) decisions

- In adults: The Scottish Medicines Consortium has advised (April 2017) that insulin aspart (Fiasp®) is accepted for use within NHS Scotland for the treatment of diabetes mellitus in adults.

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

  - Solution for injection

    - Fiasp (Novo Nordisk Ltd) ▼
      - Insulin aspart 100 unit per 1 ml Fiasp 100 units/ml solution for injection 10 ml vials | 1 vial (PST) £14.08 DT = £14.08
    - Fiasp FlexTouch (Novo Nordisk Ltd) ▼
      - Insulin aspart 100 unit per 1 ml Fiasp FlexTouch 100 units/ml solution for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PST) £30.60 DT = £30.60
    - Fiasp Penfill (Novo Nordisk Ltd)▼
      - Insulin aspart 100 unit per 1 ml Fiasp Penfill 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (PST) £28.31 DT = £28.31
    - NovoRapid (Novo Nordisk Ltd)
      - Insulin aspart 100 unit per 1 ml NovoRapid 100 units/ml solution for injection 10 ml vials | 1 vial (PST) £14.08 DT = £14.08
    - NovoRapid FlexPen (Novo Nordisk Ltd)
      - Insulin aspart 100 unit per 1 ml NovoRapid FlexPen 100 units/ml solution for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PST) £30.60 DT = £30.60
    - NovoRapid FlexTouch (Novo Nordisk Ltd)
      - Insulin aspart 100 unit per 1 ml NovoRapid FlexTouch 100 units/ml solution for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PST) £32.13 DT = £30.60
    - NovoRapid Penfill (Novo Nordisk Ltd)
      - Insulin aspart 100 unit per 1 ml NovoRapid Penfill 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (PST) £28.31 DT = £28.31
    - NovoRapid PumpCart (Novo Nordisk Ltd)
      - Insulin aspart 100 unit per 1 ml NovoRapid PumpCart 100 units/ml solution for injection 1.6 ml cartridges | 5 cartridge (PST) £15.10 DT = £15.10

Insulin glulisine

(Recombinant human insulin analogue—short acting)

- INDICATIONS AND DOSE

  - Diabetes mellitus

    - BY SUBCUTANEOUS INJECTION
      - Child: Administer immediately before meals or when necessary shortly after meals, according to requirements
      - Adult: Administer immediately before meals or when necessary shortly after meals, according to requirements
    - BY SUBCUTANEOUS INFUSION, OR BY INTRAVENOUS INFUSION
      - Child: According to requirements
      - Adult: According to requirements

- UNLICENSED USE

  - In children: Not licensed for children under 6 years.

- INTERACTIONS

  → Appendix 1: Insulins

- DIRECTIONS FOR ADMINISTRATION

  - Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

  - With intravenous use in adults: For intravenous infusion (Apidra®), give continuously in Sodium chloride 0.9%; dilute to 1 unit/ml with infusion fluid; use a co-extruded polyolefin/polyamide plastic infusion bag with a dedicated infusion line.

- NATIONAL FUNDING/ACCESS DECISIONS

  - NICE decisions

    - Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151
      - Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:
        - who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
        - whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

      Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

      www.nice.org.uk/TA151

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (October 2008) that Apidra® is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate.

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

  - Solution for injection

    - Apidra (Sanofi)
      - Insulin glulisine 100 unit per 1 ml Apidra 100 units/ml solution for injection 3 ml cartridges | 5 cartridge (PST) £28.30 DT = £28.30
      - Apidra 100 units/ml solution for injection 10 ml vials | 1 vial (PST) £16.00 DT = £16.00
    - Apidra SoloStar (Sanofi)
      - Insulin glulisine 100 unit per 1 ml Apidra 100 units/ml solution for injection 3 ml pre-filled SoloStar pen | 5 pre-filled disposable injection (PST) £28.30 DT = £28.30

Insulin lispro

(Recombinant human insulin analogue—short acting)

- INDICATIONS AND DOSE

  - Diabetes mellitus

    - BY SUBCUTANEOUS INJECTION
      - Child 2-17 years: Administer shortly before meals or when necessary shortly after meals, according to requirements
      - Adult: Administer shortly before meals or when necessary shortly after meals, according to requirements
    - BY SUBCUTANEOUS INFUSION, OR BY INTRAVENOUS INFUSION
      - Child 2-17 years: According to requirements
      - Adult: According to requirements

- UNLICENSED USE

  - In children: Not licensed for use in children under 2 years.

- CAUTIONS

  - Children under 12 years (use only if benefit likely compared to soluble insulin)
INTERACTIONS  Appendix 1: insulins

PREGNANCY  Not known to be harmful—may be used during pregnancy.

BREAST FEEDING  Not known to be harmful—may be used during lactation.

DIRECTIONS FOR ADMINISTRATION  Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens (see also NICE guidance, below). Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

With intravenous use in adults  For intravenous infusion give continuously in Glucose 5% or Sodium chloride 0.9%.

Adsorbed to some extent by plastics of infusion set. May be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

PRESCRIBING AND DISPENSING INFORMATION  Insulin lispro is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

NATIONAL FUNDING/ACCESS DECISIONS  NICE decisions

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes: who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or whose glycaemic control remains inadequate (HbA₁c over 8.5% (69 mmol/mol)) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Insulin lispro (non-proprietary)  Insulin lispro Sanofi 100 units/ml solution for injection 3ml cartridges | 5 cartridge | £24.06 DT = £28.31

Insulin lispro Sanofi 100 units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £25.04 DT = £29.46

Insulin lispro Sanofi 100 units/ml solution for injection 10ml vials | 1 vial | £14.12 DT = £16.61

Humalog (Eli Lilly and Company Ltd)  Humalog 100 units/ml solution for injection 10ml vials | 1 vial | £16.61 DT = £19.61

Humalog 100 units/ml solution for injection 3ml cartridges | 5 cartridge | £28.31 DT = £32.31

Humalog Junior KwikPen (Eli Lilly and Company Ltd)  Humalog Junior KwikPen 100 units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £25.46 DT = £29.46

Humalog KwikPen (Eli Lilly and Company Ltd)  Insulin lispro 100 unit per 1 ml Humalog KwikPen 100 units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £20.46 DT = £24.46

Insulin lispro 200 unit per 1 ml Humalog KwikPen 200 units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £58.92 DT = £65.92

INSULINS  INTERMEDIATE-ACTING

Biphasic isophane insulin (Biphasic Isophane Insulin Injection—intermediate acting)

INDICATIONS AND DOSE  Diabetes mellitus

BY SUBCUTANEOUS INJECTION  Child: According to requirements

Adult: According to requirements

SIDE-EFFECTS  Rare or very rare

Angioedema

Frequency not known

Hypokalaemia · weight increased

PRESCRIBING AND DISPENSING INFORMATION  A sterile buffered suspension of either porcine or human insulin complexed with protamine sulfate (or another suitable protamine) in a solution of insulin of the same species.

Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

MEDICAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Suspension for injection

Humulin M3 (Eli Lilly and Company Ltd)  Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Humulin M3 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £13.08 DT = £15.08

Humulin M3 100 units/ml suspension for injection 10ml vials | 1 vial | £15.68 DT = £15.68

Humulin M3 KwikPen (Eli Lilly and Company Ltd)  Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Humulin M3 KwikPen 100 units/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £21.70 DT = £24.10

Humulin M3 KwikPen 100 units/ml suspension for injection 10ml vials | 1 vial | £33.80 DT = £31.30

Mix 70/30 (Takeda)  Insulin porcine (as Insulin soluble porcine) 30 unit per 1 ml, Insulin porcine (as Insulin isophane porcine) 70 unit per 1 ml Mix 70/30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £50.71 DT = £46.95

Mix 70/30 100 units/ml suspension for injection 10ml vials | 1 vial | £80.92 DT = £75.92

Insumin Comb 15 (Sanofi)  Insulin human (as Insulin soluble human) 15 unit per 1 ml, Insulin human (as Insulin isophane human) 85 unit per 1 ml Insumin Comb 15 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £17.50 DT = £17.50

Insumin Comb 15 (Sanofi)  Insulin human (as Insulin soluble human) 25 unit per 1 ml, Insulin human (as Insulin isophane human) 75 unit per 1 ml Insumin Comb 25 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £35.70 DT = £32.70

Insumin Comb 25 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insumin Comb 25 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £75.92 DT = £75.92

Insumin Comb 50 (Sanofi)  Insulin human (as Insulin isophane human) 50 unit per 1 ml, Insulin human (as Insulin soluble human) 50 unit per 1 ml Insumin Comb 50 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £175.92 DT = £175.92

Insuman Comb (Eli Lilly and Company Ltd)  Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £15.70 DT = £15.70

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £22.40 DT = £25.46

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin soluble human) 30 unit per 1 ml, Insulin human (as Insulin isophane human) 70 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £32.61 DT = £37.61

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £61.31 DT = £68.31

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £119.50 DT = £121.61

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £210.70 DT = £221.10

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £466.95 DT = £492.95

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £759.20 DT = £829.20

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £1469.95 DT = £1579.95

Insuman Comb 30 (Sanofi)  Insulin human (as Insulin isophane human) 25 unit per 1 ml, Insulin human (as Insulin soluble human) 75 unit per 1 ml Insuman Comb 30 100 units/ml suspension for injection 3ml cartridges | 5 cartridge | £2959.95 DT = £3179.95
Isophane insulin

(Isophane Insulin Injection; Isophane Protamine Insulin Injection; Isophane insulin (NPH)—intermediate acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **BY SUBCUTANEOUS INJECTION**
- Child: According to requirements
- Adult: According to requirements

**INTERACTIONS** → Appendix 1: insulins

**PREGNANCY** Recommended where longer-acting insulins are needed.

**PRESCRIBING AND DISPENSING INFORMATION** A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulfate or another suitable protamine.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Humulin I** (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin isophane human) 100 unit per 1 ml
  - Humulin I 100 units/ml suspension for injection 10ml vials | 1 vial (PMS) £15.68 DT = £15.68
  - Humulin I 100 units/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £19.08 DT = £19.08
- **Humulin I KwikPen** (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin isophane human) 100 unit per 1 ml
  - Humulin I KwikPen 100 units/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (PMS) £21.70 DT = £21.70
- **Humalog Mix**
  - Insulin aspart (as Insulin aspart protamine) 70 unit/ml suspension for injection 10ml vials | 1 vial (PMS) £32.80 DT = £32.80
  - Humalog Mix 30 FlexPen (Novo Nordisk Ltd)
  - Insulin aspart 30 unit/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £28.79 DT = £28.79
- **Insulin lispro** (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin isophane human) 100 unit per 1 ml
  - Insulin lispro 25 unit/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £22.90 DT = £22.90
  - Insuman Basal (Sanofi)
  - Insulin lispro 25 unit/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £17.50 DT = £17.50
  - Insuman Basal SoloStar (Sanofi)
  - Insulin lispro 25 unit/ml suspension for injection 3ml pre-filled SoloStar pen | 5 pre-filled disposable injection (PMS) £21.70
  - Insuman Basal (Sanofi)
  - Insulin human (as Insulin isophane human) 100 unit per 1 ml
  - Insulin human (as Insulin isophane human) 100 unit per 1 ml Insulin Basal 100 units/ml suspension for injection 5ml vials | 1 vial (PMS) £5.61
  - Insulin Basal 100 units/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £19.08 DT = £19.08
  - Insuman Basal SoloStar (Sanofi)
  - Insulin lispro 25 unit/ml suspension for injection 3ml pre-filled SoloStar pen | 5 pre-filled disposable injection (PMS) £21.70

**Interactions** → Appendix 1: insulins

**Side-effects**
- Uncommon Skin reactions

**Prescribing and dispensing information** Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **NovoMix 30 FlexPen** (Novo Nordisk Ltd)
  - Insulin aspart 30 unit/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £28.79 DT = £28.79
- **NovoMix 30 Penfill** (Novo Nordisk Ltd)
  - Insulin aspart 30 unit/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £28.79 DT = £28.79

**Biphasic insulin aspart**

(Intermediate-acting insulin)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **BY SUBCUTANEOUS INJECTION**
- Child: Administer up to 15 minutes before or soon after a meal, according to requirements
- Adult: Administer up to 15 minutes before or soon after a meal, according to requirements

**INTERACTIONS** → Appendix 1: insulins

**SIDE-EFFECTS**
- Rare Hypoglycaemia

**Prescribing and dispensing information** Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Humalog Mix25** (Eli Lilly and Company Ltd)
  - Insulin lispro 25 unit/ml suspension for injection 10ml vials | 1 vial (PMS) £16.61 DT = £16.61
  - Humalog Mix25 100 units/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £29.46 DT = £29.46
  - Humalog Mix25 KwikPen (Eli Lilly and Company Ltd)
  - Insulin lispro 25 unit/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (PMS) £39.98 DT = £39.98

**Biphasic insulin lispro**

(Intermediate-acting insulin)

**INDICATIONS AND DOSE**

**Diabetes mellitus**
- **BY SUBCUTANEOUS INJECTION**
- Child: Administer up to 15 minutes before or soon after a meal, according to requirements
- Adult: Administer up to 15 minutes before or soon after a meal, according to requirements

**INTERACTIONS** → Appendix 1: insulins

**Prescribing and dispensing information** Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- **Humalog Mix25** (Eli Lilly and Company Ltd)
  - Insulin lispro 25 unit/ml suspension for injection 10ml vials | 1 vial (PMS) £16.61 DT = £16.61
  - Humalog Mix25 100 units/ml suspension for injection 3ml cartridges | 5 cartridge (PMS) £29.46 DT = £29.46
  - Humalog Mix25 KwikPen (Eli Lilly and Company Ltd)
  - Insulin lispro 25 unit/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (PMS) £39.98 DT = £39.98
In children 
All Wales Medicines Strategy Group (AWMSG) decisions 
AWMSG No. 3158 
In children The All Wales Medicines Strategy Group has advised (October 2016) that insulin degludec (Tresiba®) is not recommended for use within NHS Wales for the treatment of diabetes mellitus in adolescents and children from the age of 1 year.

Insulin detemir 
(Recombinant human insulin analogue–long acting) 

● INDICATIONS AND DOSE 
Diabetes mellitus 
BY SUBCUTANEOUS INJECTION 
Child: 2-17 years: According to requirements 
Adult: According to requirements 

● INTERACTIONS → Appendix 1: insulins 

● SIDE-EFFECTS 
Uncommon Refraction disorder 
PREGNANCY 
Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Solution for injection 
Levemir FlexPen (Novo Nordisk Ltd) 
Insulin human (as Insulin detemir) 100 unit per 1 ml Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection £42.00 DT + £14.00
Insulin glargine

(Recombinant human insulin analogue—long acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION**
- **Child: 2 - 17 years:** According to requirements
- **Adult:** According to requirements

Toujeo®

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** According to requirements

**INTERACTIONS** → Appendix 1: insulins

**SIDE-EFFECTS**

- Rare or very rare: Myalgia - sodium retention - taste altered

**PREGNANCY**

Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

**PRESCRIBING AND DISPENSING INFORMATION**

Insulin glargine is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1. Dose adjustments and close metabolic monitoring is recommended if switching between insulin glargine preparations.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised that Lantus® preparations (April 2013) and Toujeo® (August 2015) are accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:

- in those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
- as a once daily insulin therapy for patients who require a carer to administer their insulin

It is not recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Abasaglar (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Abasaglar 100units/ml solution for injection 3ml cartridges | 5 pre-filled disposable injection | £42.00 DT = £42.00
- Toujeo (Sanofi)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Toujeo 100units/ml solution for injection 3ml cartridges | 5 pre-filled disposable injection | £51.30 DT = £37.77

**Insulin glargine with lixisenatide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, insulin glargine above, lixisenatide p. 700.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus [in combination with metformin]

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** (consult product literature)

**INTERACTIONS** → Appendix 1: insulins - lixisenatide

**PRESCRIBING AND DISPENSING INFORMATION**

Suliqua® is available in two pen strengths, providing different dosing options. To avoid medication errors, the prescriber must ensure that the correct strength and number of dose steps is prescribed. The manufacturer of Suliqua® has provided a healthcare professional guide and letter which includes important information on dosing.

**PATIENT AND CARER ADVICE**

Manufacturer advises check pen label before each administration to avoid medication error.

A patient guide should be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Abasaglar (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Abasaglar 100units/ml solution for injection 3ml cartridges | 5 pre-filled disposable injection | £35.28 DT = £37.77
- Abasaglar KwikPen (Eli Lilly and Company Ltd)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Abasaglar KwikPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £35.28 DT = £37.77
- Lantus (Sanofi)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Lantus 100units/ml solution for injection 3ml cartridges | 5 pre-filled disposable injection | £37.77 DT = £37.77
- Semglee (Mylan)
  - Insulin human (as Insulin glargine) 100 unit per 1 ml
  - Semglee 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £29.99 DT = £37.77
- Toujeo (Sanofi)
  - Insulin human (as Insulin glargine) 300 unit per 1 ml
  - Toujeo 300units/ml solution for injection 1.5ml pre-filled SoloStar pen | 3 pre-filled disposable injection | £33.13 DT = £33.13
- Toujeo DoubleStar (Sanofi)
  - Insulin human (as Insulin glargine) 300 unit per 1 ml
  - Toujeo 300units/ml solution for injection 3ml pre-filled DoubleStar pen | 3 pre-filled disposable injection | £66.26

**Insulin zinc suspension**

(Insulin zinc suspension (mixed)—long acting)

**INDICATIONS AND DOSE**

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION**
- **Child:** According to requirements
- **Adult:** According to requirements

**INTERACTIONS** → Appendix 1: insulins

**SIDE-EFFECTS**

Hypokalaemia - weight increased

**PREGNANCY**

Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin p. 716 is recommended where longer-acting insulins are needed; insulin detemir p. 717 may also be considered.

**PRESCRIBING AND DISPENSING INFORMATION**

A sterile neutral suspension of bovine and/or porcine insulin or human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns).
3.1a Diabetes, diagnosis and monitoring

Diabetes mellitus, diagnostic and monitoring devices

Urinalysis: urinary glucose

Reagent strips are available for measuring for glucose in the urine. Tests for ketones by patients are rarely required unless they become unwell—see Blood Monitoring.

Microalbuminuria can be detected with Micro-Al Test Kit® but this should be followed by confirmation in the laboratory, since false positive results are common.

Blood glucose monitoring

Blood glucose monitoring using a meter gives a direct measure of the glucose concentration at the time of the test and can detect hypoglycaemia as well as hyperglycaemia. Patients should be properly trained in the use of blood glucose monitoring systems and to take appropriate action on the results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen.

Self-monitoring of blood-glucose concentration is appropriate for patients with type 2 diabetes:

- who are treated with insulin;
- who are treated with oral hypoglycaemic drugs e.g. sulfonylureas, to provide information on hypoglycaemia;
- to monitor changes in blood-glucose concentration resulting from changes in lifestyle or medication, and during intercurrent illness;
- to ensure safe blood-glucose concentration during activities, including driving.

In the UK blood-glucose concentration is expressed in mmol/litre and Diabetes UK advises that these units should be used for self-monitoring of blood glucose. In other European countries units of mg/100 mL (or mg/dL) are commonly used.

It is advisable to check that the meter is pre-set in the correct units.

If the patient is unwell and diabetic ketoacidosis is suspected, blood ketones should be measured according to local guidelines. Patients and their carers should be trained in the use of blood ketone monitoring systems and to take appropriate action on the results obtained, including when to seek medical attention.

Other drugs used for Diabetes, diagnosis and monitoring

Glucose, p. 1041

Blood glucose testing strips

**BLOOD GLUCOSE TESTING STRIPS**

- 4SURE testing strips (Nipro Diagnostics UK Ltd)
- 50 strip - NHS indicative price = £3.99 - Drug Tariff (Part IX)
- Accu-Chek Inform II testing strips (Roche Diagnostics Ltd)
- 50 strip - No NHS indicative price available - Drug Tariff (Part IX)
- Active testing strips (Roche Diabetes Care Ltd)
- 50 strip - NHS indicative price = £10.03 - Drug Tariff (Part IX)
- Advocate Redi-Cede® testing strips (Diabetes Care Technology Ltd)
- 50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)
- AutoSense testing strips (Advance Diagnostic Products (NI) Ltd)
- 25 strip - NHS indicative price = £4.50 - Drug Tariff (Part IX)
- Aviva testing strips (Roche Diabetes Care Ltd)
- 50 strip - NHS indicative price = £16.21 - Drug Tariff (Part IX)
- BGStar testing strips (Sanofi)
- 50 strip - NHS indicative price = £14.73 - Drug Tariff (Part IX)
- Betachek C50 cassette (National Diagnostic Products)
- 100 device - NHS indicative price = £23.98 - Drug Tariff (Part IX)
- Betachek GL testing strips (National Diagnostic Products)
- 50 strip - NHS indicative price = £14.19 - Drug Tariff (Part IX)
- Betachek Visual testing strips (National Diagnostic Products)
- 50 strip - NHS indicative price = £6.80 - Drug Tariff (Part IX)
- Breeze 2 testing discs (Bayer Pic)
- 50 strip - NHS indicative price = £15.00 - Drug Tariff (Part IX)
- CareSens N testing strips (Spirit Healthcare Ltd)
- 50 strip - NHS indicative price = £12.75 - Drug Tariff (Part IX)
- CareSens PRO testing strips (Spirit Healthcare Ltd)
- 50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)
- Compact testing strips (Roche Diabetes Care Ltd)
- 51 strip - NHS indicative price = £16.65 - Drug Tariff (Part IX)
- Contour Next testing strips (Ascensia Diabetes Care UK Ltd)
- 50 strip - NHS indicative price = £15.16 - Drug Tariff (Part IX)
- Contour Plus testing strips (Ascensia Diabetes Care UK Ltd)
- 50 strip - NHS indicative price = £18.50 - Drug Tariff (Part IX)
- Contour TS testing strips (Ascensia Diabetes Care UK Ltd)
- 50 strip - NHS indicative price = £9.50 - Drug Tariff (Part IX)
- Dario Lite testing strips (LabStyle Innovations Ltd)
- 50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)
- Dario testing strips (LabStyle Innovations Ltd)
- 50 strip - NHS indicative price = £14.95 - Drug Tariff (Part IX)
### Meters and test strips

<table>
<thead>
<tr>
<th>Meter (all)</th>
<th>Type of monitoring</th>
<th>Compatible test strips</th>
<th>Test strip net price</th>
<th>Sensitivity range (mmol/litre)</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td><strong>Accu-Chek® Active</strong></td>
<td>Blood glucose</td>
<td>Active®</td>
<td>50 strip= £10.03</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<tr>
<td><strong>Accu-Chek® Advantage</strong></td>
<td>Blood glucose</td>
<td>Advantage Plus®</td>
<td>50 strip= £10.00</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<td><strong>Accu-Chek® Aviva</strong></td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip= £16.21</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<tr>
<td><strong>Accu-Chek® Aviva Expert</strong></td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip= £16.21</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<tr>
<td><strong>Accu-Chek® Compact Plus</strong></td>
<td>Blood glucose</td>
<td>Compact®</td>
<td>3 x 17 strips= £16.65</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td><strong>Accu-Chek® Mobile</strong></td>
<td>Blood glucose</td>
<td>Mobile®</td>
<td>100 device= £0.00</td>
<td>0.3-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td><strong>Accu-Chek® Aviva Nano</strong></td>
<td>Blood glucose</td>
<td>Aviva®</td>
<td>50 strip= £16.21</td>
<td>0.6-33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
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<tr>
<td><strong>BGStar® Free of charge</strong></td>
<td>Blood glucose</td>
<td>BGStar®</td>
<td>50 strip= £14.73</td>
<td>1.1-33.3 mmol/litre</td>
<td>Sanofi</td>
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<tr>
<td><strong>Breeze 2®</strong></td>
<td>Blood glucose</td>
<td>Breeze 2®</td>
<td>50 strip= £15.00</td>
<td>0.6-33.3 mmol/litre</td>
<td>Bayer Plc</td>
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<tr>
<td><strong>CareSens N® Free of charge</strong></td>
<td>Blood glucose</td>
<td>CareSens N®</td>
<td>50 strip= £12.75</td>
<td>1.1-33.3 mmol/litre</td>
<td>Spirit Healthcare Ltd</td>
</tr>
<tr>
<td><strong>Contour®</strong></td>
<td>Blood glucose</td>
<td>Contour®</td>
<td>50 strip= £9.95</td>
<td>0.6-33.3 mmol/litre</td>
<td>Ascensia Diabetes Care UK Ltd</td>
</tr>
<tr>
<td><strong>Contour® XT</strong></td>
<td>Blood glucose</td>
<td>Contour® Next</td>
<td>50 strip= £15.16</td>
<td>0.6-33.3 mmol/litre</td>
<td>Ascensia Diabetes Care UK Ltd</td>
</tr>
<tr>
<td><strong>Element®</strong></td>
<td>Blood glucose</td>
<td>Element®</td>
<td>50 strip= £9.89</td>
<td>0.55-33.3 mmol/litre</td>
<td>Neon Diagnostics Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle® Meter no longer available</strong></td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Freedom® Meter no longer available</strong></td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Freedom Lite®</strong></td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle InsuLink®</strong></td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Lite®</strong></td>
<td>Blood glucose</td>
<td>FreeStyle Lite®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Mini® Meter no longer available</strong></td>
<td>Blood glucose</td>
<td>FreeStyle®</td>
<td>50 strip= £16.23</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Optium®</strong></td>
<td>Blood glucose</td>
<td>FreeStyle Optium®</td>
<td>50 strip= £16.12</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Optium®</strong></td>
<td>Blood ketones</td>
<td>FreeStyle Optium®/ketone</td>
<td>10 strip= £21.71</td>
<td>0-8.0 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Optium Neo®</strong></td>
<td>Blood glucose</td>
<td>FreeStyle Optium®</td>
<td>50 strip= £16.12</td>
<td>1.1-27.8 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>FreeStyle Optium Neo®</strong></td>
<td>Blood ketones</td>
<td>FreeStyle Optium®/ketone</td>
<td>10 strip= £21.71</td>
<td>0-8.0 mmol/litre</td>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td><strong>GlucoDock® module</strong></td>
<td>Blood glucose</td>
<td>GlucoDock®</td>
<td>50 strip= £14.90</td>
<td>1.1-33.3 mmol/litre For use with iPhone®, iPod touch®, and iPad®</td>
<td>Medisana Healthcare (UK) Ltd</td>
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<tr>
<td><strong>GlucoLab®</strong></td>
<td>Blood glucose</td>
<td>GlucoLab®</td>
<td>50 strip= £9.89</td>
<td>0.55-33.3 mmol/litre</td>
<td>Neon Diagnostics Ltd</td>
</tr>
<tr>
<td>Meter (all (\text{part}^{\text{TM}}))</td>
<td>Type of monitoring</td>
<td>Compatible test strips</td>
<td>Test strip net price</td>
<td>Sensitivity range (mmol/litre)</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>--------------------------------</td>
<td>--------------</td>
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<tr>
<td>GlucoMen(^{\text{TM}}) GM</td>
<td>Blood glucose</td>
<td>GlucoMen(^{\text{TM}}) GM</td>
<td>50 strip= £9.95</td>
<td>0.6–33.3 mmol/litre</td>
<td>A. Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoMen(^{\text{TM}}) LX</td>
<td>Blood glucose</td>
<td>GlucoMen(^{\text{TM}}) LX Sensor</td>
<td>50 strip= £15.76</td>
<td>1.1–33.3 mmol/litre</td>
<td>A. Menarini Diagnostics Ltd</td>
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<tr>
<td>GlucoMen(^{\text{TM}}) LX Plus</td>
<td>Blood glucose</td>
<td>GlucoMen(^{\text{TM}}) LX Sensor</td>
<td>50 strip= £15.76</td>
<td>1.1–33.3 mmol/litre</td>
<td>A. Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoMen(^{\text{TM}}) LX Plus</td>
<td>Blood ketones</td>
<td>GlucoMen(^{\text{TM}}) LX Ketone</td>
<td>10 strip= £21.06</td>
<td>0–0.8 mmol/litre</td>
<td>A. Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoMen(^{\text{TM}}) Visio</td>
<td>Blood glucose</td>
<td>GlucoMen(^{\text{TM}}) Visio Sensor</td>
<td>50 strip= £0.00</td>
<td>1.1–33.3 mmol/litre</td>
<td>A. Menarini Diagnostics Ltd</td>
</tr>
<tr>
<td>GlucoRx(^{\text{TM}}) Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>GlucoRx(^{\text{TM}})</td>
<td>50 strip= £5.45</td>
<td>1.1–33.3 mmol/litre</td>
<td>GlucoRx Ltd</td>
</tr>
<tr>
<td>GlucoRx Nexus(^{\text{TM}}) Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>GlucoRx Nexus(^{\text{TM}})</td>
<td>50 strip= £9.95</td>
<td>1.1–33.3 mmol/litre</td>
<td>GlucoRx Ltd</td>
</tr>
<tr>
<td>Glucotrend(^{\text{TM}}) Meter no longer available</td>
<td>Blood glucose</td>
<td>Active(^{\text{TM}})</td>
<td>50 strip= £10.03</td>
<td>0.6–33.3 mmol/litre</td>
<td>Roche Diabetes Care Ltd</td>
</tr>
<tr>
<td>iBGStar(^{\text{TM}})</td>
<td>Blood glucose</td>
<td>BGStar(^{\text{TM}})</td>
<td>50 strip= £14.73</td>
<td>1.1–33.3 mmol/litre</td>
<td>Sanofi</td>
</tr>
<tr>
<td>IME-DC(^{\text{TM}})</td>
<td>Blood glucose</td>
<td>IME-DC(^{\text{TM}})</td>
<td>50 strip= £14.10</td>
<td>1.1–33.3 mmol/litre</td>
<td>Arctic Medical Ltd</td>
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<tr>
<td>Mendor Discreet(^{\text{TM}})</td>
<td>Blood glucose</td>
<td>Mendor Discreet(^{\text{TM}})</td>
<td>50 strip= £14.75</td>
<td>1.1–33.3 mmol/litre</td>
<td>SpringMed Solutions Ltd</td>
</tr>
<tr>
<td>Microdot(^{\text{TM}})+ Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>Microdot(^{\text{TM}})+</td>
<td>50 strip= £9.49</td>
<td>1.1–29.2 mmol/litre</td>
<td>Cambridge Sensors Ltd</td>
</tr>
<tr>
<td>MyGlucoHealth(^{\text{TM}})</td>
<td>Blood glucose</td>
<td>MyGlucoHealth(^{\text{TM}})</td>
<td>50 strip= £15.50</td>
<td>0.6–33.3 mmol/litre</td>
<td>Entra Health Systems Ltd</td>
</tr>
<tr>
<td>Omnitest(^{\text{TM}}) 3</td>
<td>Blood glucose</td>
<td>Omnitest(^{\text{TM}}) 3</td>
<td>50 strip= £9.89</td>
<td>0.6–33.3 mmol/litre</td>
<td>B.Braun Medical Ltd</td>
</tr>
<tr>
<td>One Touch Ultra(^{\text{TM}}) Meter no longer available</td>
<td>Blood glucose</td>
<td>One Touch Ultra(^{\text{TM}})</td>
<td>50 strip= £9.99</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch Ultra 2(^{\text{TM}}) Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>One Touch Ultra(^{\text{TM}})</td>
<td>50 strip= £9.99</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
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<tr>
<td>One Touch UltraEasy(^{\text{TM}}) Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>One Touch Ultra(^{\text{TM}})</td>
<td>50 strip= £9.99</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch UltraSmart(^{\text{TM}}) Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>One Touch Ultra(^{\text{TM}})</td>
<td>50 strip= £9.99</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch(^{\text{TM}}) VerioPro Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>One Touch(^{\text{TM}}) Verio</td>
<td>50 strip= £15.12</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
</tr>
<tr>
<td>One Touch(^{\text{TM}}) Vita Free of charge from diabetes healthcare professionals</td>
<td>Blood glucose</td>
<td>One Touch(^{\text{TM}}) Vita</td>
<td>50 strip= £15.07</td>
<td>1.1–33.3 mmol/litre</td>
<td>LifeScan</td>
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<tr>
<td>SD CodeFree(^{\text{TM}})</td>
<td>Blood glucose</td>
<td>SD CodeFree(^{\text{TM}})</td>
<td>50 strip= £6.99</td>
<td>0.6–33.3 mmol/litre</td>
<td>SD Biosensor Inc</td>
</tr>
<tr>
<td>Sensocard Plus(^{\text{TM}}) Meter no longer available</td>
<td>Blood glucose</td>
<td>Sensocard(^{\text{TM}})</td>
<td>50 strip= £16.30</td>
<td>1.1–33.3 mmol/litre</td>
<td>BBI Healthcare Ltd</td>
</tr>
</tbody>
</table>
### Diabetic testing strips

<table>
<thead>
<tr>
<th>Meter (all except)</th>
<th>Type of monitoring</th>
<th>Compatible test strips</th>
<th>Test strip net price</th>
<th>Sensitivity range (mmol/litre)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SuperCheck®</td>
<td>Blood glucose</td>
<td>SuperCheck®</td>
<td>50 strip = £0.00</td>
<td>1.1–33.3 mmol/litre</td>
<td>Apollo Medical Technologies Ltd</td>
</tr>
<tr>
<td>TRUEyou®</td>
<td>Blood glucose</td>
<td>TRUEyou®</td>
<td>50 strip = £9.92</td>
<td>1.1–33.3 mmol/litre</td>
<td>Nipro Diagnostics (UK) Ltd</td>
</tr>
<tr>
<td>WaveSense JAZZ®</td>
<td>Blood glucose</td>
<td>WaveSense JAZZ®</td>
<td>50 strip = £8.74</td>
<td>1.1–33.3 mmol/litre</td>
<td>AgaMatrix Europe Ltd</td>
</tr>
</tbody>
</table>

**Diabetic testing strips** (Ascensia Diabetes Care UK Ltd)
50 strip - NHS indicative price = £2.89 - Drug Tariff (Part IX)

**Element testing strips** (Neon Diagnostics Ltd)
50 strip - NHS indicative price = £1.75 - Drug Tariff (Part IX)

**Finetest Lite testing strips** (Neon Diagnostics Ltd)
50 strip - NHS indicative price = £5.95 - Drug Tariff (Part IX)

**Fora Advanced pro G040 testing strips** (B Braun Medical Ltd)
50 strip - NHS indicative price = £9.25 - Drug Tariff (Part IX)

**FreeStyle Lite testing strips** (Abbott Laboratories Ltd)
50 strip - NHS indicative price = £16.23 - Drug Tariff (Part IX)

**FreeStyle Optium H testing strips** (Abbott Laboratories Ltd)
100 strip - No NHS indicative price available - Drug Tariff (Part IX)

**FreeStyle Optium testing strips** (Abbott Laboratories Ltd)
50 strip - NHS indicative price = £16.12 - Drug Tariff (Part IX)

**FreeStyle Precision Pro testing strips** (Abbott Laboratories Ltd)
100 strip - No NHS indicative price available - Drug Tariff (Part IX)

**FreeStyle testing strips** (Abbott Laboratories Ltd)
50 strip - NHS indicative price = £16.23 - Drug Tariff (Part IX)

**GlucO NEO testing strips** (Neon Diagnostics Ltd)
50 strip - NHS indicative price = £3.99 - Drug Tariff (Part IX)

**GlucO Dock testing strips** (Medisana Healthcare (UK) Ltd)
50 strip - NHS indicative price = £14.90 - Drug Tariff (Part IX)

**GlucO Lab testing strips** (Neon Diagnostics Ltd)
50 strip - NHS indicative price = £3.99 - Drug Tariff (Part IX)

**GlucO Men LX Sensor testing strips** (A Menarini Diagnostics Ltd)
50 strip - NHS indicative price = £15.76 - Drug Tariff (Part IX)

**GlucO Men areo Sensor testing strips** (A Menarini Diagnostics Ltd)
50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)

**GlucO RX G0 Professional testing strips** (GlucO Rx Ltd)
50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)

**GlucO RX G0 testing strips** (GlucO Rx Ltd)
50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)

**GlucO RX HCT Glucose testing strips** (GlucO Rx Ltd)
50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)

**GlucO RX Nexus testing strips** (GlucO Rx Ltd)
50 strip - NHS indicative price = £9.95 - Drug Tariff (Part IX)

**GlucO Q testing strips** (GlucO Rx Ltd)
50 strip - NHS indicative price = £5.45 - Drug Tariff (Part IX)

**GlucO Zen auto testing strips** (GlucO Zen Ltd)
50 strip - NHS indicative price = £10.85 - Drug Tariff (Part IX/100 strip - NHS indicative price = £10.85 - Drug Tariff (Part IX)

**GlucO Flex-R testing strips** (Bio-Diagnostics Ltd)
50 strip - NHS indicative price = £16.75 - Drug Tariff (Part IX)

**IME-DC testing strips** (Arctic Medical Ltd)
50 strip - NHS indicative price = £14.10 - Drug Tariff (Part IX)

**MOD2 testing strips** (Mod2)
50 strip - NHS indicative price = £14.00 - Drug Tariff (Part IX)

**MediTest Glucose testing strips** (BHR Pharmaceuticals Ltd)
50 strip - NHS indicative price = £2.33 - Drug Tariff (Part IX)

**MediSense SoftSense testing strips** (Abbott Laboratories Ltd)
50 strip - NHS indicative price = £15.05 - Drug Tariff (Part IX)

**MediTouch 2 testing strips** (Medisana Healthcare (UK) Ltd)
50 strip - NHS indicative price = £12.49 - Drug Tariff (Part IX)

**MediTouch testing strips** (Medisana Healthcare (UK) Ltd)
50 strip - NHS indicative price = £14.90 - Drug Tariff (Part IX)

**Mendor discreet testing strips** (SpringMed Solutions Ltd)
50 strip - NHS indicative price = £14.75 - Drug Tariff (Part IX)

**Microdot+ testing strips** (Cambridge Sensors Ltd)
50 strip - NHS indicative price = £14.90 - Drug Tariff (Part IX)

**Mobile cassette** (Roche Diabetes Care Ltd)
50 device - NHS indicative price = £9.99 - Drug Tariff (Part IX)

**Myglucohealth testing strips** (Entra Health Systems Ltd)
50 strip - NHS indicative price = £15.50 - Drug Tariff (Part IX)

**MyLife Pura testing strips** (Ypsomed Ltd)
50 strip - NHS indicative price = £9.50 - Drug Tariff (Part IX)

**MyLife Union testing strips** (Ypsomed Ltd)
50 strip - NHS indicative price = £9.50 - Drug Tariff (Part IX)

**OKmeter Core testing strips** (Syringa UK Ltd)
50 strip - NHS indicative price = £9.90 - Drug Tariff (Part IX)

**OmniTest 3 testing strips** (B Braun Medical Ltd)
50 strip - NHS indicative price = £9.89 - Drug Tariff (Part IX)

**OmniTest 5 testing strips** (B Braun Medical Ltd)
50 strip - NHS indicative price = £9.89 - Drug Tariff (Part IX)

**On-Call Advanced testing strips** (Point Of Care Testing Ltd)
50 strip - NHS indicative price = £13.65 - Drug Tariff (Part IX)

**OneTouch Select Plus testing strips** (LifeScan)
50 strip - NHS indicative price = £9.99 - Drug Tariff (Part IX)

**OneTouch Verio testing strips** (LifeScan)
50 strip - NHS indicative price = £15.12 - Drug Tariff (Part IX)

**Perfora testing strips** (Roche Diabetes Care Ltd)
50 strip - NHS indicative price = £7.50 - Drug Tariff (Part IX)
### Blood ketones testing strips

<table>
<thead>
<tr>
<th>Blood ketones testing strips</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD KETONES TESTING STRIPS</strong></td>
</tr>
<tr>
<td>4SURE beta-ketone testing strips (Nipro Diagnostics UK Ltd)</td>
</tr>
<tr>
<td>Fora Advanced pro GD40 Ketone testing strips (B. Braun Medical Ltd)</td>
</tr>
<tr>
<td>FreeStyle Optium H beta-ketone testing strips (Abbott Laboratories Ltd)</td>
</tr>
<tr>
<td>FreeStyle Precision Pro beta-ketone testing strips (Abbott Laboratories Ltd)</td>
</tr>
<tr>
<td>GlucoMen LX beta-ketone testing strips (A. Menarini Diagnostics Ltd)</td>
</tr>
<tr>
<td>GlucoMen area Ketone Sensor testing strips (A. Menarini Diagnostics Ltd)</td>
</tr>
<tr>
<td>GlucoRx HCT Ketone testing strips (GlucoRx Ltd)</td>
</tr>
<tr>
<td>KetoSens testing strips (Spirit Healthcare Ltd)</td>
</tr>
<tr>
<td>StatStrip beta-ketone testing strips (Nova Biomedical)</td>
</tr>
<tr>
<td>Xceed Precision Pro beta-ketone testing strips (Abbott Laboratories Ltd)</td>
</tr>
</tbody>
</table>

### Hypodermic insulin injection pens

#### HYPODERMIC INSULIN INJECTION PENS

**A U T O P E N ® 24**

- **Autopen® 24** (for use with Sanofi- Aventis 3-mL insulin cartridges), allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2-unit dosage adjustment, max. 42 units (2-unit version).
- **Autopen 24** hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units (Owen Mumford Ltd)
  - 1 device - NHS indicative price = £16.71 - Drug Tariff (Part IX)
- **Autopen 24** hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units (Owen Mumford Ltd)
  - 1 device - NHS indicative price = £16.71 - Drug Tariff (Part IX)

**C L I K S T A R ®**

- For use with Lantus®, Apidra®, and Insulan® 3-mL insulin cartridges, allowing 1-unit dose adjustment, max. 80 units.

**H U M A P E N ® L U X U R A H D**

- For use with Humulin® and Humalog® 3-mL cartridges; allowing 0.5-unit dosage adjustment, max. 30 units.
- HumaPen Luxura HD hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0-30 units (Eli Lilly and Company Ltd)
  - 1 device - NHS indicative price = £27.01 - Drug Tariff (Part IX)

**N O V O P E N ® 4**

- For use with Penfil® 3-mL insulin cartridges; allowing 1-unit dosage adjustment, max. 60 units.
- NovoPen 4 hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units (Novo Nordisk Ltd)
  - 1 device - NHS indicative price = £26.86 - Drug Tariff (Part IX)

**S I N S U E T ®**

- For use with any 10-mL vial or 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max 40 units.
- Available as starter set (Insulet® device, nozzle cap, nozzle and piston, 1 × 10-mL adaptor, 1 × 3-mL adaptor, 1 cartridge cap removal key), nozzle pack (15 nozzles), cartridge adaptor pack (15 adaptors), or vial adaptor pack (15 adaptors).
- Insulet starter set (Spirit Healthcare Ltd)
  - 1 pack - NHS indicative price = £90.00 - Drug Tariff (Part IX)

### Needle free insulin delivery systems

#### NEEDLE FREE INSULIN DELIVERY SYSTEMS

**I N S U J E T ®**

- For use with any 10-mL vial or 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max 40 units.
- Diastix testing strips (Ascensia Diabetes Care UK Ltd)
  - 50 strip - NHS indicative price = £2.89 - Drug Tariff (Part IX)
- MediTest Glucose testing strips (BHR Pharmaceuticals Ltd)
  - 50 strip - NHS indicative price = £2.53 - Drug Tariff (Part IX)
Endocrine system

3.2 Hypoglycaemia

Hypoglycaemia

Treatment of hypoglycaemia

Initially glucose p. 1041.10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. If necessary this may be repeated after 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal (if it is due) can prevent blood-glucose concentration from falling again.

Proprietary products of quick-acting carbohydrate (e.g. GlucoGel®, Dextrogel®, GSF-Syrup®, Rapilose®) are available on prescription for patients to keep on hand in case of hypoglycaemia.

Alternatively, approximately 10 g of glucose is available from 2 teaspoons of sugar, or from 3 sugar lumps, and also from non-diet versions of the following soft drinks: 110 mL of Lucozade® Energy Original (also, see note below), 100 mL of Coca-Cola®, 19 mL of Ribena® Blackcurrant (to be diluted).

Note: The carbohydrate content of some commercially available glucose-containing drinks is currently subject to change—individual product labels should be checked.

Patients should be aware that for a time, both old and new bottles and cans may be available—individual product labels should be checked.

Hypoglycaemia which causes unconsciousness is an emergency. Glucagon, below, a polypeptide hormone secreted by the alpha cells of the islets of Langerhans, increases plasma-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. Glucagon may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe on an ‘if necessary’ basis to hospitalised insulin-treated patients, so that it may be given rapidly by the nurses during an hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, glucose intravenous infusion 20% may be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 10% may also be used but larger volumes are needed. Glucose intravenous infusion 50% is not recommended because of the higher risk of extravasation injury and because administration is difficult. Close monitoring is necessary in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Patients whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

See also, emergency management of hypoglycaemia in dental practice for further advice.

Chronic hypoglycaemia

Diazoxide p. 725, administered by mouth, is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. It has no place in the management of acute hypoglycaemia.

GLYCOGENOLYTIC HORMONES

Glucagon

- INDICATIONS AND DOSE

Insulin-induced hypoglycaemia

BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION

Child: 1 month–1 year: 500 micrograms

Child: 2–17 years (body-weight up to 25 kg): 500 micrograms, if no response within 10 minutes intravenous glucose must be given

Child: 2–17 years (body-weight 25 kg and above): 1 mg, if no response within 10 minutes intravenous glucose must be given

Adult: 1 mg, if no response within 10 minutes intravenous glucose must be given

Beta-blocker poisoning (cardiogenic shock unresponsive to atropine)

BY INTRAVENOUS INJECTION

Child: 50–150 micrograms/kg (max. per dose 10 mg), to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion) 50 micrograms/kg/hour

Adult: 2–10 mg, to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion) 50 micrograms/kg/hour

Dose and indication for cardiogenic shock unresponsive to atropine

Adult: (consult product literature)

DOSE EQUVALENT AND CONVERSION

1 unit of glucagon = 1 mg of glucagon.

- UNLICENSED USE

Dose and indication for cardiogenic shock unresponsive to atropine in beta-blocker overdose not licensed.

- CONTRA-INDICATIONS

Phaeochromocytoma

- CAUTIONS

Glucoagonoma - ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency - insulinoma

- INTERACTIONS

Appendix 1: glucagon

- SIDE-EFFECTS

Common or very common Nausea

Uncommon Vomiting

Rare or very rare Abdominal pain - hypotension - hypotension - tachycardia

- DIRECTIONS FOR ADMINISTRATION

With intravenous use in children When administered by continuous intravenous infusion, do not add to infusion fluids containing calcium—precipitation may occur.

- PATIENT AND CARER ADVICE

Medicines for Children leaflet: Glucagon for hypoglycaemia

www.medicinesforchildren.org.uk/glucagon-hypoglycaemia
3.2a Chronic hypoglycaemia

GLYCOGENOLYTIC HORMONES

Diazoxide

- **INDICATIONS AND DOSE**
  - Chronic intractable hypoglycaemia
    - **BY MOUTH**
    - Adult: Initially 5 mg/kg daily in 2–3 divided doses, adjusted according to response; maintenance 3–8 mg/kg daily in 2–3 divided doses

- **CAUTIONS**
  - Aortic coarctation • aortic stenosis • arteriovenous shunt • heart failure • hyperuricaemia • impaired cardiac circulation • impaired cerebral circulation

- **INTERACTIONS**
  - → Appendix 1: diazoxide

- **SIDE-EFFECTS**
  - Abdominal pain • albuminuria • appetite decreased (long term use) • arrhythmia • azotaemia • cardiomegaly • cataract • constipation • diabetic hyperosmolar coma • diarrhoea • dizziness • dyspnoea • eosinophilia • extrapyramidal symptoms • fever • fluid retention • galactorrhoea • haemorrhage • headache • heart failure • hirsutism • hyperglycaemia • hyperuricaemia (long term use) • hypogammaglobulinaemia • hypotension • ileus • ketoacidosis • leucopenia • libido decreased • musculoskeletal pain • nausea • nephritic syndrome • oculargrycic crisis • pancreatitis • parkinsonism • pulmonary hypertension • skin reactions • sodium retention • taste altered • thrombocytopenia • tinnitus • vision disorders • voice alteration (long term use) • vomiting

- **PREGNANCY**
  - Use only if essential; alopecia and hypertrichosis reported in neonates with prolonged use; may inhibit uterine activity during labour.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT**
  - Dose adjustments
    - Dose reduction may be required.

- **MONITORING REQUIREMENTS**
  - Monitor blood pressure.
  - Monitor white cell and platelet count during prolonged use.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

  **Tablet**
  - Eudemine (RPH Pharmaceuticals AB)
  - Diazoxide 50 mg • Eudemine 50mg tablets | 100 tablet | £46.45

  **Capsule**
  - Proglycem (Imported (Germany))
  - Diazoxide 25 mg • Proglycem 25 capsules | 100 capsule | £52

Osteoporosis

**Description of condition**

Osteoporosis is a progressive bone disease characterised by low bone mass measured by bone mineral density (BMD), and microarchitectural deterioration of bone tissue. This leads to an increased risk of fragility fractures as a result. Osteoporosis is considered severe if there have been one or more fragility fractures.

Osteoporosis occurs most commonly in postmenopausal women, men over 50 years, and in patients taking long-term oral corticosteroids (glucocorticoids). Risk factors for osteoporosis include age, low body mass index (BMI), cigarette smoking, excess alcohol intake, lack of physical activity, vitamin D deficiency and low calcium intake, family history of hip fractures, a previous fracture at a site characteristic of osteoporotic fractures and early menopause. Some diseases are also known to be associated with osteoporosis such as rheumatoid arthritis and diabetes.

**Aims of treatment**

A combination of lifestyle changes and drug treatment aims to prevent bone fractures in patients with osteoporosis.

**Lifestyle changes**

- Patients should be encouraged to increase their level of physical activity, stop smoking, maintain a normal BMI level (between 20–25 kg/m²), and reduce their alcohol intake to improve their bone health and reduce the risk of fragility fractures. A For guidance on stopping smoking, see Smoking cessation p. 497.

- Patients at risk of osteoporosis should also ensure an adequate intake of calcium and vitamin D, preferably through increasing dietary intake.

- Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and can benefit from supplements. A Elderly patients also have an increased risk of falls (see Prescribing in the elderly p. 30).

**Drug treatment**

**Postmenopausal osteoporosis**

The therapeutic options for the prevention and treatment of osteoporosis in postmenopausal women are the same. Oral bisphosphonates, alendronic acid p. 727 and risedronate sodium p. 730 are considered as first-line choices for most patients with postmenopausal osteoporosis due to their broad spectrum of anti-fracture efficacy. Alendronic acid and risedronate sodium have been shown to reduce occurrence of vertebral, non-vertebral and hip fractures. Intravenous bisphosphonates (ibandronic acid p. 728 or zoledronic acid p. 732), denosumab p. 734, or raloxifene hydrochloride p. 754 are alternative options in women who are intolerant of oral bisphosphonates or in whom they are contra–indicated.

Hormone replacement therapy (HRT) is an additional option. The use of HRT for osteoporosis is generally restricted to younger postmenopausal women with menopausal symptoms who are at high risk of fractures. This is due to the risk of adverse effects such as cardiovascular disease and cancer in older postmenopausal women and women on long-term HRT therapy.

Teriparatide p. 734 is reserved for postmenopausal women with severe osteoporosis at very high risk for vertebral fractures. Its duration of treatment is limited to 24 months.

**A**
Glucocorticoid-induced osteoporosis
Glucocorticoid therapy is associated with bone loss and increased risk of fractures. The greatest rate of bone loss occurs early after initiation of glucocorticoids and increases with dose and duration of therapy. **Bone-protection treatment** should be started at the onset of therapy in patients who are at a high risk of fracture. If glucocorticoid therapy is stopped, the need to continue bone-protection treatment should be reviewed. However, bone-protection treatment should be continued with long-term glucocorticoid therapy. Complex cases of glucocorticoid-induced osteoporosis should be referred to a specialist.

Women aged 70 years or over, or with a previous fragility fracture, or taking large doses of glucocorticoids (prednisolone ≥ 7.5 mg daily or equivalent) are at high risk of fractures and should be assessed for prophylactic bone-protection. Some younger patients, particularly those with a previous history of fracture or receiving high doses of glucocorticoids can also be considered for bone-protection treatment.

The therapeutic options for prophylaxis and treatment of glucocorticoid-induced osteoporosis are the same; oral bisphosphonates, alendronic acid, or risedronate sodium are first-line options. Intravenous zoledronic acid or teriparatide are alternatives in patients intolerant of oral bisphosphonates or in whom they are contra-indicated.

Osteoporosis in men
Oral bisphosphonates, alendronic acid or risedronate sodium are recommended as first-line treatments for osteoporosis in men. Intravenous zoledronic acid or denosumab are alternatives in men who are intolerant of oral bisphosphonates or in whom they are contra-indicated; teriparatide is an additional option.

Men having long-term androgen deprivation therapy for prostate cancer have an increased fracture risk. Fracture risk should be assessed when starting this therapy. A bisphosphonate can be offered to men with confirmed osteoporosis; denosumab is an alternative if bisphosphonates are contra-indicated or not tolerated.

**Bisphosphonates: treatment duration**
There is some evidence to suggest that patients can benefit from a bisphosphonate-free period as their therapeutic effects last for some time after cessation of treatment.

Bisphosphonate treatment should be reviewed after 5 years of treatment with alendronic acid, risedronate sodium or ibandronic acid, and after 3 years of treatment with zoledronic acid. Patients over 75 years of age, or with a history of previous hip or vertebral fracture, or patients who have had one or more fragility fractures during treatment, or who are taking long-term glucocorticoid therapy can continue bisphosphonates beyond this period.

**Useful Resources**

**Other drugs used for Disorders of bone metabolism**
Calcitriol, p. 1083

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**ANABOLIC STEROIDS**

**Nandrolone**

- **INDICATIONS AND DOSE**
  - **Osteoporosis in postmenopausal women (but not recommended)**
    - BY DEEP INTRAMUSCULAR INJECTION
      - Adult (female): 50 mg every 3 weeks.
  - **CONTRA-INDICATIONS**
    - Acute porphyrias p. 1058
  - **CAUTIONS**
    - Cardiac impairment - diabetes mellitus - epilepsy - hypertension - migraine - skeletal metastases (risk of hypercalcaemia)
  - **INTERACTIONS**
    - Appendix 1: nandrolone
  - **SIDE-EFFECTS**
    - Clitoris enlarged - dysphonia - hepatic disorders - hepatic neoplasm - hirsutism - hypertension - libido increased - nausea - oedema - skin reactions - sodium retention - urine flow decreased - virilism (with high doses including voice changes - sometimes irreversible)
  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises caution in severe impairment (discontinue treatment if hepatic function worsens or if oedema, with or without congestive heart failure, develops).
  - **RENAL IMPAIRMENT**
    - Use with caution—may cause sodium and water retention.
  - **LESS SUITABLE FOR PRESCRIBING**
    - Nandrolone injection is less suitable for prescribing.
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - EXCIPIENTS: May contain Arachis (peanut) oil, benzyl alcohol
    - Nandrolone decanoate 50 mg per 1 ml Deca-Durabolin 50mg/1ml solution for injection ampoules | 1 ampoule (dose recommended) [£3.17 (excl)]

**BISPHOSPHONATES**

**Bisphosphonates**

- **DRUG ACTION**
  - Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVISORY BOARD: BISPHOSPHONATES: ATYPICAL FEMORAL FRACTURES (JUNE 2011)

Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis. The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.

Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.


The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget’s disease.
Risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease.

All patients should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients should also maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling, non-healing sores or discharge to a doctor and dentist during treatment.

Before prescribing an intravenous bisphosphonate, patients should be given a patient reminder card and informed of the risk of osteonecrosis of the jaw. Advise patients to tell their doctor if they have any problems with their mouth or teeth before starting treatment, and if the patient wears dentures, they should make sure their dentures fit properly. Patients should tell their doctor and dentist that they are receiving an intravenous bisphosphonate if they need dental treatment or dental surgery.


MHRA/CHM ADVICE: BISPHOSPHONATES: OSTEONECROSIS OF THE EXTERNAL AUDITORY CANAL (DECEMBER 2015)

Benign idiopathic osteonecrosis of the external auditory canal has been reported very rarely with bisphosphonate treatment, mainly in patients receiving long-term therapy (2 years or longer).

The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or suspected cholesteatoma.

Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cotton-bud use.

Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.

### Side-effects

- **Common or very common** Alopeica · anaemia · arthralgia · asthenia · constipation · diarrhoea · dizziness · dysphagia · electrolyte imbalance · eye inflammation · fever · gastritis · gastrointestinal discomfort · headache · influenza like illness · malaise · myalgia · nausea · oesophageal ulcer (discontinue) · oesophagitis (discontinue) · pain · peripheral oedema · renal impairment · skin reactions · taste altered · vomiting

- **Uncommon** Anaphylactic reaction · angioedema · bronchospasm · oesophageal stenosis (discontinue) · osteonecrosis

- **Rare or very rare** Atypical femur fracture · Stevens–Johnson syndrome

### Patient and Carer Advice

**Atypical femoral fractures** Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.

**Osteonecrosis of the jaw** During bisphosphonate treatment patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms.

**Osteonecrosis of the external auditory canal** Patients should be advised to report any ear pain, discharge from ear or an ear infection during treatment with a bisphosphonate.

### Indications and dose

**Treatment of postmenopausal osteoporosis**

| BY MOUTH | Adult (female): 10 mg daily, alternatively 70 mg once weekly. |

**Treatment of osteoporosis in men**

| BY MOUTH | Adult (male): 10 mg daily. |

**Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy**

| BY MOUTH | Adult (female): 10 mg daily. |

### Contra-indications

- Abnormalities of oesophagus - hypocalcaemia - other factors which delay emptying (e.g. stricture or achalasia)

### Caution

- Active gastrointestinal bleeding - atypical femoral fractures - duodenitis - dysphagia - exclude other causes of osteoporosis - gastritis - history (within 1 year) of ulcers - surgery of the upper gastrointestinal tract - symptomatic oesophageal disease - ulcers - upper gastrointestinal disorders

### Interactions

- **Common or very common** Gastrointestinal disorders - joint swelling - vertigo

- **Uncommon** Haemorrhage

- **Rare or very rare** Femoral stress fracture - oropharyngeal ulceration - photosensitivity reaction - severe cutaneous adverse reactions (SCARs)

### Side-effects, Further Information

Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

### Pregnancy

Avoid.

### Breast Feeding

Manufacturer advises avoid—no information available.

### Renal Impairment

Avoid if eGFR less than 35 mL/minute/1.73 m².

### Monitoring Requirements

Correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting treatment. Monitor serum-calcium concentration during treatment.

### Directions for Administration

Tablets should be swallowed whole and oral solution should be swallowed as a single 100 mL dose. Doses should be taken with plenty of water while sitting or standing, on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after administration.

### Patient and Carer Advice

Patients or their carers should be given advice on how to administer alendronic acid tablets and oral solution. Oesophageal reactions Patients (or their carers) should be advised to stop taking alendronic acid and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.
**Alendronic acid with colecalciferol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, alendronic acid p. 727, colecalciferol p. 1084.

**INDICATIONS AND DOSE**

**Treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency**

- **BY MOUTH**
  - Adult (female): 1 tablet once weekly.

**INTERACTIONS** → Appendix 1: bisphosphonates - vitamin D substances

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- **Bisphosphonates for treating osteoporosis (updated February 2018)** NICE TA464

This technology appraisal guidance should be applied clinically in conjunction with:

- **NICE guideline on assessing the risk of fragility fractures (CG146)**, which defines who is eligible for osteoporotic fracture risk assessment.

- **NICE quality standard on osteoporosis (QS149)**, which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment.

Alendronic acid is recommended as an option for treating osteoporosis in patients, only if:

- the person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and

- the 10-year probability of osteoporotic fracture fragility is at least 1%.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangement, until they and their NHS clinician consider it appropriate to stop.

[www.nice.org.uk/guidance/ta464](www.nice.org.uk/guidance/ta464)

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1137/16

The Scottish Medicines Consortium has advised (April 2016) that alendronic acid (Binosto®) is accepted for restricted use within NHS Scotland for the treatment of postmenopausal osteoporosis where alendronic acid is the appropriate treatment choice, but the patient is unable to swallow tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of medicines containing the same drug.

**Tablet**

- **Alendronic acid with colecalciferol (Non-proprietary)**

  Colecalciferol 70 microgram, Alendronic acid (as Alendronate sodium) 70 mg | 4 tablet (PDB) £22.80-£24.94 DT = £24.94

  Colecalciferol 140 microgram, Alendronic acid (as Alendronate sodium) 70 mg | 4 tablet (PDB) £45.25

- **Fosavance** (Merck Sharp & Dohme Ltd)

  Colecalciferol 70 microgram, Alendronic acid (as Alendronate sodium) 70 mg | 4 tablet (PDB) £22.80 DT = £24.94

- **Bentexo** (Conscient Health Ltd)

  Colecalciferol 70 microgram, Alendronic acid (as Alendronate sodium) 70 mg | 4 tablet (PDB) £22.80 DT = £24.94

**lindsay acid**

**INDICATIONS AND DOSE**

**Reduction of bone damage in bone metastases in breast cancer**

- **INITIALLY BY MOUTH**
  - Adult: 50 mg daily, alternatively (by intravenous infusion) 6 mg every 3–4 weeks

**Hypercalcaemia of malignancy**

- **BY INTRAVENOUS INFUSION**
  - Adult: 2–4 mg as a single infusion, dose to be adjusted according to serum calcium concentration

**TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS**

- **INITIALLY BY MOUTH**
  - Adult (female): 150 mg once a month, alternatively (by intravenous injection) 3 mg every 3 months, to be administered over 15–30 seconds.

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

Hypocalcaemia

**SPECIFIC CONTRA-INDICATIONS**

- With oral use Abnormalities of the oesophagus - other factors which delay emptying (e.g. stricture or achalasia)

**CAUTIONS**

- Atypical femoral fractures - cardiac disease (avoid fluid overload)

**INTERACTIONS** → Appendix 1: bisphosphonates

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Face oedema

- Uncommon Asthma exacerbated

**SPECIFIC SIDE-EFFECTS**

- Common or very common
  - With intravenous use Bundle branch block - cataract - increased risk of infection - joint disorder - oral disorders - osteoarthritis - parathyroid disorder - thirst
  - With oral use Acute phase reaction - gastrointestinal disorders - muscle cramps - musculoskeletal stiffness

- Uncommon
- pulmonary oedema - radiculopathy - renal cyst - sleep disorder - stridor - urinary retention - weight decreased

- Rare or very rare
- With intravenous use
- Hypersensitivity
- Frequency not known
- With oral use
- Oesophagitis erosive (discontinue)
- PREGNANCY
- Avoid.
- BREAST FEEDING
- Avoid—present in milk in animal studies.

- RENAL IMPAIRMENT
- When used for postmenopausal osteoporosis, avoid if eGFR less than 30 mL/minute/1.73 m².

**Dose adjustments**
- With intravenous use
  - When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 4 mg and infuse over 1 hour; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 2 mg and infuse over 1 hour.
  - With oral use
    - When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 50 mg on alternative days; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 50 mg once weekly.

- MONITORING REQUIREMENTS
- Monitor renal function and serum calcium, phosphate and magnesium.

- DIRECTIONS FOR ADMINISTRATION
- Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes after food or drink (other than water) of the day, or another oral medicine; patient should stand or sit upright for at least 1 hour after taking tablet.

  For intravenous infusion (Bondronat®), give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute requisite dose in 500 mL infusion fluid and give over 1–2 hours.

- PATIENT AND CARER ADVICE
- Patients or carers should be given advice on how to administer ibandronic acid tablets. Oesophageal reactions Patients and carers should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.

  Patient reminder card A patient reminder card should be provided to patients receiving intravenous ibandronic acid (risk of osteonecrosis of the jaw).

- NATIONAL FUNDING/ACCESS DECISIONS

  - NICE decisions
    - Bisphosphonates for treating osteoporosis (updated February 2018) NICE TA464
      - This technology appraisal guidance should be applied clinically in conjunction with:
        - NICE guideline on assessing the risk of fragility fractures (CG146), which defines who is eligible for osteoporotic fracture risk assessment.
        - NICE quality standard on osteoporosis (QS149), which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment.

      **With oral use**
      - ibandronic acid is recommended as an option for treating osteoporosis in patients, only if:
        - the person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and
        - the 10-year probability of osteoporotic fragility fracture is at least 1%.

      **With intravenous use**
      - ibandronic acid is recommended as an option for treating osteoporosis in patients, only if:
        - the person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and
        - the 10-year probability of osteoporotic fragility fracture is at least 10%, or
        - the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contra-indicated or not tolerated.

  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

    - www.nice.org.uk/guidance/ta464

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - ibandronic acid (Non-proprietary)
    - ibandronic acid (as ibandronic sodium monohydrate) 1 mg per 1 mL ibandronic acid 3 mg/3 mL solution for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £65.20–£66.00 DT = £65.40
    - Bonviva (Atnahs Pharma UK Ltd)
      - ibandronic acid (as ibandronic sodium monohydrate) 1 mg per 1 mL Bonviva 3 mg/3 mL solution for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £68.64 DT = £65.40

  **Solution for infusion**
  - ibandronic acid (Non-proprietary)
    - ibandronic acid (as ibandronic sodium monohydrate) 1 mg per 1 mL ibandronic acid 6 mg/6 mL concentrate for solution for infusion vials | 1 vial (PFS) £130.42 (Hospital only)
      - ibandronic acid 2 mg/2 mL concentrate for solution for infusion vials | 1 vial (PFS) £43.47 (Hospital only)
    - Bondronat (Atnahs Pharma UK Ltd)
      - ibandronic acid (as ibandronic sodium monohydrate) 1 mg per 1 mL Bondronat 2 mg/2 mL concentrate for solution for infusion vials | 1 vial (PFS) £89.36 (Hospital only)
      - Bondronat 6 mg/6 mL concentrate for solution for infusion vials | 1 vial (PFS) £183.69

  **Tablet**
  - ibandronic acid (Non-proprietary)
    - ibandronic acid (as ibandronic sodium monohydrate) 50 mg | 28 tablet (PFS) £186.69 DT = £26.30
    - ibandronic acid (as ibandronic sodium monohydrate) 150 mg | 150 mg tablets | 1 tablet (PFS) £19.95 DT = £1.10
    - Bondronat (Atnahs Pharma UK Ltd)
      - ibandronic acid (as ibandronic sodium monohydrate) 50 mg | 50 mg tablets | 28 tablet (PFS) £183.69 DT = £26.30
      - ibandronic acid (as ibandronic sodium monohydrate) 150 mg | 150 mg tablets | 1 tablet (PFS) £18.40 DT = £1.10
  - Iasibon (Aspire Pharma Ltd)
    - ibandronic acid (as ibandronic sodium monohydrate) 50 mg | 50 mg tablets | 28 tablet (PFS) £174.50 DT = £26.30
    - Quodixor (Aspire Pharma Ltd)
      - ibandronic acid (as ibandronic sodium monohydrate) 150 mg | 150 mg tablets | 1 tablet (PFS) £18.40 DT = £1.10

**Pamidronate disodium**

(Formerly called aminohydroxypropyldenediphosphonate disodium (APD))

- INDICATIONS AND DOSE

  **Hypercalcaemia of malignancy**
  - Adult: 15–50 mg, to be given (via cannula in a relatively large vein) as a single infusion or in divided doses over 2–4 days, dose adjusted according to serum calcium concentration; maximum 90 mg per course

  **Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma**
  - By intravenous infusion
    - Adult: 90 mg every 4 weeks, to be administered via cannula in a relatively large vein, dose may continued →


**Disorders of bone metabolism**

### Paget’s disease of bone

- **BY INTRAVENOUS INFUSION**
  - Adult: 30 mg every week for a 6 week course (total dose 180 mg), alternatively initially 30 mg once weekly for 1 week, then increased to 60 mg every 2 weeks (max. per dose 60 mg) for a 6 week course (total dose 210 mg), to be administered via cannula in a relatively large vein, course may be repeated every 6 months; maximum 360 mg per course

### Contraindications

- Atypical femoral fractures - cardiac disease (especially in elderly) - ensure adequate hydration - previous thyroid surgery (risk of hypocalcaemia)

### Interactions

- Appendix 1: bisphosphonates

### Side-effects

- **Common or very common** Appetite decreased - chills - decreased leucocytes - drowsiness - flushing - hypertension - insomnia - paraesthesia - tetany - thrombocytopenia
- **Uncommon** Agitation - dyspnoea - hypotension - muscle cramps - seizure
- **Rare or very rare** Confusion - glomerulonephritis - haematuria - heart failure - nephritis tubulointerstitial - nephrotic syndrome - oedema - pulmonary oedema - reactivation of infections - renal disorder exacerbated - renal tubular disorder - respiratory disorders - visual hallucinations - xanthopsia

### Frequency not known

- Atrial fibrillation

### Side-effects, Further information

**Oral supplements** are advised to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases or multiple myeloma at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and in those with Paget’s disease.

### Pregnancy

- Avoid - toxicity in animal studies.

### Breast Feeding

- Avoid.

### Hepatic impairment

- Manufacturer advises caution in severe hepatic impairment (no information available).

### Renal impairment

- **Dose adjustments** Max. infusion rate 20 mg/hour. Avoid if eGFR less than 30 mL/minute/1.73 m², except in life-threatening hypercalcaemia if benefit outweighs risk.
- If renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

### Monitoring requirements

- Monitor serum electrolytes, calcium and phosphate - possibility of convulsions due to electrolyte changes.
- Assess renal function before each dose.

### Directions for administration

- For **slow intravenous infusion** (Pamidronate disodium, Hospira, Medac, Wockhardt), give intermittently in Glucose 5% or Sodium chloride 0.9%; give at a rate not exceeding 1 mg/minute; not to be given with infusion fluids containing calcium. For **Pamidronate disodium** (Medac, Hospira, Wockhardt) dilute with infusion fluid to a concentration of not more than 90 mg in 250 mL

### Patient and carer advice

- A patient reminder card should be provided (risk of osteonecrosis of the jaw).
- **Driving and skilled tasks** Patients should be warned against performing skilled tasks (e.g. cycling, driving or operating machinery) immediately after treatment (somnolence or dizziness can occur).

### Medicinal forms

- There can be variation in the licensing of different medicines containing the same drug.

#### Solution for infusion

- **Pamidronate disodium (Non-proprietary)**
  - **Pamidronate disodium 3 mg per 1 ml** Pamidronate disodium 15mg/5ml solution for infusion vials | 1 vial (Hospital only) | 5 vial (Hospital only) €14.15 (Hospital only)
  - **Pamidronate disodium 30mg/10ml solution for infusion vials** | 1 vial (Hospital only) €55.00–€98.66 (Hospital only)
  - **Pamidronate disodium 60mg/20ml solution for infusion vials** | 1 vial (Hospital only) €110.00 (Hospital only)
  - **Pamidronate disodium 90mg/30ml solution for infusion vials** | 1 vial (Hospital only) €165.00 (Hospital only)

- **Pamidronate disodium 9 mg per 1 ml** Pamidronate disodium 90mg/10ml solution for infusion vials | 1 vial (Hospital only) €170.45 (Hospital only)

- **Pamidronate disodium 15 mg per 1 ml** Pamidronate disodium 60mg/4ml solution for infusion ampoules | 1 ampoule (Hospital only) €119.32
  - Pamidronate disodium 15mg/1ml solution for infusion ampoules | 4 ampoules (Hospital only) €119.32
  - **Pamidronate disodium 90mg/6ml solution for infusion ampoules** | 1 ampoule (Hospital only) €170.46
  - Pamidronate disodium 30mg/2ml solution for infusion ampoules | 2 ampoules (Hospital only) €119.32

### Risedronate sodium

#### Indications and dose

**Paget’s disease of bone**

- **BY MOUTH**
  - Adult: 30 mg daily for 2 weeks, course may be repeated if necessary after at least 2 months

#### Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures

- **BY MOUTH**
  - Adult (female): 5 mg daily, alternatively 35 mg once weekly.

#### Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women

- **BY MOUTH**
  - Adult (female): 5 mg daily.

#### Treatment of osteoporosis in men at high risk of fractures

- **BY MOUTH**
  - Adult (male): 35 mg once weekly.

### Contraindications

- Hypocalcaemia

### Caution

- Atypical femoral fractures - oesophageal abnormalities - other factors which delay transit or emptying (e.g. stricture or achalasia)

### Interactions

- Appendix 1: bisphosphonates

### Side-effects

- **Uncommon** Gastrointestinal disorders
- **Rare or very rare** Glosisitis
- **Frequency not known** Amblyopia - apnoea - chest pain - corneal lesion - dry eye - hypersensitivity - hypersensitivity vasculitis - increased risk of infection - leg cramps - liver disorder - muscle weakness - neoplasms - nocturia - tinnitus - toxic epidermal necrolysis - weight decreased

### Pregnancy

- Avoid.

### Breast feeding

- Avoid.

### Renal impairment

- Avoid if eGFR less than 30 mL/minute/1.73 m².

### Monitoring requirements

- Correct hypocalcaemia before starting.
- Correct other disturbances of bone and mineral metabolism (e.g. vitamin-D deficiency) at onset of treatment.

### Directions for administration

Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after...
**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer risedronate sodium tablets.

Oesophageal reactions. Patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Bisphosphonates for treating osteoporosis (updated February 2018) NICE TA464

This technology appraisal guidance should be applied clinically in conjunction with:

- NICE guideline on assessing the risk of fragility fractures (CG146), which defines who is eligible for osteoporotic fracture risk assessment.
- NICE quality standard on osteoporosis (QS149), which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment.

Risedronate sodium is recommended as an option for treating osteoporosis in patients, only if:

- the person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and
- the 10-year probability of osteoporotic fragility fracture is at least 1%.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta464

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, tablets, effervescent tablets, capsules, granules, injectable solutions, sublingual tablets, and topical products.

**Tablet**

- **Risedronate sodium (Non-proprietary)**
  - Risedronate sodium 5 mg
  - Risedronate sodium 30 mg

**Injectable**

- **Risedronate sodium**
  - Injection 3 mg/0.5 mL
  - Injection 30 mg/0.5 mL

**Transdermal film**

- **Risedronate sodium**
  - Film 3 mg (NICE-approved indication: cancer)

**Solution**

- **Risedronate sodium**
  - Solution 3 mg/0.5 mL

**Suspension**

- **Risedronate sodium**
  - Suspension 3 mg/0.5 mL

**CONTRA-INDICATIONS**

Acute gastro-intestinal inflammatory conditions

**CAUTIONS**

Atypical femoral fractures - maintain adequate fluid intake during treatment

**INTERACTIONS**

- Appendix 1: bisphosphonates
- Side-effects: Proteinuria - respiratory disorder
- Pregnancy: Avoid.
- Breastfeeding: Manufacturer advises avoid—no information available.
- Renal impairment: Avoid if eGFR less than 10 mL/minute/1.73 m².

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**Risedronate with calcium carbonate and colecalciferol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, risedronate sodium p. 730, calcium carbonate p. 1045, colecalciferol p. 1084.

**INDICATIONS AND DOSE**

**Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures**

- **BY MOUTH**
  - Adult: 1 tablet once weekly on day 1 of the weekly cycle, followed by 1 sachet daily on days 2–6 of the weekly cycle

**INTERACTIONS**

- Appendix 1: bisphosphonates - calcium salts - vitamin D substances

**DIRECTIONS FOR ADMINISTRATION**

Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet. Granules should be stirred in a glass of water and after dissolution complete taken immediately.

**PRESCRIBING AND DISPENSING INFORMATION**

**Actonel Combi**

- effervescent granules contain calcium carbonate 2.5 g (calcium 1 g or Ca²⁺ 25 mmol) and colecalciferol 22 micrograms (880 units)/sachet.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer risedronate with calcium carbonate and colecalciferol tablets and granules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablets/Granules**

- **Actonel Combi** (Theramex HQ UK Ltd)

  - Actonel Combi 35 mg tablets and 1000 mg/880 unit effervescent granules

  - 4 week supply (POM) £19.12

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**Sodium clodronate**

**INDICATIONS AND DOSE**

**Osteolytic lesions, hypercaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma**

- **BY MOUTH**
  - Adult: 1.6 g daily in 1–2 divided doses, then increased if necessary up to 3.2 g daily in 2 divided doses

**LORON 520**

**Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma**

- **BY MOUTH**
  - Adult: Initially 2 tablets daily in 1–2 divided doses, increased if necessary up to 4 tablets daily
Dose adjustments Max. initial dose 1200 mg daily if eGFR 30–50 mL/minute/1.73 m². Use half normal dose if eGFR 10–30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Monitor renal function, serum calcium and serum phosphate before and during treatment.

- **DIRECTIONS FOR ADMINISTRATION** Avoid food for 2 hours before and 1 hour after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer sodium clodronate capsules and tablets.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Tablet

**CAUTIONARY AND ADVISORY LABELS**

- Bonefos (Bayer Plc)
- Loron (Intrapharm Laboratories Ltd)

**Sodium clodronate 800 mg** Bonefos 800mg tablets

| 60 tablet | £146.43 DT + £146.43
|-----------|---------------------|

**Sodium clodronate 520 mg** Loron 520mg tablets

| 60 tablet | £114.44 DT + £114.44
|-----------|---------------------|

**Sodium clodronate (Non-proprietary)**

- Sodium clodronate 400 mg

| 30 capsule | £34.96 | 120 capsule | £139.83 DT + £139.83
|------------|--------|------------|---------------------|

- Bonefos (Bayer Plc)

**Sodium clodronate 400 mg** Bonefos 400mg capsules

| 120 capsule | £139.83 DT + £139.83
|-------------|---------------------|

**Sodium clodronate 400 mg** Clasteon 400mg capsules

| 30 capsule | £34.96 | 120 capsule | £139.83 DT + £139.83
|------------|--------|------------|---------------------|

### Zoledronic acid

**INDICATIONS AND DOSE**

**Prevention of skeletal related events in advanced malignancies involving bone (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 4 mg every 3–4 weeks, calcium 500 mg daily and vitamin D 400 units daily should also be taken

**Tumour-induced hypercalcaemia (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 4 mg for 1 dose

**Paget's disease of bone (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 5 mg for 1 dose, at least 500 mg elemental calcium twice daily (with vitamin D) for at least 10 days is recommended following infusion

**Osteoporosis (including corticosteroid-induced osteoporosis) in men and postmenopausal women**

- **BY INTRAVENOUS INFUSION**
  - Adult: 5 mg once yearly as a single dose, in patients with a recent low-trauma hip fracture, the dose should be given at least 2 weeks after hip fracture repair, before first infusion given 50,000–125,000 units of vitamin D

- **CAUTIONS** Atypical femoral fractures - cardiac disease (avoid fluid overload) - comitant medicines that affect renal function

- **INTERACTIONS** Appendix 1: bisphosphonates

- **SIDE-EFFECTS**
  - Common or very common Appetite decreased - chills - flushing

- **Rare or very rare** Confusion - Fanconi syndrome acquired - pancytopenia

- **Frequency not known** Acute phase reaction

**SIDE-EFFECTS, FURTHER INFORMATION** Renal impairment and renal failure have been reported; ensure patient is hydrated before each dose and assess renal function.

**CONCEPTION AND CONTRACEPTION** Contra-indicated in women of child-bearing potential.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe hepatic impairment (limited information available).

**RENEAL IMPAIRMENT** Avoid in tumour-induced hypercalcaemia if serum creatinine above 400 micromol/litre. Avoid in advanced malignancies involving bone if eGFR less than 30 mL/minute/1.73 m² (or if serum creatinine greater than 265 micromol/litre). Avoid in Paget’s disease, treatment of postmenopausal osteoporosis and osteoporosis in men if eGFR less than 35 mL/minute/1.73 m².

**Dose adjustments** In advanced malignancies involving bone, if eGFR 50–60 mL/minute/1.73 m² reduce dose to 3.5 mg every 3–4 weeks; if eGFR 40–50 mL/minute/1.73 m² reduce dose to 3.3 mg every 3–4 weeks; if eGFR 30–40 mL/minute/1.73 m² reduce dose to 3 mg every 3–4 weeks; if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

- **MONITORING REQUIREMENTS**
  - Correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypercalcaemia) before starting. Monitor serum electrolytes, calcium, phosphate and magnesium.

- **Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated.

**DIRECTIONS FOR ADMINISTRATION**

- **When used for Prevention of skeletal related events in advanced malignancies involving bone or Tumour-induced hypercalcaemia** For intravenous infusion, infuse over at least 15 minutes; administer as a single intravenous solution in a separate infusion line. If using 4 mg/5 mL concentrate for solution for infusion or preparing a reduced dose of 4 mg/100 mL solution for infusion for patients with renal impairment, dilute requisite dose according to product literature.

- **When used for Paget's disease of bone or Osteoporosis (including corticosteroid-induced osteoporosis) in men and postmenopausal women** For intravenous infusion, give via a vented infusion line over at least 15 minutes.

**PATIENT AND CARER ADVICE** A patient reminder card should be provided (risk of osteonecrosis of the jaw).

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE decisions**
  - Bisphosphonates for treating osteoporosis (updated February 2018) NICE TA464

This technology appraisal guidance should be applied clinically in conjunction with:

- NICE guideline on assessing the risk of fragility fractures (CG146), which defines who is eligible for osteoporotic fracture risk assessment.

- NICE quality standard on osteoporosis (QS149), which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment.

www.getintopharma.com
Disorders of bone metabolism 733

Zoledronic acid is recommended as an option for treating osteoporosis in patients, only if:
- the person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and
- the 10-year probability of osteoporotic fragility fracture is at least 10%, or
- the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contra-indicated or not tolerated.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta464

Scottish Medicines Consortium (SMC) decisions

SMC No. 29/02
The Scottish Medicines Consortium has advised (May 2003) that zoledronic acid (Zometa®) is accepted for restricted use within NHS Scotland for the prevention of skeletal related events in patients with breast cancer and multiple myeloma if prescribed by an oncologist.

SMC No. 317/06
The Scottish Medicines Consortium has advised (October 2006) that zoledronic acid (Aclasta®) is accepted for use within NHS Scotland for the treatment of Paget’s disease of bone in patients for whom the use of a bisphosphonate is appropriate.

SMC No. 447/08
The Scottish Medicines Consortium has advised (March 2008) that zoledronic acid (Aclasta®) is accepted for restricted use within NHS Scotland for the treatment of osteoporosis in postmenopausal women in those for whom oral treatment options for osteoporosis are inappropriate, when initiated by a specialist.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Infusion**
- **Zoledronic acid (Non-proprietary)**
  - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml Zoledronic acid 4mg/100ml infusion bags | 1 vial £174.14
  - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml Zoledronic acid 5mg/100ml infusion bags | 1 vial £217.68

- **Aclasta** (Novartis Pharmaceuticals UK Ltd)
  - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml Aclasta 5mg/100ml infusion bottles | 1 bottle £253.38

- **Zerlinda** (Actavis UK Ltd)
  - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml Zerlinda 4mg/100ml infusion bags | 1 bag £150.00

- **Zometa** (Novartis Pharmaceuticals UK Ltd)
  - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml Zometa 4mg/100ml infusion bottles | 1 bottle £174.14

**Solution for infusion**
- **Zoledronic acid (Non-proprietary)**
  - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml Zoledronic acid 4mg/100ml solution for infusion vials | 1 vial £174.14
  - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml Zoledronic acid 5mg/100ml solution for infusion vials | 1 vial £180.00
  - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml Zoledronic acid 5mg/100ml solution for infusion vials | 1 vial £253.38
  - Zoledronic acid (as Zoledronic acid monohydrate) 800 microgram per 1 ml Zoledronic acid 4mg/5ml concentrate for solution for infusion vials | 1 vial £174.14
  - Zoledronic acid (as Zoledronic acid monohydrate) 800 microgram per 1 ml Zoledronic acid 4mg/5ml solution for infusion vials | 1 vial £184.04

**Calcitonin (salmon)** (Salcatonin)

**INDICATIONS AND DOSE**

- Hypercalcaemia of malignancy
  - BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: 100 units every 6–8 hours (max. per dose 400 units every 6–8 hours), adjusted according to response
  - BY INTRAVENOUS INFUSION
  - Adult: Up to 10 units/kg, in severe or emergency cases, to be administered by slow intravenous infusion over at least 6 hours

- Paget’s disease of bone
  - BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: 100 units daily, adjusted according to response for maximum 3 months (6 months in exceptional circumstances), a minimum dosage regimen of 50 units three times a week has been shown to achieve clinical and biochemical improvement

**Prevention of acute bone loss due to sudden immobility**
- BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: Initially 100 units daily in 1–2 divided doses, then reduced to 50 units daily at the start of mobilisation, usual duration of treatment is 2 weeks; maximum 4 weeks

**CONTRA-INDICATIONS** Hypocalcaemia

**CAUTIONS** Heart failure; history of allergy (skin test advised); risk of malignancy—avoid prolonged use (use lowest effective dose for shortest possible time)

**INTERACTIONS** Appendix 1: calcitonin (salmon)

**SIDE-EFFECTS**
- Common or very common Abdominal pain - arthralgia - diarrhoea - dizziness - fatigue - flushing - headache - musculoskeletal pain - nausea - secondary malignancy (long term use) - taste altered - vomiting
- Uncommon Hypersensitivity - hypertension - influenza like illness - oedema - polyuria - skin reactions - visual impairment
- Rare or very rare Bronchospasm - throat swelling - tongue swelling
- Frequency not known Hypocalcaemia - tremor

**PREGNANCY** Avoid unless potential benefit outweighs risk (toxicity in animal studies).

**BREAST FEEDING** Avoid; inhibits lactation in animals.

**RENAI IMPAIRMENT** Use with caution.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous infusion, give intermittently in Sodium chloride 0.9%. Diluted solution given without delay. Dilute in 500 mL give over at least 6 hours; glass or hard plastic containers should not be used; some loss of potency on dilution and administration.
Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Calcitonin (salmon) (Non-proprietary)
  Calcitonin (salmon) 50 unit per 1 ml [Calcitonin (salmon) 50 units/ml solution for injection ampoules | 5 ampoules (POM)]
  £167.50 DT = £167.50
- Calcitonin (salmon) 100 unit per 1 ml [Calcitonin (salmon) 100 units/ml solution for injection ampoules | 5 ampoules (POM)]
  £220.00 DT = £220.00
- Calcitonin (salmon) 200 unit per 1 ml [Calcitonin (salmon) 200 units/ml solution for injection vials | 1 vial (POM)]
  £352.00 DT = £352.00

Calcium regulating drugs

Teriparatide

Indications and dose
Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures | Treatment of corticosteroid-induced osteoporosis
- By subcutaneous injection
- Adult: 20 micrograms daily for maximum duration of treatment 24 months (course not to be repeated)

Contra-indications
Bone metastases - hyperparathyroidism - metabolic bone diseases - Paget’s disease - pre-existing hypercalcaemia - previous radiation therapy to the skeleton - skeletal malignancies - unexplained raised alkaline phosphatase

Side-effects
- Common or very common: Anaemia - asthenia - chest pain - gastrointestinal disorders - headache - hypercalcaemia - hyperhidrosis - hypotension - muscle complaints - palpitations - sciatica - skin reactions - syncope - vomiting
- Uncommon: Arthralgia - back pain - emphysema - hypercalcaemia - hyperuricaemia - nephrolithiasis - tachycardia - urinary disorders - weight increased
- Rare or very rare: Oedema - renal impairment

Pregnancy
Avoid.

Breast feeding
Avoid.

Renal impairment
Caution in moderate impairment; avoid if severe.

Prescribing and dispensing information
Teriparatide is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1

National funding/access decisions

NICE decisions
- Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (updated February 2018) NICE TA161
Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:
  - who are unable to take alendronate and risedronate, or have a contra-indication to or are intolerant of alendronate and risedronate, or have had an unsatisfactory response to treatment with alendronate or risedronate, and
  - who are 65 years or older and have a T-score of -4 standard deviations (SD) or below, or a T-score of -3.5 SD or below plus more than two fractures, or who are aged 55-64 years and have a T-score of -4 SD or below plus more than two fractures.
Women who are currently receiving treatment, but for whom treatment would not have been recommended, should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta161

Mhra/Chm advice: denosumab: atypical femoral fractures (February 2013)
Atypical femoral fractures have been reported rarely in patients receiving denosumab for the long-term treatment (2.5 or more years) of postmenopausal osteoporosis.
Patients should be advised to report any new or unusual thigh, hip, or groin pain during treatment with denosumab.
Discontinuation of denosumab in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

Drug action
Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.
Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia.

Osteonecrosis of the jaw Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving denosumab 120 mg for cancer. Risk factors include smoking, old age, poor oral hygiene, invasive dental procedures (including tooth extractions, dental implants, oral surgery), comorbidity (including dental disease, anaemia, coagulopathy, infection), advanced cancer, previous treatment with bisphosphonates, and concomitant treatments (including chemotherapy, antiangiogenic biologics, corticosteroids, and radiotherapy to head and neck). The following precautions are now recommended to reduce the risk of ONJ:

- Denosumab 120 mg (cancer indication)
  - A dental examination and appropriate preventative dentistry before starting treatment are now recommended for all patients
  - Do not start denosumab in patients with a dental or jaw condition requiring surgery, or in patients who have unhealed lesions from dental or oral surgery
- Denosumab 60 mg (ostoporosis indication)
  - Check for ONJ risk factors before starting treatment. A dental examination and appropriate preventative dentistry are now recommended for patients with risk factors
- All patients should be given a patient reminder card and informed of the risk of ONJ. Advise patients to tell their doctor if they have any problems with their mouth or teeth before starting treatment, if they wear dentures they should make sure their dentures fit properly before starting treatment, to maintain good oral hygiene, receive routine dental check-ups during treatment, and immediately report any oral symptoms such as dental mobility, pain, swelling, non-healing sores or discharge to a doctor and dentist. Patients should tell their doctor and dentist that they are receiving denosumab if they need dental treatment or dental surgery.

Hypocalcaemia Denosumab is associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment. Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later in treatment. Plasma-calcium concentration monitoring is recommended for denosumab 120 mg (cancer indication):

- before the first dose
- within two weeks after the initial dose
- if suspected symptoms of hypocalcaemia occur
- consider monitoring more frequently in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)

Plasma-calcium concentration monitoring is recommended for denosumab 60 mg (osteoporosis indication):

- before each dose
- within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)
- if suspected symptoms of hypocalcaemia occur
All patients should be advised to report symptoms of hypocalcaemia to their doctor (e.g. muscle spasms, twitching, cramps, numbness or tingling in the fingers, toes, or around the mouth).


Osteonecrosis of the external auditory canal has been reported with denosumab and this should be considered in patients who present with ear symptoms including chronic ear infections or in those with suspected cholesteatomas. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. The MHRA recommends advising patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.

MHRA/CHM ADVISE: DENOSUMAB (XGEVA®) FOR GIANT CELL TUMOUR OF BONE: RISK OF CLINICALLY SIGNIFICANT HYPERCALCAEMIA FOLLOWING DISCONTINUATION (JUNE 2018)

Cases of clinically significant hypercalcaemia (rebound hypercalcaemia) have been reported up to 9 months after discontinuation of denosumab treatment for giant cell tumour of bone. The MHRA recommends that prescribers should monitor patients for signs and symptoms of hypercalcaemia after discontinuation, consider periodic assessment of serum calcium, re-evaluate the patient’s calcium and vitamin D supplementation requirements, and advise patients to report symptoms of hypercalcaemia.

Denosumab is not recommended in patients with growing skeletons.

MHRA/CHM ADVISE: DENOSUMAB (XGEVA®) FOR ADVANCED MALIGNANCIES INVOLVING BONE: STUDY DATA SHOW NEW PRIMARY MALIGNANCIES REPORTED MORE FREQUENTLY COMPARED TO ZOLEDRONIC ACID (ZOLEDRONATE) (JUNE 2018)

A pooled analysis has shown an increased rate of new primary malignancies in patients given Xgeva® (1-year cumulative incidence 1.1%) compared with those given zoledronic acid (0.6%), when used for the prevention of skeletal-related events with advanced malignancies involving bone. No treatment-related pattern in individual cancers or cancer groupings was apparent.

- CONTRA-INDICATIONS Hypocalcaemia
  - XGEVA® Unhealed lesions from dental or oral surgery
- CAUTIONS Atypical femoral fractures - hypocalcaemia - osteonecrosis of the jaw—consider temporary interruption of treatment if occurs
- SIDE-EFFECTS
  --common or very common Abdominal discomfort - cataract - constipation - hypocalcaemia (including fatal cases) - increased risk of infection - pain - sciatica - second primary malignancy - skin reactions
  - uncommon Cellulitis (seek prompt medical attention) - hypercalcaemia (on discontinuation)
  - rare or very rare Atypical femur fracture - osteonecrosis
- CONCEPTION AND CONCEPTION: Ensure effective contraception in women of child-bearing potential, during treatment and for at least 5 months after stopping treatment.
- PREGNANCY Manufacturer advises avoid—toxicity in animal studies; risk of toxicity increases with each trimester.
- BREAST FEEDING Manufacturer advises avoid.
- RENAL IMPAIRMENT Increased risk of hypocalcaemia if creatinine clearance less than 30 mL/minute.
- MONITORING REQUIREMENTS Correct hypocalcaemia and vitamin D deficiency before starting. Monitor plasma-calcium concentration during therapy.
- PATIENT AND CARER ADVICE Atypical femoral fractures Patients should be advised to report any new or unusual thigh, hip, or groin pain during treatment with denosumab. Osteonecrosis of the jaw All patients should be informed to maintain good oral hygiene, receive routine dental check-
las, and immediately report any oral symptoms such as
dental mobility, pain, or swelling to a doctor and dentist.
Hypocalcaemia All patients should be advised to report
symptoms of hypocalcaemia to their doctor (e.g. muscle
spasms, twitches, cramps, numbness or tingling in
the fingers, toes, or around the mouth).
Patient reminder card A patient reminder card should be
provided (risk of osteonecrosis of the jaw).

- NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
Denosumab for the prevention of osteoporotic fractures in
postmenopausal women (October 2010) NICE TA204
Denosumab (Prolia ®) is recommended as a treatment
option for the primary prevention of osteoporotic fragility
fractures in postmenopausal women at increased risk of
fractures:
- who are unable to comply with the special instructions
  for administering alendronate and risedronate, or have
  an intolerance of, or a contra-indication to, those
  treatments and
- who comply with particular combinations of bone
  mineral density measurement, age, and independent
  risk factors for fracture, as indicated in the full NICE
guidance.
Denosumab (Prolia ®) is recommended as a treatment
option for the secondary prevention of osteoporotic fragility
fractures only in postmenopausal women at increased risk
of fractures who are unable to comply with the special
instructions for administering alendronate and
risedronate, or have an intolerance of, or a contra-
indication to, those treatments.

Patients whose treatment was started within the NHS
before this guidance was published should have the option
to continue treatment, without change to their funding
arrangements, until they and their NHS clinician consider
it appropriate to stop.

www.nice.org.uk/guidance/ta204

Denosumab for the prevention of skeletal-related events in
adults with bone metastases from solid tumours (October
2012) NICE TA265
Denosumab (Xgeva ®) is recommended for the prevention
of skeletal-related events in adults with bone metastases
from breast cancer and from solid tumours other than
prostate if:
- bisphosphonates would otherwise be prescribed, and
- the manufacturer provides denosumab with the discount
  agreed in the patient access scheme.
Denosumab is not recommended for preventing skeletal-
related events in adults with bone metastases from
prostate cancer.

Patients with bone metastases from solid tumours
currently receiving denosumab whose disease does not
meet the above criteria can continue treatment until they
and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta265

Scottish Medicines Consortium (SMC) decisions
SMC No. 651/10
The Scottish Medicines Consortium has advised (December
2010) that denosumab (Prolia ®) is accepted for restricted
use within NHS Scotland for the treatment of osteoporosis
in postmenopausal women at increased risk of fractures
who have a bone mineral density T-score < −2.5 and > −4.0
and for whom oral bisphosphonates are unsuitable.

- MEDICINAL FORMS There can be variation in the licensing of
different medicines containing the same drug.

Solution for injection

- Denosumab 60 mg per 1 ml

  Prolia (Amgen Ltd)

  Denosumab 60 mg/1ml solution for injection
  pre-filled disposable injection (Pack) £183.00
  DT = £183.00

- Xgeva (Amgen Ltd)

  Denosumab 70 mg per 1 ml Xgeva 120mg/1.7ml solution for
  injection vials | 1 vial (Pack) £309.86 DT = £309.86

5 Dopamine responsive conditions

DOPAMINERGIC DRUGS >> DOPAMINE RECEPTOR AGONISTS

Dopamine-receptor agonists

Overview
Bromocriptine p. 419 is used for the treatment of
galactorrhoea, and for the treatment of prolactinomas (when
it reduces both plasma prolactin concentration and tumour
size). Bromocriptine also inhibits the release of growth
hormone and is sometimes used in the treatment of
acromegaly, but somatostatin analogues (such as octreotide
p. 950) are more effective.

Cabergoline p. 421 has similar side-effects to
bromocriptine, however patients intolerant of bromocriptine
may be able to tolerate cabergoline (and vice versa).

Quinagolide below has actions and uses similar to those of
ergot-derived dopamine agonists, but its side-effects differ
slightly.

Suppression of lactation

Although bromocriptine and cabergoline are licensed to
suppress lactation, they are not recommended for routine
suppression (or for the relief of symptoms of postpartum
pain and engorgement) that can be adequately treated with
simple analgesics and breast support. If a dopamine-receptor
agonist is required, cabergoline is preferred. Quinagolide is
not licensed for the suppression of lactation.

Quinagolide

- DRUG ACTION Quinagolide is a non-ergot dopamine D₂
  agonist.

- INDICATIONS AND DOSE

Hyperprolactinaemia

- BY MOUTH

  Adult: Initially 25 micrograms once daily for 3 days,
  dose to be taken at bedtime, increased in steps of
  25 micrograms every 3 days; usual dose
  75–150 micrograms daily, for doses higher than
  300 micrograms daily increase in steps of
  75–150 micrograms at intervals of not less than
  4 weeks

- UNLICENSED USE Not licensed for the suppression of
  lactation.

- CAUTIONS Acute porphyrias p. 1058 - history of psychotic
  illness - history of serious mental disorders

- FURTHER INFORMATION

  - Hyperprolactinemic patients In hyperprolactinaemic patients,
    the source of the hyperprolactinaemia should be
    established (i.e. exclude pituitary tumour before
    treatment).

- INTERACTIONS >> Appendix 1: dopamine receptor agonists

- SIDE-EFFECTS

  - Common or very common Abdominal pain - appetite
decreased - constipation - diarrhoea - dizziness - fatigue
  - flushing - headache - hypotension - insomnia - nasal
  congestion - nausea - oedema - syncope - vomiting

  - Rare or very rare Acute psychosis - drowsiness

www.getintopharma.com
**Gonadotrophin responsive conditions**

**Cetrorelix** below and ganirelix p. 738 are luteinising hormone releasing hormone antagonists, which inhibit the release of gonadotrophins (luteinising hormone and follicle stimulating hormone). They are used in the treatment of infertility by assisted reproductive techniques. **Gonadorelin analogues**

Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility, male hypersexuality with severe sexual deviation, anaemia due to uterine fibroids (together with iron supplementation), breast cancer, prostate cancer and before intra-uterine surgery. Use of leuprorelin acetate and triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding.

**Breast pain (mastalgia)**

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and reduction in dietary fat; withdrawal of an oral contraceptive or of hormone replacement therapy may help to resolve the pain.

Mild, non-cyclical breast pain is treated with simple analgesics; moderate to severe pain, cyclical pain or symptoms that persist for longer than 6 months may require specific drug treatment.

Danazol is licensed for the relief of severe pain and tenderness in benign fibrocystic breast disease which has not responded to other treatment.

Tamoxifen p. 953 may be a useful adjunct in the treatment of mastalgia (unlicensed indication) especially when symptoms can definitely be related to cyclic oestrogen production; it may be given on the days of the cycle when symptoms are predicted.

Treatment for breast pain should be reviewed after 6 months and continued if necessary. Symptoms recur in about 50% of women within 2 years of withdrawal of therapy but may be less severe.

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES**

**ANTI-GONADOTROPHIN-RELEASING HORMONES**

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**Gonadotrophins**

**Gonadotrophin-affecting drugs**

Danazol p. 742 is licensed for the treatment of *endometriosis* and for the relief of severe pain and tenderness in *benign fibrocystic breast disease* where other measures have proved unsatisfactory. It may also be effective in the long-term management of *hereditary angioedema* (unlicensed indication).

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**6**

**Gonadotrophin responsive conditions**

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**Gonadotrophins**

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**ALLERGY AND CROSS-SENSITIVITY**

Quinagolide should not be used in patients with hypersensitivity to quinagolide (does not apply to hypersensitivity to ergot alkaloids).

**CONCEPTION AND CONTRACEPTION**

Advise non-hormonal contraception if pregnancy not desired.

**PREGNANCY**

Discontinue when pregnancy confirmed unless medical reason for continuing (specialist advice needed).

**BREAST FEEDING**

Suppresses lactation.

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid (no information available).

**RENAL IMPAIRMENT**

Avoid—no information available.

**MONITORING REQUIREMENTS**

Monitor blood pressure for a few days after starting treatment and following dosage increase.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks

**Sudden onset of sleep**

Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions Hypotensive reactions can be disturbing in some patients during the first few days of treatment with dopamine-receptor agonists, particular care should be exercised when driving or operating machinery.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

10, 21

- Quinagolide (Non-proprietary)
  - Quinagolide 50 microgram tablets and Quinagolide 25 microgram tablets | 6 tablet [POM] £30.00 - £37.50 DT = £37.49
- Quinagolide (as Quinagolide hydrochloride)
  - 25 microgram Quinagolide 25 microgram tablets | 3 tablet [POM] £5.75
  - Quinagolide (as Quinagolide hydrochloride)
  - 50 microgram Quinagolide 50 microgram tablets | 3 tablet [POM] £7.00
  - Quinagolide (as Quinagolide hydrochloride)
  - 75 microgram Quinagolide 75 microgram tablets | 30 tablet [POM] £75.00 DT = £75.00
- Norprolac (Ferring Pharmaceuticals Ltd)
  - Quinagolide (as Quinagolide hydrochloride)
  - 25 microgram Norprolac 25 microgram tablets | 3 tablet [POM] £6.50
  - Quinagolide (as Quinagolide hydrochloride)
  - 50 microgram Norprolac 50 microgram tablets | 3 tablet [POM] £8.00

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**Gonadotrophin-responsive conditions**

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**Gonadotrophins**

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**Gonadotrophin-affecting drugs**

Danazol p. 742 is licensed for the treatment of *endometriosis* and for the relief of severe pain and tenderness in *benign fibrocystic breast disease* where other measures have proved unsatisfactory. It may also be effective in the long-term management of *hereditary angioedema* (unlicensed indication).
738  Gonadotrophin responsive conditions

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- **Cetrolide** (Merck Serono Ltd)
  - Cetrorelax (as Cetrorelax acetate) 250 microgram
  - Cetrolide 250microgram powder and solvent for injection vials | 1 vial (£20) 127.13

**Ganirelix**

**INDICATIONS AND DOSE**
- **Adjunct in the treatment of female infertility (initiated under specialist supervision)**
  - **BY SUBCUTANEOUS INJECTION**
    - **Adult:** 500 micrograms once daily, increased if necessary up to 500 micrograms twice daily, starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and busuvelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)
  - **BY INTRANASAL ADMINISTRATION**
    - **Adult:** 150–300 micrograms 4 times a day, (150 micrograms equivalent to one spray), to be administered during waking hours. Start in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 2–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and busuvelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

**SIDE-EFFECTS**
- **Common or very common**  Skin reactions
- **Uncommon**  Headache - malaise - nausea
- **Rare or very rare**  Dyspnoea - facial swelling - hypersensitivity
- **Frequency not known**  Abdominal distension - ovarian hyperstimulation syndrome - pelvic pain

**PREGNANCY**  Avoid in confirmed pregnancy—toxicity in animal studies.

**BREAST FEEDING**  Avoid — no information available.

**HEPATIC IMPAIRMENT**  Manufacturer advises avoid in moderate to severe impairment (no information available).

**RENAI IMPAIRMENT**  Avoid in moderate to severe renal impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Fyremadel** (Ferring Pharmaceuticals Ltd)
  - Ganirelix 500 microgram per 1 ml
  - Fyremadel 250micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£5)

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES > GONADOTROPIN-RELEASING HORMONES**

**Buserelin**

**DRUG ACTION**  Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle-stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**
- **Endometriosis**
  - **BY INTRANASAL ADMINISTRATION**
    - **Adult:** 300 micrograms 3 times a day maximum duration of treatment 6 months (do not repeat), to be started on days 1 or 2 of menstruation; administer one 150 microgram spray into each nostril

**SIDE-EFFECTS**
- **Common or very common**  Skin reactions
- **Uncommon**  Headache - malaise - nausea
- **Rare or very rare**  Dyspnoea - facial swelling - hypersensitivity
- **Frequency not known**  Abdominal distension - ovarian hyperstimulation syndrome - pelvic pain

**PITUITARY DESENSITISATION BEFORE INDUCTION OF OVULATION BY GONADOTROPHINS FOR IN VITRO FERTILISATION (UNDER EXPERT SUPERVISION)**
- **BY SUBCUTANEOUS INJECTION**
  - **Adult:** 200–500 micrograms once daily, increased if necessary up to 500 micrograms twice daily, starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and busuvelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

**CONTRA-INDICATIONS**
- When used for endometriosis  Hormone dependent tumours - undiagnosed vaginal bleeding - use longer than 6 months (do not repeat)
- When used for pituitary desensitisation  Hormone dependent tumours - undiagnosed vaginal bleeding

**CAUTIONS**
- **Depression - diabetes - hypertension - patients with metabolic bone disease (decrease in bone mineral density can occur) - polycystic ovarian disease**

**SIDE-EFFECTS**
- **Common or very common**  Depression - mood altered
- **Rare or very rare**  Auditory disorder - hypotension - leucopenia - pituitary tumour benign - thrombocytopenia - tinnitus

**SPECIFIC SIDE-EFFECTS**
- With intranasal use  Altered smell sensation - epistaxis - hoarseness - nasal irritation - taste altered

**SIDE-EFFECTS, FURTHER INFORMATION**
- During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer.

www.getintopharma.com
susceptible patients this tumour 'flare' may cause spinal cord compression, ureteric obstruction or increased bone pain.

- **CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.
- **DIRECTIONS FOR ADMINISTRATION**
  - With subcutaneous use
  - With intranasal use

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer buserelin nasal spray.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **Suprecur** (Sanofi)
    - Buserelin (as Buserelin acetate) 1 mg per 1 ml
      - 5.5mg/5.5ml solution for injection vials | 2 vial POM £33.02
  - **Suprefact** (Sanofi)
    - Buserelin (as Buserelin acetate) 1 mg per 1 ml
      - 5.5mg/5.5ml solution for injection vials | 2 vial POM £34.37

- **Spray**
  - **Suprecur** (Sanofi)
    - Buserelin (as Buserelin acetate) 150 microgram per
      - 1 dose Suprecur 150micrograms/dose nasal spray | 168 dose POM £105.16
  - **Suprefact** (Sanofi)
    - Buserelin (as Buserelin acetate) 100 microgram per
      - 1 dose Suprefact 100micrograms/dose nasal spray | 336 dose POM £122.24

**Goserelin**

- **DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

- **INDICATIONS AND DOSE**

  - **ZOLADEX LA**
    - Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer | Advanced breast cancer | Oestrogen-receptor-positive early breast cancer
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 3.6 mg every 28 days, to be administered into the anterior abdominal wall

  - **Endometriosis**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 3.6 mg every 28 days maximum duration of treatment 6 months (do not repeat), to be administered into the anterior abdominal wall

  - **Endometrial thinning before intra-uterine surgery**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 3.6 mg, dose may be repeated after 28 days if uterus is large or to allow flexible surgical timing, to be administered into the anterior abdominal wall

  - **Before surgery in women who have anaemia due to uterine fibroids**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 3.6 mg, dose given to achieve pituitary down-regulation (usually 1–3 weeks) then gonadotrophin is administered (stopping gonadotrophin on administration of chorionic gonadotrophin at appropriate stage of follicular development), to be administered into the anterior abdominal wall

- **CONTRA-INDICATIONS** Undiagnosed vaginal bleeding - use longer than 6 months in endometriosis (do not repeat)

- **CAUTIONS**
  - Depression - diabetes - hypertension - patients with metabolic bone disease (decrease in bone mineral density can occur) - polycystic ovarian disease - risk of spinal cord compression in men - risk of ureteric obstruction in men

- **SIDE-EFFECTS**
  - **Common or very common** Alopecia - arthralgia - bone pain - breast abnormalities - depression - glucose tolerance impaired - gynaecomastia - headache - heart failure - hot flush - hyperhidrosis - mood altered - myocardial infarction - neoplasm complications - paraesthesia - sexual dysfunction - skin reactions - spinal cord compression - vulvovaginal disorders - weight increased
  - **Uncommon** Hypercalcaemia (in women) - urethral obstruction
  - **Rare or very rare** Ovarian and fallopian tube disorders - pituitary haemorrhage - pituitary tumour - psychotic disorder

- **Frequency not known** Abdominal cramps - body hair change - constipation - diarrhoea - fatigue - hepatic function abnormal - interstitial pneumonia - muscle complaints - nausea - nervousness - peripheral oedema (when used for gynaecological conditions) - premature menopause - pulmonary embolism - QT interval prolongation - sleep disorder - uterine leiomyoma degeneration - voice alteration - vomiting - vulvovaginal infection - withdrawal bleed

**SIDE-EFFECTS, FURTHER INFORMATION** Tumour flare can occur when androgen deprivation therapy is initiated.
Leuprolerin acetate

**DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

### PROSTAP 3 DCS

Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 11.25 mg every 3 months

Endometriosis

- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 11.25 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 11.25 mg every 3 months for maximum 6 months (course not to be repeated)

### PROSTAP SR DCS

Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 3.75 mg every month

Endometriosis

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 3.75 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 3.75 mg every month for maximum 6 months (course not to be repeated)

**CONTRA-INDICATIONS**

- **GENERAL CONTRA-INDICATIONS**
  - Undiagnosed vaginal bleeding

- **SPECIFIC CONTRA-INDICATIONS**
  - When used for endometriosis use longer than 6 months (do not repeat)

- **CAUTIONS**
  - Diabetes - family history of osteoporosis - patients with metabolic bone disease (decrease in bone mineral density can occur) - risk of spinal cord compression in men with prostate cancer - risk of ureteric obstruction in men with prostate cancer

**SIDE-EFFECTS**

- **Common or very common**

- **Uncommon**
  - Alopecia - diarrhoea - fever - myalgia - palpitations - visual impairment - vomiting

- **Rare or very rare**
  - Haemorrhage

- **Frequency not known**
  - Anaemia - glucose tolerance impaired - hypertension - hypotension - leucopenia - paralytic ileus - pulmonary embolism - QT interval prolongation - seizure - spinal fracture - thrombocytopenia - urinary tract obstruction

**SIDE-EFFECTS, FURTHER INFORMATION** In prostate cancer, during the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain.

**CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

**PREGNANCY** Avoid—teratogenic in animal studies.

**BREAST FEEDING** Avoid.

**MONITORING REQUIREMENTS**

- Men at risk of tumour ‘flare’ should be monitored closely during the first month of therapy.

**DIRECTIONS FOR ADMINISTRATION** Rotate injection site to prevent atrophy and nodule formation.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Zoladex (AstraZeneca UK Ltd)**
  - Goserelin (as Goserelin acetate) 3.6 mg Zoladex 3.6mg implant Safesystem pre-filled syringes | 1 pre-filled disposable injection
  - £10.00 DT = £70.00

- **Zoladex LA (AstraZeneca UK Ltd)**
  - Goserelin (as Goserelin acetate) 10.8 mg Zoladex LA 10.8mg implant Safesystem pre-filled syringes | 1 pre-filled disposable injection
  - £235.00 DT = £235.00

- **Goserelin (as Goserelin acetate) 7.2 mg** (AstraZeneca UK Ltd)
  - Zoladex LA 7.2mg implant Safesystem pre-filled disposable injection
  - £235.00 DT = £235.00

- **Goserelin (as Goserelin acetate) 3.6 mg** (AstraZeneca UK Ltd)
  - ZOLADEX 3.6 mg implant Safesystem pre-filled syringes | 1 pre-filled disposable injection
  - £235.00 DT = £235.00

<table>
<thead>
<tr>
<th>Powder and solvent for suspension for injection</th>
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<tr>
<td><strong>Prostap 3 DCS</strong> (Takeda UK Ltd)</td>
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Nafarelin

- **DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

- **INDICATIONS AND DOSE**
  
  **Endometriosis**
  
  - **BY INTRANASAL ADMINISTRATION**
    - Adult (female): 200 micrograms twice daily for maximum 6 months (do not repeat), one spray in one nostril in the morning, and one spray in the other nostril in the evening (starting on days 2–4 of menstruation).

  Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under expert supervision)
  
  - **BY INTRANASAL ADMINISTRATION**
    - Adult: 400 micrograms twice daily, one spray in each nostril, to be started in early follicular phase (day 2) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down regulation achieved (usually within 4 weeks) then maintained (usually for 8–12 days) during gonadotrophin administration (stopping gonadotrophin and nafarelin on administration of choric gonadotrophin at follicular maturity), discontinue if down-regulation not achieved within 12 weeks.

- **CONTRA-INDICATIONS** Undiagnosed vaginal bleeding • use longer than 6 months in the treatment of endometriosis (do not repeat)

- **CAUTIONS** Patients with metabolic bone disease (decrease in bone mineral density can occur)

- **SIDE-EFFECTS**
  - **Common or very common** Artificial menopause • breast abnormalities • chest pain • depression • dysphoria • emotional lability • headaches • hirsutism • hot flush • hypersensitivity • hypertension • hypotension • insomnia • myalgia • oedema • oestrogen deficiency • paraesthesia • rash • seborrhoea • sexual dysfunction • skin reactions • uterine haemorrhage • vulvovaginal dryness • weight changes
  - **Uncommon** Alopecia • arthralgia • ovarian cyst (may require discontinuation)
  - **Frequency not known** Ovarian hyperstimulation syndrome • palpitations • vision blurred

- **CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first dose should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Avoid.

- **DIRECTIONS FOR ADMINISTRATION** Avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer nafarelin nasal spray.

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Triptorelin

**DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.
Reduction in size of uterine fibroids

▶ BY INTRAMUSCULAR INJECTION
- Adult: 3 mg every 4 weeks for at least 3 months, maximum duration of treatment 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**GONAPEPTYL DEPOT®**

**Advanced prostate cancer**

▶ BY SUBCUTANEOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION
- Adult: 3.75 mg every 4 weeks

**Endometriosis | Reduction in size of uterine fibroids**

▶ BY SUBCUTANEOUS INJECTION, OR BY DEEP INTRAMUSCULAR INJECTION
- Adult: 3.75 mg every 4 weeks maximum duration of 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**SALVACYL®**

**Male hypersexuality with severe sexual deviation**

▶ BY INTRAMUSCULAR INJECTION
- Adult: 11.25 mg every 12 weeks

**CONTRA-INDICATIONS** In endometriosis do not use for longer than 6 months (do not repeat) - undiagnosed vaginal bleeding

**SALVACYL®** Severe osteoporosis

**CAUTIONS**

**GENERAL CAUTIONS** Patients with metabolic bone disease (decrease in bone mineral density can occur)

**SPECIFIC CAUTIONS**

- When used for prostate cancer Risk factors for osteoporosis - risk of spinal cord compression in men - risk of ureteric obstruction in men

**SALVACYL®** Increased risk of sensitivity to restored testosterone if treatment interrupted—consider administration of an antiandrogen before stopping treatment - transient increase in serum testosterone occurs on initiation—consider administration of an antiandrogen

**SIDE-EFFECTS**

▶ Common or very common Asthenia · depression · dizziness · dysuria · gastrointestinal discomfort · gynaecomastia · haemorrhage · headache · hot flush · hyperhidrosis · hypersensitivity · joint disorders · menstrual cycle irregularities · mood altered · muscle complaints · nausea · oedema · ovarian and fallopian tube disorders · pain · painful sexual intercourse · paraesthesia · pelvic pain · sexual dysfunction · sleep disorders · vulvovaginal dryness

▶ Uncommon Alopecia · appetite abnormal · asthma exacerbatet · breast pain · chills · constipation · diarrhoea · drowsiness · dry mouth · dyspnoea · embolism · gout · hypertension · muscle weakness · skin reactions · testicular disorders · tinnitus · vision disorders · vomiting · weight changes

▶ Rare or very rare Abnormal sensation in eye · chest pain · confusion · diabetes mellitus · difficulty standing · fever · flatulence · hypotension · influenza like illness · memory loss · musculoskeletal stiffness · nasopharyngitis · orthopnoea · osteoarthropathy · taste altered · vertigo

▶ Frequency not known Angioedema · anxiety · bone disorder · malaise · QT interval prolongation

**SIDE-EFFECTS, FURTHER INFORMATION** During the initial stage increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased pain.

**CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid.

**MONITORING REQUIREMENTS**

- When used for Prostate cancer Men at risk of tumour ‘flare’ should be monitored closely during the first month of therapy.

**DIRECTIONS FOR ADMINISTRATION** Rotate injection site to prevent atrophy and nodule formation.

**PRESCRIBING AND DISPENSING INFORMATION**

**DECAPETYL® SR 22.5MG** Each vial includes an overage to allow accurate administration of a 22.5 mg dose.

**DECAPETYL® SR 3MG** Each vial includes an overage to allow accurate administration of 3 mg dose.

**DECAPETYL® SR 11.25MG** Each vial includes an overage to allow accurate administration of an 11.25 mg dose.

**NATIONAL FUNDING/ACCESS DECISIONS**

**All Wales Medicines Strategy Group (AWMSG) decisions** The All Wales Medicines Strategy Group has advised (March 2017) that triptorelin (Decapeptyl® SR) is recommended as an option for use within NHS Wales as an adjuvant treatment to radiotherapy and as a neoadjuvant treatment prior to radiotherapy, in patients with high-risk localised or locally advanced prostate cancer.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**

▶ Decapetyl SR (Ipsen Ltd)

Triptorelin (as Triptorelin acetate) 3 mg Decapetyl SR 3mg powder and solvent for suspension for injection vials | 1 vial £69.00 DT = £69.00

Triptorelin 11.25 mg Decapetyl SR 11.25mg powder and solvent for suspension for injection vials | 1 vial £207.00 DT = £207.00

Triptorelin (as Triptorelin embonate) 22.5 mg Decapetyl SR 22.5mg powder and solvent for suspension for injection vials | 1 vial £414.00 DT = £414.00

▶ Gonapeptyl Depot (Ferring Pharmaceuticals Ltd)

Triptorelin (as Triptorelin acetate) 3.75 mg Gonapeptyl Depot 3.75mg powder and solvent for suspension for injection pre-filled syringes | 1 pre-filled disposable injection £81.69 DT = £81.69

▶ Salvacyl (Ipsen Ltd)

Triptorelin 11.25mg Salvacyl 11.25mg powder and solvent for suspension for injection vials | 1 vial £248.00 DT = £207.00

### 6.1 Hereditary angioedema

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES**

**ANTI-GONADOTROPIN-RELEASING HORMONES**

**Danazol**

**DRUG ACTION** Danazol inhibits pituitary gonadotrophins; it combines androgenic activity with antioestrogenic and antiprogestogenic activity.

**INDICATIONS AND DOSE**

**Endometriosis**

▶ BY MOUTH
- Adult: 200–800 mg daily in up to 4 divided doses usually for 3–6 months, dose to be adjusted to achieve amenorrhoea, in women of child-bearing potential, treatment should start during menstruation, preferably on day 1

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**BNF 78**

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Severe pain and tenderness in benign fibrocystic breast disease not responding to other treatment

- **BY MOUTH**
  - Adult: 300 mg daily in divided doses usually for 3–6 months, in women of child-bearing potential, treatment should start during menstruation, preferably on day 1

### Hereditary angioedema

- **BY MOUTH**
  - Adult: Initially 100–200 mg daily, dose to be reduced according to response, in women of child-bearing potential, treatment should start during menstruation, preferably on day 1

### UNLICENSED USE

- **Not licensed for use in hereditary angioedema.**

### CONTRA-INDICATIONS

- Acute porphyrias p. 1058
- androgen-dependent tumours
- thromboembolic disease
- undiagnosed genital bleeding

### CAUTIONS

- Cardiac impairment (avoid if severe)
- diabetes mellitus
- elderly
- epilepsy
- history of thrombosis or thromboembolic disease
- hypertension
- lipoprotein disorder
- migraine
- polycythaemia

### INTERACTIONS

→ Appendix 1: danazol

### SIDE-EFFECTS

- Alopecia
- aminoolevulinic acid synthetase induction
- anxiety
- appetite increased
- breast atrophy
- carpal tunnel syndrome
- clitoris enlarged
- contact lens intolerance
- cutaneous lupus erythematosus
- depressed mood
- dizziness
- embolism and thrombosis
- emotional lability
- eosinophilia
- epigastric pain
- epilepsy exacerbated
- face oedema
- fatigue
- fever
- fluid retention
- flushing
- glucose tolerance impaired
- haematuria
- headaches
- hepatic disorders
- hirsutism
- hypertension
- idiopathic intracranial hypertension
- insulin resistance
- joint disorders
- leucopenia
- libido disorder
- menstrual cycle irregularities
- muscle contractions involuntary
- muscle cramps
- myocardial infarction
- nausea
- neoplasms
- pain
- palpatations
- pancreatitis
- photosensitivity reaction
- polycythaemia
- respiratory disorders
- seborrhoea
- skin reactions
- speech pitch disorder
- spermatogenesis reduced
- splenic peliosis
- tachycardia
- throbbing pain
- thrombocytopenia
- tremor
- vertigo
- vision disorders
- voice alteration
- vulvovaginal disorders
- weight increased

**SIDE-EFFECTS, FURTHER INFORMATION**

Withdraw if virilisation effects occur—may be irreversible on continued use.

### CONCEPTION AND CONTRACEPTION

Ensure patients with amenorrhoea are not pregnant. Non-hormonal contraceptive methods should be used, if appropriate.

### PREGNANCY

Avoid; has weak androgenic effects and virilisation of female fetus reported.

### BREAST FEEDING

No data available but avoid because of possible androgenic effects in infant.

### HEPATIC IMPAIRMENT

Manufacturer advises caution; avoid in marked impairment.

### RENAL IMPAIRMENT

Caution in renal impairment (avoid if severe).

### MONITORING REQUIREMENTS

Manufacturer advises periodic monitoring of hepatic function and haematological state (including biannual hepatic ultrasonography for treatment exceeding 6 months or repeated courses of treatment).

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

#### Capsule

- **Danazol (Non-proprietary)**
  - **Danazol 100 mg** Danazol 100 mg capsules | 28 capsule £18.40
  - **Danazol 200 mg** Danazol 200 mg capsules | 56 capsule £30.27

- **Danol (Sanofi)**
  - **Danazol 100 mg** Danol 100 mg capsules | 60 capsule £16.38
  - **Danazol 200 mg** Danol 200 mg capsules | 60 capsule £32.41

### 7 Hypothalamic and anterior pituitary hormone related disorders

#### Hypothalamic and anterior pituitary hormones

### Anterior pituitary hormones

#### Corticotrophins

Tetracosactide p. 744 (tetracosactrin), an analogue of corticotropin (ACTH), is used to test adrenocortical function; failure of the plasma cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency.

Both corticotropin and tetracosactide were formerly used as alternatives to corticosteroids in conditions such as Crohn’s disease; their value was limited by the variable and unpredictable therapeutic response and by the waning of their effect with time.

#### Gonadotrophins

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) together, or follicle-stimulating hormone alone (as in follitropin), are used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene citrate p. 766, or in superovulation treatment for assisted conception (such as in vitro fertilisation).

The gonadotrophins are also occasionally used in the treatment of hypogonadotropic hypogonadism and associated oligospermia. There is no justification for their use in primary gonadal failure.

#### Growth hormone

Growth hormone is used to treat deficiency of the hormone in children and in adults. In children it is used in Prader-Willi syndrome, Turner syndrome, chronic renal insufficiency, short children considered small for gestational age at birth, and short stature homeobox-containing gene (SHOX) deficiency.

Growth hormone of human origin (HGH; somatotrophin) has been replaced by a growth hormone of human sequence, somatropin p. 748, produced using recombinant DNA technology. Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is licensed to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.

#### Hypothalamic hormones

Gonadorelin p. 744 when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating hormone (FSH). It has not proved to be very helpful,
however, in distinguishing hypothalamic from pituitary lesions. Gonadorelin analogues are indicated in endometriosis and infertility and in breast and prostate cancer.

### 7.1 Adrenocortical function testing

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES ▶ CORTICOTROPINS**

#### Tetracosactide (Tetracosactrin)

- **INDICATIONS AND DOSE**
  - Diagnosis of adrenocortical insufficiency (diagnostic 30-minute test)
    - By intravenous injection, or by intramuscular injection
    - Adult: 250 micrograms for 1 dose
  - Diagnosis of adrenocortical insufficiency (diagnostic 5-hour test)
    - By intramuscular injection using depot injection
    - Adult: 1 mg for 1 dose
  - Alternative to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis (formerly used but value was limited by the variable and unpredictable therapeutic response and by the waning of effect with time)
    - By intramuscular injection using depot injection
    - Adult: Initially 1 mg daily, alternatively initially 1 mg every 12 hours, (in acute cases), then reduced to 1 mg every 2–3 days, followed by 1 mg once weekly, alternatively 500 micrograms every 2–3 days

- **CONTRA-INDICATIONS** Acute psychosis - adrenogenital syndrome - allergic diseases - asthma - avoid injections containing benzyl alcohol in neonates - Cushings syndrome - infectious diseases - peptic ulcer - primary adrenocortical insufficiency - refractory heart failure

- **CAUTIONS** Active infectious diseases (should not be used unless adequate disease-specific therapy is being given) - active systemic diseases (should not be used unless adequate disease-specific therapy is being given) - diabetes mellitus - diverticulitis - history of asthma - history of atopic allergy - history of eczema - history of hayfever - history of hypersensitivity - hypertension - latent amoebiasis (may become activated) - latent tuberculosis (may become activated) - myasthenia gravis - ocular herpes simplex - osteoporosis - predisposition to thromboembolic - psychological disturbances may be triggered - recent intestinal anastomosis - reduced immune response (should not be used unless adequate disease-specific therapy is being given) - ulcerative colitis

**CAUTIONS, FURTHER INFORMATION**

- Risk of anaphylaxis. Should only be administered under medical supervision. Consult product literature.
- Hypertension. Patients already receiving medication for moderate to severe hypertension must have their dosage adjusted if treatment started.
- Diabetes mellitus. Patients already receiving medication for diabetes mellitus must have their dosage adjusted if treatment started.


- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with history of hypersensitivity to tetracosactide/corticotrophins or excipients.

- **PREGNANCY** Avoid (but may be used diagnostically if essential).
- **BREAST FEEDING** Avoid (but may be used diagnostically if essential).
- **HEPATIC IMPAIRMENT** For depot injection, manufacturer advises caution in cirrhosis (may enhance effect of tetracosactide therapy).
- **RENAL IMPAIRMENT** Use with caution in patients with renal impairment.
- **EFFECT ON LABORATORY TESTS** May suppress skin test reactions.
  - Post administration total plasma cortisol levels during 30-minute test for diagnosis of adrenocortical insufficiency might be misleading due to altered cortisol binding globulin levels in some special clinical situations including, patients on oral contraceptives, post-operative patients, critical illness, severe liver disease and nephrotic syndrome.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Synacthen (Mallinckrodt Specialty Pharmaceuticals Ireland Ltd)
  - Tetracosactide acetate 250 microgram per 1 ml
  - Synacthen 250micrograms/1ml solution for injection ampoules
  - 1 ampoule (£38.00) + £38.00

**Suspension for injection**

- EXCIPIENTS: May contain benzyl alcohol
- Synacthen Depot (Mallinckrodt Specialty Pharmaceuticals Ireland Ltd)
  - Tetracosactide acetate 1 mg per 1 ml
  - Synacthen Depot 1mg/1ml suspension for injection ampoules
  - 1 ampoule (£346.28) + £346.28

### 7.2 Assessment of pituitary function

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES ▶ GONADOTROPIN-RELEASING HORMONES**

#### Gonadorelin

(Gonadotrophin-releasing hormone; GnRH; LH-RH)

- **INDICATIONS AND DOSE**
  - Assessment of pituitary function
    - By subcutaneous injection, or by intravenous injection
    - Adult: 100 micrograms for 1 dose

- **CAUTIONS** Pituitary adenoma

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7.3 Gonadotrophin replacement therapy

**GONADOTROPHINS**

**Choriogonadotropin alfa**
(Human chorionic gonadotropin)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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</thead>
<tbody>
<tr>
<td>Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene</td>
</tr>
</tbody>
</table>

- **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.

<table>
<thead>
<tr>
<th>CONTRA-INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active thromboembolic disorders - ectopic pregnancy in previous 3 months - hypotalalamic malignancy - mammary malignancy - ovarian enlargement or cyst (unless caused by polycystic ovarian disease) - ovarian malignancy - pituitary malignancy - uterine malignancy</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>CAUTIONS</th>
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<tbody>
<tr>
<td>Acute porphyrinas p. 1058</td>
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<table>
<thead>
<tr>
<th>SIDE-EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common or very common Abdominal pain - fatigue - headache - nausea - ovarian hyperstimulation syndrome - vomiting</td>
</tr>
<tr>
<td>Uncommon Breast pain - depression - diarrhoea - irritability - restlessness</td>
</tr>
<tr>
<td>Rare or very rare Rash - shock - thromboembolism</td>
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<thead>
<tr>
<th>MEDICINAL FORMS</th>
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<tbody>
<tr>
<td>There can be variation in the licensing of different medicines containing the same drug.</td>
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**Solution for injection**

- **Bemfola** (Gedeon Richter (UK) Ltd)
  - Folitropin alfa 600 unit per 1 ml Bemfola 225units/0.375ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £70.50
  - Bemfola 300units/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £94.00
  - Bemfola 150units/0.25ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £47.00
  - Bemfola 75units/0.125ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £23.50
  - Bemfola 450units/0.75ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £141.00

- **Gonal-f** (Merck Serono Ltd)
  - Folitropin alfa 600 unit per 1 ml Gonal-f 900units/1.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £338.40
  - Gonal-f 300units/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £112.80
  - Gonal-f 450units/0.75ml solution for injection pre-filled pen | 1 pre-filled disposable injection | £225.60

- **Ovaleap** (Theramex HQ UK Ltd)
  - Folitropin alfa 600 unit per 1 ml Ovaleap 450units/0.75ml solution for injection vials | 1 cartridge | £75.20
  - Ovaleap 900units/1.5ml solution for injection vials | 1 cartridge | £169.20

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<thead>
<tr>
<th>Powder and solvent for solution for injection</th>
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| Folitropin alfa 75 unit Gonal-f 75unit powder and solvent for solution for injection vials | 1 vial | £25.22
| Folitropin alfa 450 unit Gonal-f 450unit powder and solvent for solution for injection vials | 1 vial | £51.32
| Folitropin alfa 1050 unit Gonal-f 1,050unit powder and solvent for solution for injection vials | 1 vial | £351.08

**Follitropin alfa**
(Recombinant human follicle stimulating hormone)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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<tbody>
<tr>
<td>Infertility in women with proven hypopituitarism or who have not responded to clomifene</td>
</tr>
</tbody>
</table>

- **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.
  - Hypogonadotrophic hypogonadism

- **BY SUBCUTANEOUS INJECTION**
  - Adult (male): (consult product literature).
Follitropin alfa with lutropin alfa

The properties listed below are those particular to the combination only. For the properties of the components please consider, follitropin alfa p. 745, lutropin alfa below.

- **INDICATIONS AND DOSE**
  - Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovaluation treatment for assisted conception (such as in vitro fertilisation)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder and solvent for solution for injection**
    - **Pergovernis** (Merck Serono Ltd)
      - **Luveris**
      - Lutropin alfa 75 unit, Follitropin alfa 150 unit
        - **Pergovernis** (Merck Serono Ltd)
          - **Vial**
            - 150 unit/75 unit powder and solvent for solution for injection vials | £72.35

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Follitropin delta

- **DRUG ACTION**
  - Follitropin delta is a recombinant human follicle stimulating hormone, which causes development of multiple mature follicles.

- **INDICATIONS AND DOSE**
  - Superovaluation treatment for assisted conception (such as in vitro fertilisation) (initiated under specialist supervision)
  - **BY SUBCUTANEOUS INJECTION**

- **CONTRA-INDICATIONS**
  - Ovarian cysts (not caused by polycystic ovarian syndrome) - ovarian enlargement (not caused by polycystic ovarian syndrome) - tumours of breast - tumours of hypothalamus - tumours of ovaries - tumours of pituitary - tumours of uterus - vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 1058 - history of tubal disease (increased risk of ectopic pregnancy)

- **SIDE-EFFECTS**
  - **Common or very common**
    - Fatigue - headache - nausea - ovarian and fallopian tube disorders - pelvic disorders - uterine pain
  - **Uncommon**
    - Abdominal discomfort - breast abnormalities - constipation - diarrhoea - dizziness - drowsiness - mood swings - vaginal haemorrhage - vomiting
  - **Rare or very rare**
    - Thromboembolism

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - If ovarian hyperstimulation syndrome occurs, the patient should be advised to withhold hCG and avoid intercourse or use barrier contraceptive methods for at least 4 days.

- **PREGNANCY**
  - Manufacturer advises avoid—not indicated during pregnancy.

- **BREAST FEEDING**
  - Manufacturer advises avoid—not indicated during breastfeeding.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises regular monitoring of ovarian response with ultrasound alone, or in combination with serum estradiol levels.
  - Frequent monitoring of follicular development is required to reduce the risk of ovarian hyperstimulation syndrome during treatment, and for at least 2 weeks after triggering of final follicular maturation—consult product literature.

- **DIRECTIONS FOR ADMINISTRATION**
  - Manufacturer recommends the cartridge should be used with the Rekovelle® injection pen. The first injection should be performed under direct medical supervision; self-administration should only be performed by patients who are well motivated, adequately trained and have access to expert advice.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Follitropin delta is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

- **HANDLING AND STORAGE**
  - Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for further information regarding storage conditions outside refrigerator.

- **PATIENT AND CARER ADVICE**
  - Conception and contraception
  - Manufacturer advises that patients planning to conceive should be warned that there is a risk of multiple pregnancy.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **Rekovelle** (Ferring Pharmaceuticals Ltd)
    - Follitropin delta 33.33 microgram per ml
      - **Rekovelle**
        - 12 micrograms/0.33 ml solution for injection cartridges | 1 cartridge | £118.31
      - **Rekovelle**
        - 36 micrograms/0.8 ml solution for injection cartridges | 1 cartridge | £354.94
      - **Rekovelle**
        - 72 micrograms/2.16 ml solution for injection cartridges | 1 cartridge | £709.89

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Lutropin alfa

(Recombinant human luteinising hormone)

- **INDICATIONS AND DOSE**
  - Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene (in conjunction with follicle-stimulating hormone) | Superovaluation treatment for assisted conception (such as in vitro fertilisation) (in conjunction with follicle-stimulating hormone)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Mammary carcinoma - ovarian carcinoma - ovarian enlargement or cyst (unless caused by polycystic ovarian disease) - tumours of hypothalamus - tumours of pituitary - undiagnosed vaginal bleeding - uterine carcinoma

- **CAUTIONS**
  - Acute porphyrias p. 1058

- **SIDE-EFFECTS**
  - **Common or very common**
    - Breast pain - diarrhoea - gastrointestinal discomfort - headache - nausea - ovarian and fallopian tube disorders - pelvic pain - vomiting
  - **Rare or very rare**
    - Thromboembolism

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - **Luveris** (Merck Serono Ltd)
    - Lutropin alfa 75 unit
      - Luveris 75 unit powder and solvent for solution for injection vials | 1 vial | £31.38

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Menotrophin

- **INDICATIONS AND DOSE**
  - Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)
    - By subcutaneous injection, or by deep intramuscular injection
    - Adult (female): Adjusted according to response.

- **SIDE-EFFECTS**
  - Common or very common: Gastrointestinal discomfort, headache, nausea, ovarian hyperstimulation syndrome, pelvic pain, vomiting
  - Uncommon: Deep vein thrombosis

- **PREGNANCY**
  - Avoid.

- **BREAST FEEDING**
  - Avoid.

- **CONTRA-INDICATIONS**
  - Ovarian cysts (not caused by polycystic ovarian syndrome)
  - Tumours of breast
  - Tumours of hypotalamus
  - Tumours of ovaries
  - Tumours of pituitary
  - Tumours of prostate
  - Tumours of uterus
  - Vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 1058: history of tubal disease

- **PRESCRIBING AND DISPENSING INFORMATION**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Avoid.
  - (Consult product literature).

- **MEDICINAL FORMS**
  - Powder and solvent for solution for injection
    - Menotrophin 75 unit (Ferring Pharmaceuticals Ltd) $180.18
    - Menotrophin 150 unit (Ferring Pharmaceuticals Ltd) $360.36
    - Menotrophin 600 unit (Pegvisomant is a genetically modified selective growth hormone receptor antagonist.

- **RECEPTOR ANTAGONISTS**
  - Pegvisomant (Pharmacia Ltd)
    - Follicle stimulating hormone human (as Urofollitropin)
      - 75 unit $279.00
      - 150 unit $558.00

Urofollitropin

- **INDICATIONS AND DOSE**
  - Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)
    - By subcutaneous injection, or by deep intramuscular injection
    - Adult (female): Adjusted according to response.

- **CONTRA-INDICATIONS**
  - Ovarian cysts (not caused by polycystic ovarian syndrome)
  - Tumours of breast
  - Tumours of hypotalamus
  - Tumours of ovaries
  - Tumours of pituitary
  - Tumours of uterus
  - Vaginal bleeding of unknown cause

- **CAUTIONS**
  - Acute porphyrias p. 1058

- **SIDE-EFFECTS**
  - Common or very common: Breast tenderness, constipation, diarrhoea, gastrointestinal discomfort, headache, hot flush, increased risk of infection, muscle spasms, nausea, ovarian hyperstimulation syndrome, pain, pelvic pain, rash, vaginal discharge, vaginal haemorrhage, vomiting

- **PREGNANCY**
  - Avoid.

- **BREAST FEEDING**
  - Avoid.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Urofollitropin is purified extract of human post-menopausal urine containing follicle-stimulating hormone (FSH).

- **PATIENT AND CARER ADVICE**
  - Conception and contraception: Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Powder and solvent for solution for injection
    - Fostimon (Pharmasure Ltd)
      - Follicle stimulating hormone human (as Urofollitropin)
        - 75 unit $279.00
        - 150 unit $558.00

7.4 Growth hormone disorders

Other drugs used for Growth hormone disorders
Pasireotide, p. 951

PITUITARY AND HYPOthalamic HORMONES AND ANALOGUES

GROWTH HORMONE RECEPTOR ANTAGONISTS

Pegvisomant

- **DRUG ACTION**
  - Pegvisomant is a genetically modified analogue of human growth hormone and is a highly selective growth hormone receptor antagonist.

- **INDICATIONS AND DOSE**
  - Treatment of acromegaly in patients with inadequate response to surgery, radiation, or both, and to treatment with somatostatin analogues (initiated by a specialist)
    - By subcutaneous injection
    - Adult: Initially 80 mg for 1 dose, followed by 10 mg daily, then increased in steps of 5 mg daily, adjusted according to response; maximum 30 mg per day

- **CAUTIONS**
  - Abnormal liver function tests and/or signs or symptoms of liver injury (further investigations may be
required before treatment initiation—consult product literature) - diabetes mellitus (adjustment of antidiabetic therapy may be necessary).

### SIDE-EFFECTS

- **Common or very common** Arthralgia - arthritis - asthenia - constipation - diarrhoea - dizziness - dyspnoea - dyspepsia - eye pain - fever - gastrointestinal discomfort - gastrointestinal disorders - haemorrhage - headaches - hyperglycaemia - hypertension - hypoglycaemia - influenza like illness - lipohypertrophy - myalgia - nausea - numbness - oedema - skin reactions - sleep disorders - sweat changes - tremor - vomiting - weight increased


- **Frequency not known** Anger - angioedema - hepatic function abnormal - laryngospasm

### SIDE-EFFECTS, FURTHER INFORMATION

**Injection-site reactions** Rotate injection sites to avoid lipohypertrophy.

**Abnormal hepatic function** Manufacturer advises interrupt treatment if liver function tests at least 5 times the upper limit of normal or transaminase levels at least 3 times the upper limit of normal and bilirubin increased—consult product literature. Discontinue if liver injury is confirmed.

**CONCEPTION AND CONTRACEPTION** Possible increase in female fertility.

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (no information available); temporary or permanent withdrawal may be needed—consult product literature.

### MONITORING REQUIREMENTS

- Manufacturer advises assess liver function tests before treatment initiation and monitor liver function tests during treatment—consult product literature.
- Manufacturer advises monitor serum IGF-1 concentrations.

### NATIONAL FUNDING/ACCESS DECISIONS

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (November 2017) that pegvisomant (Somavert®) is accepted for use within NHS Scotland for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-1 [insulin-like growth factor-1] concentrations or was not tolerated. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**All Wales Medicines Strategy Group (AWMSG) decisions**

The All Wales Medicines Strategy Group has advised (November 2017) that pegvisomant (Somavert®) is recommended as an option for use within NHS Wales for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise insulin-like growth factor-1 (IGF-1) concentrations or was not tolerated. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Powder and solvent for solution for injection

- **Somavert (Pfizer Ltd)**
  - **Pegvisomant 10 mg** Somavert 10mg powder and solvent for solution for injection vials | 30 vial (£3,500.00 (Hospital only)) | £1,500.00 (Hospital only)
  - **Pegvisomant 15 mg** Somavert 15mg powder and solvent for solution for injection vials | 30 vial (£3,250.00 (Hospital only)) | £2,500.00 (Hospital only)
  - **Pegvisomant 20 mg** Somavert 20mg powder and solvent for solution for injection vials | 1 vial (£3,000.00 (Hospital only)) | £1,500.00 (Hospital only)
  - **Pegvisomant 25 mg** Somavert 25mg powder and solvent for solution for injection vials | 30 vial (£3,750.00 (Hospital only)) | £3,000.00 (Hospital only)
  - **Pegvisomant 30 mg** Somavert 30mg powder and solvent for solution for injection vials | 30 vial (£4,500.00 (Hospital only)) | £3,750.00 (Hospital only)

### PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES

#### Somatropin (Recombinant Human Growth Hormone)

- **INDICATIONS AND DOSE**
  - **Gonadal dysgenesis (Turner syndrome)**
    - By subcutaneous injection
    - Adult: 1.4 mg/m² daily, alternatively 45–50 micrograms/kg daily
  - **Deficiency of growth hormone**
    - By subcutaneous injection
    - Adult: Initially 150–300 micrograms daily, then increased if necessary up to 1 mg daily, dose to be increased gradually, use minimum effective dose (requirements may decrease with age).
    - Dose equivalences and conversion
    - Dose formerly expressed in units; somatropin 1 mg = 3 units.
  - **CONTRA-INDICATIONS**
    - Evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting) - not to be used after renal transplantation - severe obesity in Prader-Willi syndrome - severe respiratory impairment in Prader-Willi syndrome
  - **CAUTIONS**
    - Diabetes mellitus (adjustment of antidiabetic therapy may be necessary) - disorders of the epiphysis of the hip (monitor for limping) - history of malignant disease - hypoaldrenism (initiation or adjustment of glucocorticoid replacement therapy may be necessary) - hypothyroidism—manufacturers recommend periodic thyroid function tests but limited evidence of clinical value - initiation of treatment close to puberty not recommended in child born small for corrected gestational age - papilloedema - relative deficiencies of other pituitary hormones - resolved intracranial hypertension (monitor closely) - Silver-Russell syndrome

#### SIDE-EFFECTS

- **Common or very common** Carpal tunnel syndrome - fluid retention - headache - joint disorders - lipoatrophy - myalgia - oedema - parasthesia
  - **Uncommon** Gynaecomastia - idiopathic intracranial hypertension
  - **Rare or very rare** Hyperglycaemia - hyperinsulinism - hypothyroidism - osteonecrosis of femur - pancreatitis - slipped capital femoral epiphysis
  - **Frequency not known** Leukaemia - musculoskeletal stiffness

### SIDE-EFFECTS, FURTHER INFORMATION

Fundscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported).
Treatment should be discontinued if growth velocity increases by less than 50% from baseline in the first year of treatment.

> Somatropin for adults with growth hormone deficiency (August 2003) NICE TA64

Somatropin is recommended in adults only if the following 3 criteria are fulfilled:

- Severe growth hormone deficiency, established by an appropriate method,
- Impaired quality of life, measured by means of a specific questionnaire,
- Already receiving treatment for another pituitary hormone deficiency.

Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months.

Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved. Treatment for adult-onset growth hormone deficiency should be stopped only when the patient and the patient’s physician consider it appropriate.

Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone disorders; maintenance treatment can be prescribed in the community under a shared-care protocol.

www.nice.org.uk/TA64

**Solution for injection**

**EXCipients:** May contain Benzyl alcohol.

- **Norditropin NordiFlex** (Novo Nordisk Ltd)
  - Somatropin (epr) 3.3 mg per 1 ml
    - Norditropin NordiFlex 5mg/1.5ml solution for injection pre-filled pen (Novo Nordisk) £115.90 DT + £115.90
  - Somatropin (epr) 6.7 mg per 1 ml
    - Norditropin NordiFlex 10mg/1.5ml solution for injection pre-filled pen (Novo Nordisk) £231.80 DT + £231.80
  - Somatropin (epr) 10 mg per 1 ml
    - Norditropin NordiFlex 15mg/1.5ml solution for injection pre-filled pen (Novo Nordisk) £347.70 DT + £347.70

- **Norditropin SimplexX** (Novo Nordisk Ltd)
  - Somatropin (epr) 3.3 mg per 1 ml
    - Norditropin SimplexX 5mg/1.5ml solution for injection cartridges | 1 cartridge (Novo Nordisk) £139.05 DT + £139.05
  - Somatropin (epr) 6.7 mg per 1 ml
    - Norditropin SimplexX 10mg/1.5ml solution for injection cartridges | 1 cartridge (Novo Nordisk) £257.0 DT + £257.0
  - Somatropin (epr) 10 mg per 1 ml
    - Norditropin SimplexX 15mg/1.5ml solution for injection cartridges | 1 cartridge (Novo Nordisk) £319.05 DT + £319.05

- **NutropinAq** (ipSEN Ltd)
  - Somatropin (rbe) 3.3 mg per 1 ml
    - NutropinAq 10mg/2ml solution for injection cartridges | 1 cartridge (Nutropin) £203.00 DT + £203.00
  - Somatropin (rbe) 5 mg per 1 ml
    - NutropinAq 20mg/4ml solution for injection cartridges | 1 cartridge (Nutropin) £368.74 DT + £368.74

- **Omnitrope SurePal** (Sanoz Ltd)
  - Somatropin (rbe) 3.333 mg per 1 ml
    - Omnitrope SurePal 5mg/1.5ml solution for injection cartridges | 5 cartridge (Novo Nordisk) £368.74 DT + £368.74

- **Saizen** (Merck Serono Ltd)
  - Somatropin (rnc) 5.825 mg per 1 ml
    - Saizen 6mg/1.03ml solution for injection cartridges | 1 cartridge (Saizen) £139.08 DT + £139.08
  - Somatropin (rnc) 8 mg per 1 ml
    - Saizen 12mg/1.5ml solution for injection cartridges | 1 cartridge (Saizen) £278.16 DT + £278.16

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
### Sex hormone responsive conditions

#### Sex hormones

**Oestrogens and HRT**

Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia.

In terms of oestrogenic activity, natural oestrogens (estradiol p. 756 (oestradiol), estrone (oestrone), and estriol p. 832 (oestriol)) have a more appropriate profile for hormone replacement therapy (HRT) than synthetic oestrogens (ethinylestradiol p. 759 (ethinylöstradiol) and mestranol). Tibolone p. 760 has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a progestogen should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.

#### Hormone replacement therapy

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal osteoporosis but other drugs are preferred. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation used for a few weeks and repeated if necessary.

Systemic therapy with an oestrogen or drugs with oestrogenic properties alleviates the symptoms of oestrogen deficiency such as vasomotor symptoms. Tibolone combines oestrogenic and progestogenic activity with weak androgenic activity; it is given continuously, without cyclical progestogen.

HRT may be used in women with early natural or surgical menopause (before age 45 years), since they are at high risk of osteoporosis. For early menopause, HRT can be given until the approximate age of natural menopause (i.e. until age 50 years). Alternatives to HRT should be considered if osteoporosis is the main concern.

Clonidine hydrochloride p. 145 may be used to reduce vasomotor symptoms in women who cannot take an oestrogen, but clonidine hydrochloride may cause unacceptable side-effects.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. For details of these risks see HRT Risk table.

The minimum effective dose of HRT should be used for the shortest duration. Treatment should be reviewed at least annually and for osteoporosis alternative treatments considered. HRT does not prevent coronary heart disease or protect against a decline in cognitive function and it should not be prescribed for these purposes. Experience of treating women over 65 years with HRT is limited.
For the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years.

For the treatment of menopausal symptoms in women with breast cancer see Breast cancer p. 942.

Risk of breast cancer
It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use; tibolone has only a limited effect on mammographic density.

Risk of endometrial cancer
The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

Risk of ovarian cancer
Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer; this excess risk disappears within a few years of stopping.

Risk of venous thromboembolism
Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use. In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits. Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

Risk of stroke
Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment.

Risk of coronary heart disease
HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Choice
The choice of HRT for an individual depends on an overall balance of indication, risk, and convenience. A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are not suitable for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.

An oestrogen alone is suitable for continuous use in women without a uterus. However, in endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered in these circumstances. An oestrogen may be given by mouth or by transdermal administration, which avoids first-pass metabolism.

Surgery
Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery; it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective surgery), prophylaxis with unfractionated or low molecular weight heparin and graduated compression hosiery is advised.

Reasons to stop HRT
Hormone replacement therapy should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment

Ethinylestradiol
Ethinylestradiol p. 759 (ethinyl-oestradiol) is licensed for short-term treatment of symptoms of oestrogen deficiency, for osteoporosis prophylaxis if other drugs cannot be used and for the treatment of female hypogonadism and menstrual disorders. Ethinylestradiol is occasionally used under specialist supervision for the management of hereditary anaemorrhagic telangiectasia (but evidence of benefit is limited). It is also used licensed for the palliative treatment of prostate cancer.

Raloxifene
Raloxifene hydrochloride p. 754 is licensed for the treatment and prevention of postmenopausal osteoporosis; unlike hormone replacement therapy, raloxifene hydrochloride does not reduce menopausal vasomotor symptoms.

Progestogens and progesterone receptor modulators
There are two main groups of progestogen, progesterone and its analogues (dydrogesterone and medroxyprogesterone acetate p. 810) and testosterone analogues (norethisterone p. 764 and norgestrel). The newer progestogens (desogestrel p. 805, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel p. 806 is the active isomer of norgestrel and has twice its potency. Progesterone p. 765 and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

Where endometriosis requires drug treatment, it may respond to a progestogen, e.g. norethisterone, administered on a continuous basis. Danazol p. 742 and gonadorelin analogues are also available. Although oral progestogens have been used widely for menorrhagia (see Heavy menstrual bleeding p. 753) they are
HRT Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>Age range (years)</th>
<th>Background incidence per 1000 women in Europe not using HRT</th>
<th>Additional cases per 1000 women using oestrogen only HRT (estimated)</th>
<th>Additional cases per 1000 women using combined (oestrogen-progestogen) HRT (estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over 5 years</td>
<td>Over 10 years</td>
<td>For 5 years’ use</td>
</tr>
<tr>
<td>Breast cancer†</td>
<td>50-59</td>
<td>10</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Endometrial cancer*</td>
<td>50-59</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Venous thromboembolism†</td>
<td>50-59</td>
<td>5</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>50-59</td>
<td>8</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Coronary heart disease†</td>
<td>70-79</td>
<td>29-44</td>
<td>—</td>
<td>NS</td>
</tr>
</tbody>
</table>

Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference. Taken from MHRA/CHM (Drug Safety Update) and a prophylactic dose of a low molecular weight heparin may decrease the risk of fetal loss (use under specialist supervision only). See also MHRA/CHM (Drug Safety Update) and a prophylactic dose of a low molecular weight heparin may decrease the risk of fetal loss (use under specialist supervision only).

1. Tibolone increases the risk of breast cancer but to a lesser extent than with combined HRT.
2. Evidence suggests an increased risk of endometrial cancer with tibolone. After 2.7 years of use (in women of average age 68 years), 1 extra case of endometrial hyperplasia and 4 extra cases of endometrial cancer were diagnosed compared with placebo users.
3. The risk of endometrial cancer cannot be reliably estimated in those using combined HRT because the addition of progestogen for at least 10 days per 28-day cycle greatly reduces the additional risk, and addition of a daily progestogen eliminates the additional risk. The risk of endometrial cancer in women who have not used HRT increases with body mass index (BMI); the increased risk of endometrial cancer in users of oestrogen-only HRT or tibolone is more apparent in women who are not overweight.
4. Limited data does not suggest an increased risk of thromboembolism with tibolone compared with combined HRT or women not taking HRT.
5. Although the level of risk of thromboembolism associated with non-oral routes of administration of HRT has not been established, it may be lower for the transdermal route.
6. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment; risk of stroke is age-dependent and therefore the absolute risk of stroke with tibolone increases with age.
7. Increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause.
8. There is insufficient data to draw a conclusion on the risk of coronary heart disease with tibolone.

Cancer

Progestogens also have a role in neoplastic disease.

**Progestosterone receptor modulators**

Ulipristal acetate p. 804 is a progestosterone receptor modulator with a partial progestosterone antagonist effect. Ulipristal acetate is used in the pre-operative treatment of moderate to severe symptoms of uterine fibroids (see important safety information in ulipristal acetate). Ulipristal acetate is also used as an hormonal emergency contraceptive.

**Endometriosis**

**Description of condition**

Endometriosis is the growth of endometrial-like tissue outside the uterus. Endometriosis is a condition affecting women mainly of reproductive age and, although its exact cause is unknown, it is an oestrogen-dependent condition and is associated with menstruation. Endometriosis is typically associated with symptoms such as pelvic pain, painful periods and subfertility. Women with endometriosis report pain, which can be frequent, chronic and severe, as well as tiredness, more sick days, and a significant physical, sexual, psychological and social impact. Endometriosis is an important cause of subfertility and this can also have a significant effect on quality of life.

Women may also have endometriosis without symptoms, so it is difficult to know how common the disease is in the population. It is also unclear whether endometriosis is...
always progressive or can remain stable or improve with time.

**Aims of treatment**

The aim of treatment is to reduce the severity of symptoms, improve the quality of life, and to improve fertility if this is affected.

**Drug treatment**

Management options for endometriosis include drug treatment and surgery. Most drug treatments for endometriosis work by suppressing ovarian function and are contraceptive. Surgical treatment aims to remove or destroy endometriotic lesions. The choice of treatment depends on the woman’s preferences and priorities in terms of pain management and fertility. A short trial (such as 3 months) of paracetamol or an NSAID alone or in combination should be considered for first-line management of endometriosis-related pain. If pain relief is inadequate, consider other forms of pain management and referral for further assessment.

Hormonal treatment (with a combined oral contraceptive or a progestogen) should be offered to women with suspected, confirmed or recurrent endometriosis. The patient should be informed that hormonal treatment for endometriosis can reduce pain and has no permanent negative effect on subsequent fertility. If initial hormonal treatment for endometriosis is not effective, not tolerated or is contra-indicated, the woman should be referred to a gynaecologist or specialist endometriosis service for possible further treatment, which could include other hormonal treatments or surgery. For use of drugs to treat neuropathic pain, see Neuropathic pain.

**Surgery**

Women with suspected or confirmed endometriosis should be asked about their symptoms, preferences and priorities with respect to pain and fertility, to guide surgical decision-making. For deep endometriosis involving the bowel, bladder or ureter, gonadotrophin-releasing hormones given for 3 months before surgery should be considered. Excision rather than ablation should be considered to treat endometriomas, taking into account the woman’s desire for fertility and her ovarian reserve. After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, a combined hormonal contraceptive), to prolong the benefits of surgery and manage symptoms. A hysterectomy may be indicated if, for example, the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments. For use of drugs to treat neuropathic pain, see Neuropathic pain.

**Surgical management if fertility is a priority**

If fertility is a priority, the management of endometriosis-related subfertility should have multidisciplinary involvement with input from a fertility specialist. Women with endometriosis who are trying to conceive should not be offered hormonal treatment, because it does not improve spontaneous pregnancy rates.

**Useful Resources**


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**Heavy menstrual bleeding**

**Description of condition**

Heavy menstrual bleeding, also known as menorrhagia, is excessive menstrual blood loss of 80 mL or more, or for a duration of more than 7 days, which results in the need to change menstrual products every 1–2 hours. Heavy menstrual bleeding occurs regularly, every 24–35 days.

**Drug treatment**

The choice of treatment should be guided by the presence or absence of fibroids (including size, number and location), polyps, endometrial pathology or adenomyosis, other symptoms (such as pressure or pain), co-morbidities, and patient preference.

In females with heavy menstrual bleeding and unidentified pathology, fibroids less than 3 cm in diameter causing no distortion of the uterine cavity, or suspected or diagnosed adenomyosis, a levonorgestrel-releasing intra-uterine system p. 806 is the first-line treatment option. Patients should be advised that irregular menstrual bleeding can occur particularly during the first months of use and that the full benefit of treatment may take at least 6 months.

If a levonorgestrel-releasing intra-uterine system p. 806 is unsuitable, either tranexamic acid p. 110, an NSAID, a combined hormonal contraceptive, or a cyclical oral progestogen should be considered. Progestogen-only contraceptives may suppress menstruation and be beneficial to females with heavy menstrual bleeding. A non-hormonal treatment is recommended in patients actively trying to conceive.

If drug treatment is unsuccessful or declined by the patient, or if symptoms are severe, referral to a specialist for alternative drug treatment or surgery should be considered.

In females with fibroids of 3 cm or more in diameter, referral to a specialist should be considered. Treatment options include tranexamic acid, an NSAID, ulipristal acetate p. 804, a levonorgestrel-releasing intra-uterine system p. 806, a combined hormonal contraceptive, a cyclical oral progestogen, uterine artery embolisation, or surgery. Treatment choice depends on the size, number and location of the fibroids, and severity of symptoms. If drug treatment is required while investigations and definitive treatment is being organised, either tranexamic acid, or an NSAID, or both, can be given.

Intermittent ulipristal acetate can be offered to females who are not eligible for surgery and have a haemoglobin concentration of 10.2 g/100 mL (102 g/litre) or less. If the haemoglobin concentration is more than 10.2 g/100 mL (102 g/litre), ulipristal acetate may be considered. The use of ulipristal acetate is associated with a risk of rare but serious liver injury; liver function should be monitored during treatment, see Important safety information, and Monitoring requirements in ulipristal acetate.

The effectiveness of drug treatment (excluding ulipristal acetate) for heavy menstrual bleeding may be limited in females with fibroids that are substantially greater than 3 cm in diameter. Treatment with a gonadotrophin-releasing hormone analogue or ulipristal acetate before hysterectomy and myomectomy should be considered if uterine fibroids are causing an enlarged or distorted uterus.

**Useful Resources**


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**8.1 Female sex hormone responsive conditions**

Other drugs used for Female sex hormone responsive conditions Clonidine hydrochloride, p. 145. Ulipristal acetate, p. 804
Sex hormone responsive conditions

### CALCULIUM REGULATING DRUGS > BONE RESORPTION INHIBITORS

**Raloxifene hydrochloride**

- **INDICATIONS AND DOSE**
  - **Treatment and prevention of postmenopausal osteoporosis**
    - **BY MOUTH**
      - Adult: 60 mg once daily
  - **Breast cancer [chemoprevention in postmenopausal women at moderate to high risk] (initiated under specialist supervision)**
    - **BY MOUTH**
      - Adult: 60 mg once daily for 5 years
  - **UNLICENSED USE** Not licensed for chemoprevention of breast cancer in the UK. Licensed for this indication in USA.
  - **CONTRA-INDICATIONS** Cholestasis - endometrial cancer - history of venous thromboembolism - undiagnosed uterine bleeding
  - **CAUTIONS** Avoid in Acute porphyrias p. 1058 - breast cancer (manufacturer advises avoid during treatment for breast cancer) - history of oestrogen-induced hypertriglyceridaemia (monitor serum triglycerides) - risk factors for stroke - risk factors for venous thromboembolism (discontinue if prolonged immobilisation)
  - **INTERACTIONS** → Appendix 1: raloxifene
  - **SIDE-EFFECTS**
    - Common or very common: Influenza - leg cramps - peripheral oedema - vasodilatation
    - Uncommon: Embolism and thrombosis
    - Rare or very rare: Breast abnormalities - gastrointestinal discomfort - gastrointestinal disorder - headaches - nausea - rash - thrombocytopaenia - vomiting
  - **HEPATIC IMPAIRMENT** Manufacturer advises avoid (risk of increased exposure).
  - **RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - **NICE decisions**
      - Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women (updated February 2018) NICE TA160
        - Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.
        - Women who are currently receiving treatment, but for whom treatment would not have been recommended, should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop. www.nice.org.uk/guidance/ta160
      - Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (updated February 2018) NICE TA161
        - Raloxifene is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:
          - who are unable to comply with the special instructions for the administration of alendronate and risedronate, or have a contra-indication to or are intolerant of alendronate and risedronate, and
          - have a combination of T-score, age and number of independent clinical risk factors for fracture, as indicated in the full NICE guidance.
        - Women who are currently receiving treatment, but for whom treatment would not have been recommended, should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop. www.nice.org.uk/guidance/ta161
  - **MEDICINAL FORMS**
    - **Tablet**
      - Raloxifene hydrochloride (Non-proprietary)
        - Raloxifene hydrochloride 60 mg | 28 tablet (P) £17.06 DT = £3.49 | 84 tablet (P) £10.47–£13.50
      - Evirex (Somex Pharma)
        - Raloxifene hydrochloride 60 mg | 28 tablet (P) £5.10 DT = £3.49
      - Evista (Daiichi Sankyo UK Ltd)
        - Raloxifene hydrochloride 60 mg | Evista 60mg tablets | 28 tablet (P) £17.06 DT = £3.49
      - Razylan (Aspire Pharma Ltd)
        - Raloxifene hydrochloride 60 mg | Razylan 60mg tablets | 28 tablet (P) £17.06 DT = £3.49

### OESTROGENS

**Conjugated oestrogens (equine)**

- **INDICATIONS AND DOSE**
  - **PREMARIN® TABLETS**
    - **Menopausal symptoms**
      - **BY MOUTH**
        - Adult: 0.3–1.25 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus
    - **Postmenopausal osteoporosis prophylaxis**
      - **BY MOUTH**
        - Adult: 0.625–1.25 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus
  - **CONTRA-INDICATIONS** Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - acute thrombophlebitis - Dubin–Johnson syndromes (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - liver disease (where liver function tests have failed to return to normal) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - Rotor syndromes (or monitor closely) - thrombophilic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism
  - **CAUTIONS** Acute porphyrias p. 1058 - diabetes (increased risk of heart disease) - factors predisposing to thromboembolism - history of breast nodules (closely monitor breast status—risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease (closely monitor breast status—risk of breast cancer) - hypophysyal tumours - increased risk of gall-bladder disease reported - migraine - migraine-like headaches - presence of antiphospholipid antibodies (increased risk of thrombotic events) - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - risk of breast cancer
  - **CAUTIONS, FURTHER INFORMATION**
    - **Risk of breast cancer** It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.
    - Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

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Risk of endometrial cancer. The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.

In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

Risk of ovarian cancer. Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

Risk of venous thromboembolism. Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

Risk of stroke. Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke.

Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

Risk of coronary heart disease. HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Other conditions. The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

**INTERACTIONS** → Appendix 1: hormone replacement therapy

**SIDE-EFFECTS**

**Common or very common** Alopecia · arthralgia · breast abnormalities · depression · leg cramps · menstrual cycle irregularities · vaginal discharge · weight changes

**Uncommon** Anxiety · cervical abnormalities · contact lens intolerance · dizziness · embolism and thrombosis · gallbladder disorder · gastrointestinal discomfort · headaches · hirsutism · libido disorder · mood altered · nausea · oedema · skin reactions · vulvovaginal candidiasis

**Rare or very rare** Angioedema · asthma exacerbated · cerebrovascular insufficiency · chorea exacerbated · colitis ischaemic · epilepsy exacerbated · galactorrhoea · glucose tolerance impaired · hypocalcaemia · jaundice cholestatic · myocardial infarction · neoplasms · pancreatitis · pelvic pain · vomiting

**Frequency not known** Endometrial hyperplasia · erythema nodosum

**SIDE-EFFECTS, FURTHER INFORMATION**

Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. Continuous combined HRT commonly produces irregular breakthrough bleeding in the first 4–6 months of treatment. Bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation to exclude serious gynaecological pathology.

**CONCEPTION AND CONTRACEPTION** HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

**PREGNANCY** Manufacturer advises avoid—not indicated during pregnancy.

**BREAST FEEDING** Avoid until weaning or for 6 months after birth (adverse effects on lactation).

**HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Premarin** (Pfizer Ltd)  
  Conjugated oestrogens 300 microgram Premarin 0.3mg tablets  
  84 tablet (P 06 ) £6.07 DT + £6.07
  Conjugated oestrogens 625 microgram Premarin 0.625mg tablets  
  84 tablet (P 04 ) £4.02 DT + £4.02
  Conjugated oestrogens 1.25 mg Premarin 1.25mg tablets  
  84 tablet (P 03 ) £3.58 DT + £3.58

Combinations available: Conjugated oestrogens with medroxyprogesterone, p. 761

**Conjugated oestrogens with bazedoxifene acetate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, conjugated oestrogens (equine) p. 754.

**INDICATIONS AND DOSE**

Menopausal symptoms (in women with at least 12 months since last menses for whom treatment with progestogen-containing therapy is not appropriate)

- **BY MOUTH**
  - Adult: 0.45/20 mg daily continuously

**DOSE EQUIVALENCE AND CONVERSION**

- Dose expressed as x/y mg conjugated oestrogens/bazedoxifene.

**INTERACTIONS** → Appendix 1: hormone replacement therapy

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · constipation · diarrhea · drowsiness · dry mouth · hot flush · muscle complaints · nausea · peripheral oedema · skin reactions · vulvovaginal candidiasis
- **Uncommon** Cholecytitis
- **Rare or very rare** Embolism and thrombosis
- **Frequency not known** Dry eye · eye disorders · eye inflammation · eye pain · palpatations · vision disorders
Estradiol

**INDICATIONS AND DOSE**

**BEDOL®**

**Menopausal symptoms | Osteoporosis prophylaxis**
- **BY MOUTH**
  - Adult: 2 mg daily, started on day 1–5 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progestogen for 12–14 days of each cycle in women with a uterus

**ELLESTE SOLO® MX**

**Menopausal symptoms**
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progestogen for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 40, subsequently adjust according to response

**Osteoporosis prophylaxis**
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progestogen for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 80, subsequently adjust according to response

**ELLESTE-SOLO® 1-MG**

**Menopausal symptoms**
- **BY MOUTH**
  - Adult: 1 mg daily, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progestogen for 12–14 days of each cycle in women with a uterus

**ELLESTE-SOLO® 2-MG**

**Menopausal symptoms not controlled with lower strength | Osteoporosis prophylaxis**
- **BY MOUTH**
  - Adult: 2 mg daily, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be given with cyclical progestogen for 12–14 days of each cycle in women with a uterus

**ESTRADERM MX®**

**Menopausal symptoms**
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progestogen for at least 12 days of each cycle in women with a uterus, therapy should be initiated with Evorel 50 patch; subsequently adjust according to response; dose may be reduced to Evorel 25 patch after first month if necessary for menopausal symptoms only

**FEMSEVEN®**

**Menopausal symptoms | Osteoporosis prophylaxis**
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch once weekly continuously, to be used with cyclical progestogen for at least 12 days of each cycle in women with a uterus, initiate therapy with FemSeven 50 patches for the first few months, subsequently adjust according to response

**OESTROGEL®**

**Menopausal symptoms**
- **TO THE SKIN**
  - Adult: Apply 1.5 mg once daily continuously, increased if necessary up to 3 mg after 1 month continuously, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical progestogen for at least 12 days of each cycle in women with a uterus

**Dose equivalence and conversion**
- With topical use
  - For Oestrogel®, 2 measures is equivalent to estradiol 1.5 mg.

**PROGYNOVA®**

**Menopausal symptoms**
- **BY MOUTH**
  - Adult: 1–2 mg daily continuously, to be started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progestogen for 12–14 days of each cycle in women with a uterus

Each cycle in women with a uterus, initiate therapy with MX50; subsequently adjust according to response.
Female sex hormone responsive conditions

Osteoporosis prophylaxis

- **BY MOUTH**
  - Adult: 2 mg daily continuously, to be taken with cyclical progesterogen for 12–14 days of each cycle in women with a uterus

**PROGYNONA® TS**

Menopausal symptoms | Osteoporosis prophylaxis
- **BY TRANSDermal APPLICATION**
  - Adult: Apply 1 patch once weekly continuously, alternatively apply 1 patch once weekly for 3 weeks, followed by a 7-day patch-free interval (cyclical), to be used with cyclical progesterogen for 12–14 days of each cycle in women with a uterus, initiate therapy with Progynova TS 50, subsequently adjust according to response, women receiving Progynova TS 100 patches for menopausal symptoms may continue with this strength for osteoporosis prophylaxis

**SANDRENA®**

Menopausal symptoms
- **TO THE SKIN**
  - Adult: Apply 1 mg daily, to be applied over area 1–2 times size of hand; with cyclical progesterogen for 12–14 days of each cycle in women with a uterus, dose may be adjusted after 2–3 cycles to lowest effective dose; usual dose 0.5–1.5 mg daily

**ZUMENON®**

Menopausal symptoms
- **BY MOUTH**
  - Adult: Initially 1 mg daily, to be started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), increased if necessary to 2 mg daily, to be taken with a cyclical progesterogen for 12–14 days of each cycle in women with a uterus

Osteoporosis prophylaxis
- **BY MOUTH**
  - Adult: 2 mg daily, to be taken with a cyclical progesterogen for 12–14 days of each cycle in women with a uterus

- **CONTRA-INDICATIONS**
  - Active arterial thromboembolic disease (e.g. angina or myocardial infarction) – active thrombophlebitis – Dubin-Johnson syndrome (or monitor closely) – history of breast cancer – history of recurrent venous thromboembolism (unless already on anticoagulant treatment) – oestrogen-dependent cancer – recent or active thromboembolic disease (e.g. angina or myocardial infarction) – Rotor syndrome (or monitor closely) – thrombophilic disorder – undiagnosed vaginal bleeding – untreated endometrial hyperplasia – venous thromboembolism

- **CAUTIONS**
  - Acute porphyrias p. 1058 – diabetes (increased risk of heart disease) – history of breast nodules (closely monitor breast status (risk of breast cancer) – history of endometrial hyperplasia; factors predisposing to thromboembolism – history of fibrocystic disease (closely monitor breast status (risk of breast cancer) – hypophyseal tumours – increased risk of gall-bladder disease – migraine (or migraine-like headaches) – presence of antiphospholipid antibodies (increased risk of thrombotic events) – prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer – risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) – symptoms of endometriosis may be exacerbated – uterine fibroids may increase in size

- **CAUTIONS, FURTHER INFORMATION**
  - Risk of breast cancer: It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.
  - Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

- **Risk of endometrial cancer**: The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.

  In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously.

  However, this should be weighed against the increased risk of breast cancer.

- **Risk of ovarian cancer**: Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

- **Risk of venous thromboembolism**: Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.

  In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

  Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

  **Risk of stroke**: Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

  **Risk of coronary heart disease**: HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

  **Other conditions**: The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **INTERACTIONS** → Appendix 1: hormone replacement therapy

- **SIDE-EFFECTS**

  **GENERAL SIDE-EFFECTS**
  - **Common or very common**
    - Headaches
    - Nausea
    - Skin reactions
  - **Uncommon**
    - Hypertension

  **SPECIFIC SIDE-EFFECTS**
  - **Common or very common**
    - With transdermal use: Abdominal pain – breast abnormalities – menstrual cycle irregularities – uterine disorders – vaginal discharge – weight changes
  - **Uncommon**

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vascular disease • tumour growth • visual impairment • vulvovaginal candidiasis

▶ With transdermal use Anemia • breast neoplasm benign • depression • flatulence • increased risk of infection • leucopenia • mood swings • venous thromboembolism • vertigo • vomiting

▶ Rare or very rare

▶ With oral use Angioedema • cerebrovascular insufficiency • chorea • contact lens intolerance • haemolytic anaemia • hepatic disorders • hirsutism • malaise • myocardial infarction • sexual dysfunction • steepening of corneal curvature • vaginal discharge • vomiting

▶ With transdermal use Epilepsy exacerbated • galactorrhoea • glucose tolerance impaired • libido disorder

▶ Frequency not known

▶ With oral use Carbohydrate metabolism change • epilepsy exacerbated • hyperglycaemia • increased risk of coronary artery disease • neoplasms • pancreatitis • systemic lupus erythematosus (SLE)

SIDE-EFFECTS, FURTHER INFORMATION Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. Continuous combined HRT commonly produces regular breakthrough bleeding in the first 4–6 months of treatment. Bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation to exclude serious gynaecological pathology.

CONCEPTION AND CONTRAETUTION HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

PREGNANCY Not known to be harmful.

BREAST FEEDING Avoid; adverse effects on lactation.

HEPATIC IMPAIRMENT Avoid in liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until determination of fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

PREGNANCY Not known to be harmful.

BREAST FEEDING Avoid; adverse effects on lactation.

HEPATIC IMPAIRMENT Avoid in liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

MONITORING REQUIREMENTS

▶ History of breast nodules or fibrocystic disease—closely monitor breast status (risk of breast cancer).

▶ The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

DIRECTIONS FOR ADMINISTRATION

▶ With transdermal use Patch should be removed after 3–4 days (or once a week in case of 7-day patch) and replaced with fresh patch on slightly different site; recommended sites: clean, dry, unbroken areas of skin on trunk below waistline; not to be applied on or near breasts or under waistband. If patch falls off in bath allow skin to cool before applying new patch.

PATIENT AND CARER ADVICE

▶ With transdermal use Patient counselling is advised for estradiol patches (administration).

▶ With topical use Patient counselling is advised for estradiol gels (administration).

OSTROGEL® With topical use Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 5 minutes before covering with clothing. Not to be applied on or near breasts or on vulval region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application.

SANDRENA® With topical use Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

Bedol (ReSource Medical UK Ltd)

Estradiol 2 mg Bedol 2mg tablets | 84 tablet £5.07 DT = £5.06

Elette Solo (Mesa Pharmaceuticals Ltd)

Estradiol 1 mg Elleste Solo 1mg tablets | 84 tablet £5.06 DT = £5.06

Estradiol 2 mg Elleste Solo 2mg tablets | 84 tablet £5.06 DT = £5.06

Progynova (Bayer Plc)

Estradiol valerate 1 mg Progynova 1mg tablets | 84 tablet £7.30 DT = £7.30

Estradiol valerate 2 mg Progynova 2mg tablets | 84 tablet £7.30 DT = £7.30

Zumenon (Mylan)

Estradiol 1 mg Zumenon 1mg tablets | 84 tablet £6.89 DT = £5.06

Estradiol 2 mg Zumenon 2mg tablets | 84 tablet £6.89 DT = £5.06

Transdermal patch

Elette Solo MX (Mesa Pharmaceuticals Ltd)

Estradiol 40 microgram per 24 hour Elleste Solo MX 40 transdermal patches | 8 patch £5.19 DT = £5.19

Estradiol 80 microgram per 24 hour Elleste Solo MX 80 transdermal patches | 8 patch £5.99 DT = £5.99

Estraderm MX (Merus Labs Luxco S.a R.L.)

Estradiol 25 microgram per 24 hour Estraderm MX 25 patches | 8 patch £5.50 DT = £3.42 | 24 patch £16.46 DT = £16.46

Estradiol 50 microgram per 24 hour Estraderm MX 50 patches | 8 patch £5.51 DT = £3.88 | 24 patch £16.46 DT = £11.66

Estradiol 75 microgram per 24 hour Estraderm MX 75 patches | 8 patch £6.42 DT = £4.12 | 24 patch £19.27

Estradiol 100 microgram per 24 hour Estraderm MX 100 patches | 8 patch £6.66 DT = £4.28 | 24 patch £19.99 DT = £19.99

Estraderm (Novartis Pharmaceuticals UK Ltd)

Estradiol 25 microgram per 24 hour Estraderm 25micrograms/24hours patches | 8 patch £5.99 DT = £3.42

Estradiol 37.5 microgram per 24 hour Estraderm 37.5micrograms/24hours patches | 8 patch £6.00 DT = £6.00

Estradiol 50 microgram per 24 hour Estraderm 50micrograms/24hours patches | 8 patch £6.02 DT = £3.88

Estradiol 75 microgram per 24 hour Estraderm 75micrograms/24hours patches | 8 patch £7.00 DT = £4.12

Estradiol 100 microgram per 24 hour Estraderm 100micrograms/24hours patches | 8 patch £7.27 DT = £4.28

Evorel (Janssen-Cilag Ltd)

Estradiol 25 microgram per 24 hour Evorel 25 patches | 8 patch £3.42 DT = £3.42

Estradiol 50 microgram per 24 hour Evorel 50 patches | 4 patch £6.04 | 8 patch £3.88 DT = £3.88 | 24 patch £11.66 DT = £11.66

Estradiol 75 microgram per 24 hour Evorel 75 patches | 8 patch £14.12 DT = £14.12

Estradiol 100 microgram per 24 hour Evorel 100 patches | 8 patch £4.28 DT = £4.28

FemSeven (Theramex HQ UK Ltd)

Estradiol 50 microgram per 24 hour FemSeven 50 patches | 4 patch £6.04 DT = £6.04 | 12 patch £18.02 DT = £18.02

Estradiol 75 microgram per 24 hour FemSeven 75 patches | 4 patch £6.98

Estradiol 100 microgram per 24 hour FemSeven 100 patches | 4 patch £7.28 DT = £7.28

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**CONTRA-INDICATIONS** Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis. Acute porphyrias p. 1035 - Dubin-Johnson and Rotor syndromes (or monitor closely). Gallstones - heart disease associated with pulmonary hypertension - heart disease associated with risk of embolus - history during pregnancy of cholestatic jaundice - history during pregnancy of chorea - history during pregnancy of pemphigoid gestationis - history during pregnancy of purpura - history of breast cancer - history of haemolytic uraemic syndrome - liver disease (where liver function tests have failed to return to normal). Migraine with aura - oestrogen-dependent cancer - sclerosing treatment for varicose veins - severe or multiple risk factors for arterial disease - severe or multiple risk factors for venous thromboembolism - systemic lupus erythematosus with (or unknown) antiphospholipid antibodies - thrombophilic disorder - transient cerebral ischaemic attacks without headaches - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism, or history of recurrent venous thromboembolism (unless already on anticoagulant treatment).

**CAUTIONS** Active trophoblastic disease (until return to normal). Risk factors for arterial disease - plasma-gonadotrophin concentration) - seek specialist advice - cardiovascular disease (sodium retention with oedema, thromboembolism) - Crohn’s disease - diabetes (increased risk of heart disease) - gene mutations associated with breast cancer (e.g. BRCA 1) - history of breast nodules or fibrocystic disease - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - history of severe depression (especially if induced by hormonal contraceptive) - antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for arterial disease - risk factors for venous thromboembolism - anglophobic disorder (including lupus anticoagulant); (in adolescents, avoid for age and gender). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from treatment.

- Risk of venous thromboembolism Use with caution if any of the following factors present but avoid if two or more factors present:
  - family history of venous thromboembolism in first-degree relative aged under 45 years (avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
  - obesity—body mass index ≥ 30 kg/m² (avoid if body mass index ≥ 35 kg/m² unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative); long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast); history of superficial thrombophlebitis;
  - age over 35 years (avoid if over 50 years); smoking.

- Risk factors for arterial disease Use with caution if any one of the following factors present but avoid if two or more factors present:
  - family history of arterial disease in first degree relative aged under 45 years (avoid if other heart disease present);
  - diabetes mellitus (avoid if diabetes complications present);
  - hypertension—blood pressure above 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (In adolescents, avoid if blood pressure very high); smoking (avoid if smoking 40 or more cigarettes daily);
  - age over 35 years (avoid if over 50 years);
  - obesity (avoid if body mass index ≥ 35 kg/m² unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
  - migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over
760 Sex hormone responsive conditions

**Tibolone**

**INDICATIONS AND DOSE**
Short-term treatment of symptoms of oestrogen deficiency (including women being treated with gonadotrophin releasing hormone analogues)

Osteoporosis prophylaxis in women at high risk of fractures when other fractures contra-indicated or not tolerated

- **BY MOUTH**
  - Adult: 2.5 mg daily

**CONTRA-INDICATIONS**
Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thromboprophylaxis - acute porphyrias p. 1058 - Dubin-Johnson and Rotor syndrome (or monitor closely) - history of breast cancer - history of cardiovascular disease - history of cerebrovascular disease - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - history of thromboembolism - history of thromboprophylaxis - hormone-dependent tumours - liver disease (where liver function tests have failed to return to normal) - oestrogen-dependent cancer - thrombophilic disorder - uninvestigated or undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

**CAUTIONS**
- Diabetes (increased risk of heart disease)
- epilepsy - factors predisposing to thromboembolism - history of breast nodules - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease - closely monitor breast status (risk of breast cancer) - history of liver disease - hypertriglyceridaemia - hyperphysical tumours - migraine (or migraine-like headaches) - presence of antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - risk of stroke

**SIDE-EFFECTS**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension

**Tablet**
- Ethinylestradiol (Non-proprietary)
  - Ethinylestradiol 2 microgram tablets | 100 tablet [P] £200.00
  - Ethinylestradiol 10 microgram tablets | 21 tablet [P] £200.00
  - Ethinylestradiol 50 microgram tablets | 21 tablet [P] £200.00

- Ethinylestradiol 1 mg tablets | 28 tablet [P] £200.00

**PREGNANCY**
- Not known to be harmful.
- Avoid until weaning or for 6 months after birth (adverse effects on lactation).

**HEPATIC IMPAIRMENT**
- Avoid.

**INTERACTIONS**
- Appendix 1: hormone replacement therapy

**SIDE-EFFECTS, FURTHER INFORMATION**
Cyclical HRT (where a progestogen is taken for 6–12 days of each 28–day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. Continuous combined HRT commonly produces irregular breakthrough bleeding in the first 4–6 months of treatment. Bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation to exclude serious gynaecological pathology.

**SIDE-EFFECTS**
- Frequency not known Arthralgia - dementia - depression - diziness - erythema nodosum - gallbladder disorder - headaches - increased risk of ischaemic stroke - myalgia - neoplasms - vision disorders

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension

**Tablet**
- Ethinylestradiol (Non-proprietary)
  - Ethinylestradiol 2 microgram tablets | 100 tablet [P] £200.00
  - Ethinylestradiol 10 microgram tablets | 21 tablet [P] £200.00
  - Ethinylestradiol 50 microgram tablets | 21 tablet [P] £200.00

- Ethinylestradiol 1 mg tablets | 28 tablet [P] £200.00

**PREGNANCY**
- Avoid; toxicity in animal studies.

**BREAST FEEDING**
- Avoid.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution; avoid in acute disease.

**RENAIL IMPAIRMENT**
- Monitoring Patients with renal impairment should be closely monitored (risk of fluid retention).

**PRESCRIBING AND DISPENSING INFORMATION**
Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogues) and as (or with) an oral contraceptive. Also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding). If transferring from cyclical HRT, start at end of regimen; if transferring from continuous-combined HRT, start at any time.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Tibolone (Non-proprietary)
  - Tibolone 2.5 mg tablets | 28 tablet [P] £10.36–11.90 DT = £7.66

- Livial (Merck Sharp & Dohme Ltd)
  - Livial 2.5 mg tablets | 28 tablet [P] £10.36 DT = £7.66

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OESTROGENS COMBINED WITH PROGESTOGENS

Conjugated oestrogens with medroxyprogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, conjugated oestrogens (equine) p. 754, medroxyprogesterone acetate p. 810.

- **INDICATIONS AND DOSE**
  - **PREMIQUE® LOW DOSE TABLETS**
    - Menopausal symptoms in women with a uterus
      - BY MOUTH
      - Adult: 1 tablet daily continuously

- **INTERACTIONS** → Appendix 1: hormone replacement therapy

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Modified-release tablet**
    - Premique (Pfizer Ltd)
      - Conjugated oestrogens 300 microgram, Medroxyprogesterone acetate 1.5 mg Premique Low Dose 0.3mg/1.5mg modified-release tablets | 84 tablet | £6.52 DT | £6.52

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Estradiol with dydrogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 756.

- **INDICATIONS AND DOSE**
  - **FEMOSTON® 1 MG/10 MG**
    - Menopausal symptoms in women with a uterus
      - BY MOUTH
      - Adult: 1 tablet daily for 14 days, white tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, grey tablet to be taken, subsequent courses repeated without interval, Femoston® 1 mg/10 mg given initially and Femoston® 2 mg/10 mg substituted if symptoms not controlled

    - Osteoporosis prophylaxis in women with a uterus
      - BY MOUTH
      - Adult: 1 tablet daily for 14 days, white tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, grey tablet to be taken, subsequent courses repeated without interval

  - **FEMOSTON® 2 MG/10 MG**
    - Menopausal symptoms in women with a uterus
      - BY MOUTH
      - Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval, Femoston® 1 mg/10 mg given initially and Femoston® 2 mg/10 mg substituted if symptoms not controlled

    - Osteoporosis prophylaxis in women with a uterus
      - BY MOUTH
      - Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then

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1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval

- **FEMOSTON® CONTI 0.5 MG/2.5 MG**
  - Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
    - BY MOUTH
    - Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase

  - Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
    - BY MOUTH
    - Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase


- **CAUTIONS** Conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, asthma, or cardiac dysfunction. Diabetes (progestogens can decrease glucose tolerance). History of depression - in those susceptible to thromboembolism (particular caution with high dose).

- **INTERACTIONS** → Appendix 1: hormone replacement therapy

- **SIDE-EFFECTS**


  - Rare or very rare Angioedema. Myocardial infarction.


  - Hepatic impairment Avoid.

  - Renal impairment Use with caution.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - Femoston 1/10 (Mylan) Femoston 1/10mg tablets | 84 tablet | £16.16
    - Femoston 2/10 (Mylan) Femoston 2/10mg tablets | 84 tablet | £16.16
    - Femoston-conti (Mylan) Estradiol 500 microgram, Dydrogesterone 2.5 mg Femoston-conti 0.5mg/2.5mg tablets | 84 tablet | £24.43 DT | £24.43
    - Estradiol 1 mg, Dydrogesterone 5 mg Femoston-conti 1mg/5mg tablets | 84 tablet | £24.43 DT | £24.43
Estradiol with levonorgestrel

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 756, levonorgestrel p. 906.

**INDICATIONS AND DOSE**

**FEMSEVEN CONTI®**

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch once weekly continuously

**FEMSEVEN SEQUI®**

Menopausal symptoms in women with a uterus
- **BY TRANSDERMAL APPLICATION**
  - Adult: Apply 1 patch once weekly for 2 weeks, phase 1 patches to be applied, then apply 1 patch once weekly for 2 weeks, phase 2 patches to be applied, subsequent courses are repeated without interval

**INTERACTIONS** → Appendix 1: hormone replacement therapy

**PATIENT AND CARER ADVICE** Patient counselling is advised for estradiol with levonorgestrel patches (application).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Transdermal patch**
- **FemSeven Conti®** (Theramex HQ UK Ltd)
  - Estradiol 50 microgram per 24 hour, Levonorgestrel 7 microgram per 24 hour, FemSeven Conti patches | 4 patch [POD] £15.48 | 12 patch [POD] £44.12 DT = £44.12
- **FemSeven Sequi®** (Theramex HQ UK Ltd)
  - Estradiol 50 microgram per 24 hour, Levonorgestrel 7 microgram per 24 hour, FemSeven Sequi patches | 4 patch [POD] £13.18 | 12 patch [POD] £37.54

Estradiol with medroxyprogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 756, medroxyprogesterone acetate p. 810.

**INDICATIONS AND DOSE**

**INDIVINA® TABLETS**

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 3 years previously
- Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 3 years previously
- **BY MOUTH**
  - Adult: Initially 1/2.5 mg daily taken continuously, adjust according to response, to be started at end of scheduled bleed if changing from cyclical HRT

**TRIDESTRA®**

Menopausal symptoms in women with a uterus
- Osteoporosis prophylaxis in women with a uterus
  - **BY MOUTH**
    - Adult: 1 tablet daily for 16 days, white tablet to be taken, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 12 days, white tablet to be taken, subsequent courses are repeated without interval

**INTERACTIONS** → Appendix 1: hormone replacement therapy

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Indivina®** (Orion Pharma (UK) Ltd)
  - Estradiol valerate 1 mg, Medroxyprogesterone acetate 2.5 mg | 84 tablet [POD] £20.58 DT = £20.58
  - Estradiol valerate 2 mg, Medroxyprogesterone acetate 5 mg | 84 tablet [POD] £20.58 DT = £20.58
  - Estradiol valerate 1 mg, Medroxyprogesterone acetate 5 mg | 84 tablet [POD] £20.58 DT = £20.58
- **Tridestra®** (Orion Pharma (UK) Ltd)
  - Tridestra tablets | 91 tablet [POD] £20.49

Estradiol with norethisterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 756, norethisterone p. 764.
1 tablet daily for 12 days; grey tablet to be taken, subsequent courses are repeated without interval

**ELLESTE-DUET® CONTI**

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously

Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- BY MOUTH
  - Adult: 1 tablet daily continuous basis, if changing from cyclical HRT begin treatment at the end of scheduled bleed

**EVOREL® CONTI**

Menopausal symptoms in women with a uterus

Osteoporosis prophylaxis in women with a uterus

- BY TRANSDERMAL APPLICATION
  - Adult: Apply 1 patch twice weekly continuously

**EVOREL® SEQUI**

Menopausal symptoms in women with a uterus

Osteoporosis prophylaxis in women with a uterus

- BY TRANSDERMAL APPLICATION
  - Adult: Apply 1 patch twice weekly for 2 weeks, Evorel® 50 patch to be applied and started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), then apply 1 patch twice weekly, Evorel® Conti patch to be applied, subsequent courses are repeated without interval

**KLIOVANCE®**

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously

Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

- BY MOUTH
  - Adult: 1 tablet daily continuously, to be started at end of scheduled bleed if changing from cyclical HRT

**NOVOFEM®**

Menopausal symptoms in women with a uterus

Osteoporosis prophylaxis in women with a uterus

- BY MOUTH
  - Adult: 1 tablet daily for 16 days, red tablets to be taken, then 1 tablet daily for 12 days, white tablets to be taken, subsequent courses are repeated without interval; start treatment with red tablet at any time or if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase

**TRISEQUENS®**

Menopausal symptoms in women with a uterus

Osteoporosis prophylaxis in women with a uterus

- BY MOUTH
  - Adult: 1 tablet daily for 12 days, blue tablets to be taken, followed by 1 tablet daily for 10 days, white tablet to be taken, then 1 tablet daily for 6 days, red tablet to be taken, subsequent courses are repeated without interval

**INTERACTIONS**

- Appendix 1: hormone replacement therapy

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**EVOREL® SEQUI**

Patients and carers should be advised on the application of Evorel® Sequi patches.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Clinorette (ReSource Medical UK Ltd)
    - Clinorette tablets | 84 tablet (£23)
  - Elleste Duet (Meda Pharmaceuticals Ltd)
    - Elleste Duet 1mg tablets | 84 tablet (£20)
    - Elleste Duet 2mg tablets | 84 tablet (£20)
  - Norethisterone acetate 1mg, Estradiol 2mg tablets | 84 tablet (£20 DT = £17.02
  - Kliovance (Novo Nordisk Ltd)
    - Norethisterone acetate 1mg, Estradiol 2mg Kliovance tablets | 84 tablet (£20 DT = £17.02
  - Novofem (Novo Nordisk Ltd)
    - Novofem tablets | 84 tablet (£20 DT = £17.02
  - Trisequens (Novo Nordisk Ltd)
    - Trisequens tablets | 84 tablet (£20 DT = £17.02

**Transdermal patch**

- Evorel Conti (Janssen-Cilag Ltd)
  - Estradiol 50 microgram per 24 hour, Norethisterone acetate 170 microgram per 24 hour Evorel Conti patches | 8 patch (£37.22 DT = £37.22
- Evorel Sequi (Janssen-Cilag Ltd)
  - Evorel Sequi patches | 8 patch (£20 DT = £11.09

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**Estradiol with norgestrel**

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 756.

**INDICATIONS AND DOSE**

**CYCLO-PROGYNOLA® 2MG TABLETS**

Menopausal symptoms in women with a uterus

Osteoporosis prophylaxis in women with a uterus

- BY MOUTH
  - Adult: 1 tablet daily for 11 days, white tablet to be taken; start on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily for 10 days, brown tablet to be taken, followed by a 7-day tablet free interval

**INTERACTIONS**

- Appendix 1: hormone replacement therapy

**SIDE-EFFECTS**

- Common or very common Gastrointestinal discomfort - haemorrhage - headaches - menstrual cycle irregularities - nausea - skin reactions - weight changes
- Uncommon Breast abnormalities - depressed mood - dizziness - erythema nodosum - oedema - palpitations - visual impairment
- Rare or very rare Anxiety - contact lens intolerance - fatigue - hirsutism - muscle cramps - sexual dysfunction - vaginal discharge - vomiting
- Frequency not known Angioedema - dementia - gallbladder disorder - myocardial infarction - neoplasms - stroke - venous thromboembolism

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Form unstated

- Cyclo-Progynola (Meda Pharmaceuticals Ltd)
  - Cyclo-Progynola 2mg tablets | 2 tablet (£30)

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**PROGESTOGENS**

### Norethisterone

#### Indications and dose

**Endometriosis**
- **By mouth**
  - Adult: 10–15 mg daily for 4–6 months or longer, to be started on day 5 of cycle; increased to 20–25 mg daily if required, dose only increased if spotting occurs and reduced once bleeding has stopped

**Dysfunctional uterine bleeding (to arrest bleeding)**
- **By mouth**
  - Adult: 5 mg 3 times a day for 10 days

**Dysfunctional uterine bleeding (to prevent bleeding)**
- **By mouth**
  - Adult: 5 mg twice daily, to be taken from day 19 to day 26 of cycle

**Dysmenorrhoea**
- **By mouth**
  - Adult: 5 mg 3 times a day for 3–4 cycles, to be taken from day 5–24 of cycle

**Premenstrual syndrome (but not recommended)**
- **By mouth**
  - Adult: 5 mg 2–3 times a day for several cycles, to be taken from day 19–26 of cycle

**Postponement of menstruation**
- **By mouth**
  - Females of childbearing potential: 5 mg 3 times a day, to be started 3 days before expected onset (menstruation occurs 2–3 days after stopping)

**Breast cancer**
- **By mouth**
  - Adult: 40 mg daily, increased if necessary to 60 mg daily

**Short-term contraception**
- **By deep intramuscular injection**
  - Females of childbearing potential: 200 mg, to be administered within first 5 days of cycle or immediately after parturition (duration 8 weeks). To be injected into the gluteal muscle, then 200 mg after 8 weeks if required

**Contraception**
- **By mouth**
  - Females of childbearing potential: 350 micrograms daily, dose to be taken at same time each day, starting on day 1 of cycle then continuously, if administration delayed for 3 hours or more it should be regarded as a 'missed pill'

#### Contraindications

**General Contraindications**
- Avoid in patients with a history of liver tumours - breast cancer (unless progestogens are being used in the management of this condition) - genital cancer (unless progestogens are being used in the management of this condition) - history during pregnancy of idiopathic jaundice - history during pregnancy of pemphigoid gestationis (non-contraceptive indications) - history during pregnancy of severe pruritus (non-contraceptive indications) - when used as a contraceptive, history of breast cancer (can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable)

**Specific Contraindications**
- With oral use Acute porphyrias p. 1058 - severe arterial disease - undiagnosed vaginal bleeding

#### Cautions

**General Cautions**
- Asthma - cardiac dysfunction - conditions that may worsen with fluid retention - diabetes (progestogens can decrease glucose tolerance - monitor patient closely) - epilepsy - history of depression - hypertension - migraines - susceptibility to thromboembolism (particular caution with high dose)

**Specific Cautions**
- When used for contraception active throphoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration) - seek specialist advice - arterial disease - functional ovarian cysts - history of jaundice in pregnancy - malabsorption syndromes - past ectopic pregnancy - sex-steroid dependent cancer - systemic lupus erythematosus with positive (or unknown) anti-phospholipid antibodies

- With intramuscular use for contraception disturbances of lipid metabolism - history during pregnancy of deterioration of osteosclerosis - history during pregnancy of pruritus - possible risk of breast cancer

#### Interactions

- Use as a contraceptive in comorbidities The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.

- Breast cancer risk with contraceptive use There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

#### Side-effects

**General Side-effects**
- Common or very common Menstrual cycle irregularities
- Uncommon Breast tenderness
- Frequency not known Hepatic cancer - thromboembolism

**Specific Side-effects**
- Common or very common
  - With intramuscular use Dizziness - haemorrhage - headache - hypersensitivity - nausea - skin reactions - weight increased

- Uncommon
  - With intramuscular use Abdominal distension - depressed mood

- Frequency not known
  - With oral use Appetite change - depression - fatigue - gastrointestinal disorder - headaches - hypertension - libido disorder - nervousness - rash - weight change

#### Pregnancy

- With oral use Masculinisation of female fetuses and other defects reported with non-contraceptive use.

**Breast Feeding**
- Progestogen-only contraceptives do not affect lactation. Higher doses (used in malignant conditions) may suppress lactation and alter milk composition—use lowest effective dose.

- With intramuscular use Withhold breast-feeding for neonates with severe or persistent jaundice requiring medical treatment.

#### Hepatic Impairment

- When used as a contraceptive; caution in severe liver disease and recurrent cholestatic jaundice, avoid in liver tumour. Avoid in non-contraceptive indications.

#### Renal Impairment

- Use with caution in non-contraceptive indications.
PATIENT AND CARER ADVICE
Diarrhoea and vomiting with oral contraceptives. Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

Starting routine for oral contraceptives. One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if norethisterone is started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special order manufacturers include: oral suspension

Solution for injection
- Noristerat (Bayer Plc) Norethisterone enantate 200 mg per 1 ml Noristerat 200mg/1ml solution for injection ampoules | 1 ampoule | £4.05
- Norethisterone (Non-proprietary) Norethisterone 5 mg Norethisterone 5mg tablets | 30 tablet | £2.40 DT = £2.35
- Noriday (Pfizer Ltd) Norethisterone 350 microgram Noriday 350microgram tablets | 84 tablet | £2.10 DT = £2.10
- Primolut N (Bayer Plc) Norethisterone 5 mg Primolut N 5mg tablets | 30 tablet | £2.26 DT = £2.35
- Utovan (Pfizer Ltd) Norethisterone 5 mg Utovan 5mg tablets | 30 tablet | £1.40 DT = £2.35 | 90 tablet | £4.21

Combinations available: Estradiol with norethisterone, p. 762

INDICATIONS AND DOSE
CRINONE® VAGINAL GEL
Infertility due to inadequate luteal phase
- BY VAGINA
  - Adult: 1 applicatorful daily, to be started either after documented ovulation or on day 18–21 of cycle, in vitro fertilisation, daily application continued for 30 days after laboratory evidence of pregnancy

CYCLOGEST® PESSARIES
Premenstrual syndrome | Post-natal depression
- BY VAGINA, OR BY RECTUM
  - Adult: 200–800 mg daily, doses above 200 mg to be given in 2 divided doses, for premenstrual syndrome start on day 12–14 and continue until onset of menstruation (but not recommended); rectally if barrier methods of contraception are used, in patients who have recently given birth or in those who suffer from vaginal infection or recurrent cystitis

GESTONE® SOLUTION FOR INJECTION
Dysfunctional uterine bleeding
- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: 5–10 mg daily for 5–10 days until 2 days before expected onset of menstruation, to be administered into buttocks

Recurrent miscarriage due to inadequate luteal phase (but not recommended) or following in vitro fertilisation or gamete intra-fallopian transfer
- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: 25–100 mg 2–7 times a week from day 15, or day of embryo or gamete transfer, until 8–16 weeks of pregnancy, to be administered into buttocks; maximum 200 mg per day

LUBION®
Supplementation of luteal phase during assisted reproductive technology (ART) treatment in women for whom vaginal preparations are inappropriate
- BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
  - Adult: 25 mg once daily from day of oocyte retrieval up to week 12 of pregnancy

LUTIGEST®
Luteal support as part of an Assisted Reproductive Technology (ART) treatment programme
- BY VAGINA
  - Adult: 100 mg 3 times a day, to be started the day after oocyte retrieval, and continued for 30 days once pregnancy is confirmed

UTROGESTAN® CAPSULES
Progestogen opposition of oestrogen HRT
- BY MOUTH
  - Adult: 200 mg once daily on days 15–26 of each 28-day oestrogen HRT cycle, alternatively 100 mg once daily on days 1–25 of each 28-day oestrogen HRT cycle

SUPPLEMENTATION OF LUTEAL PHASE DURING ASSISTED REPRODUCTIVE TECHNOLOGY (ART) CYCLES
- BY VAGINA
  - Adult: 1 capsule 3 times a day from day of embryo transfer until at least week 7 of pregnancy up to week 12 of pregnancy

CONTRA-INDICATIONS Acute porphyrias p. 1058 - avoid in patients with a history of liver tumours - breast cancer (unless progestogens are being used in the management of this condition) - genital cancer (unless progestogens are being used in the management of this condition) - history

- **CAUTIONS**
  
  Asthma. Cardiac dysfunction. Conditions that may worsen with fluid retention. Diabetes. Progestogens can decrease glucose tolerance—monitor patient closely.

  - Epilepsy. History of depression. Hypertension. Migraine. Susceptibility to thromboembolism (particular caution with high dose)

- **SIDE-EFFECTS**
  
  - Common or very common
  
  With oral use: Headache. Menstrual cycle irregularities.
  

  - Uncommon
  

  - Rare or very rare
  
  With oral use: Depression. Nausea.

  - Frequency not known
  

  With rectal use: Diarrhoea. Flatulence.


- **PREGNANCY**
  
  Not known to be harmful.

- **BREAST FEEDING**
  
  Avoid—present in milk.

- **HEPATIC IMPAIRMENT**
  
  Avoid in hepatic impairment. Avoid in active liver disease including disorders of hepatic excretion (e.g., Dublin-Johnson or Rotor Syndromes), infective hepatitis (until liver function returns to normal) and liver tumours.

- **RENAL IMPAIRMENT**
  
  Use with caution.

- **DIRECTIONS FOR ADMINISTRATION**
  
  With oral use: Capsules should be taken at bedtime on an empty stomach.

- **PATIENT AND CARER ADVICE**
  
  With oral use: Patient counselling is advised for progesterone capsules (administration).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **LUTIGEST®**

  **Scottish Medicines Consortium (SMC) decisions**

  The Scottish Medicines Consortium has advised (October 2016) that progesterone (Lutigest®) is accepted for use within NHS Scotland for luteal support as part of an assisted reproductive technology (ART) treatment program for infertile women. This advice is contingent upon the continuing availability of the Patient Access Scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.

  **LUBION®**

  **Scottish Medicines Consortium (SMC) decisions**

  SMC No. SMC2017

  The Scottish Medicines Consortium has advised (July 2018) that progesterone (Lubion®) is accepted for use within NHS Scotland for luteal support as part of an Assisted Reproductive Technology (ART) treatment program in infertile women who are unable to use or tolerate vaginal preparations.
Male sex hormone responsive conditions

8.2 Male sex hormone responsive conditions

**Androgens, anti-androgens and anabolic steroids**

**Androgens**

Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids.

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used.

**Anti-androgens**

**Cyproterone acetate**

Cyproterone acetate p. 770 is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertility (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermatogram. As hepatic tumours have been produced in animal studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also licensed for use alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy and has been used as an adjunct in prostatic cancer and in the treatment of acne and hirsutism in women.

**Dutasteride and finasteride**

Dutasteride p. 787 and finasteride p. 787 are alternatives to alpha-blockers particularly in men with a significantly enlarged prostate. Finasteride is also licensed for use with doxazosin p. 783 in the management of benign prostatic hyperplasia.

A low strength of finasteride is licensed for treating male-pattern baldness in men.

**Anabolic steroids**

Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They are used in the treatment of some aplastic anaemias. Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is unjustified; some athletes abuse them.

**Androgens**

**CONTRA-INDICATIONS**

- Breast cancer in males
- History of liver tumours
- Hypercalcaemia
- Prostate cancer

**CAUTIONS**

- Cardiac impairment
- Diabetes mellitus
- Elderly
- Epilepsy
- Hypertension
- Ischaemic heart disease
- Migraine
- Pre-pubertal boys (fusion of epiphyses is hastened and may result in short stature)—statural growth and sexual development should be monitored—skeletal metastases—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)—sleep apnoea—step treatment or reduce dose if severe polycythaemia occurs—tumours—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)

**8.2 Male sex hormone responsive conditions**

**Androgens, anti-androgens and anabolic steroids**

**Androgens**

Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids.

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used.

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Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They are used in the treatment of some aplastic anaemias. Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is unjustified; some athletes abuse them.

**ANDROGENS**

**Androgens**

**CONTRA-INDICATIONS**

- Breast cancer in males
- History of liver tumours
- Hypercalcaemia
- Prostate cancer

**CAUTIONS**

- Cardiac impairment
- Diabetes mellitus
- Elderly
- Epilepsy
- Hypertension
- Ischaemic heart disease
- Migraine
- Pre-pubertal boys (fusion of epiphyses is hastened and may result in short stature)—statural growth and sexual development should be monitored—skeletal metastases—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)—sleep apnoea—step treatment or reduce dose if severe polycythaemia occurs—tumours—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)
SIDE-EFFECTS
- Common or very common: Headache, hot flush, hypertension, polycythaemia, prostate abnormalities, skin reactions, weight increased
- Uncommon: Alopecia, asthenia, behaviour abnormal, depression, dizziness, dyspnoea, dysuria, gynaecomastia, hyperhidrosis, insomnia, nausea, sexual dysfunction
- Rare or very rare: Pulmonary oedema, microembolism, sperm abnormalities
- Frequency not known: Anxiety, epiphyses premature fusion, fluid retention, jaundice, oedema, paraesthesia, precocious puberty, prostate cancer, seborrhoea, sleep apnoea, urinary tract obstruction

SIDE-EFFECTS, FURTHER INFORMATION
Stop treatment or reduce dose if severe polycythaemia occurs.

PREGNANCY
Avoid—causes masculinisation of female fetus.

BREAST FEEDING
Avoid.

HEPATIC IMPAIRMENT
Avoid if possible—fluid retention and dose-related toxicity.

RENAL IMPAIRMENT
Caution—potential for fluid retention.

MONITORING REQUIREMENTS
- Monitor haematocrit and haemoglobulin before treatment, every three months for the first year, and yearly thereafter.
- Monitor prostate and PSA in men over 45 years.

PATIENT AND CARER ADVICE
Androgenic effects in women: Women should be advised to report any signs of virilisation e.g. deepening of the voice or hirsutism.

Testosterone

INDICATIONS AND DOSE
TESTAVAN®

Hypogonadism due to androgen deficiency in men
- BY TRANSDERMAL APPLICATION
  - Adult: Apply 23 mg once daily; increased in steps of 23 mg, adjusted according to response; maximum 69 mg per day

DOSE EQUIVALENCE AND CONVERSION
- For Testavan®: One pump actuation delivers 1.15 g of gel containing 23 mg of testosterone.

TESTIM®

Hypogonadism due to testosterone deficiency in men
- BY TRANSDERMAL APPLICATION
  - Adult: Apply 50 mg once daily, subsequent application adjusted according to response; maximum 100 mg per day

DOSE EQUIVALENCE AND CONVERSION
- For Testim®: One tube of 5 g contains 50 mg testosterone.

TESTOGEL® 50MG/5G

Hypogonadism due to androgen deficiency in men
- BY TRANSDERMAL APPLICATION
  - Adult: Apply 50 mg once daily; increased in steps of 25 mg, adjusted according to response; maximum 100 mg per day

DOSE EQUIVALENCE AND CONVERSION
- For Testogel® 50mg/5g: One sachet of 5 g contains 50 mg of testosterone.

TOSTRAN®

Hypogonadism due to testosterone deficiency in men
- BY TRANSDERMAL APPLICATION
  - Adult: Apply 60 mg once daily, subsequent application adjusted according to response; maximum 80 mg per day

DOSE EQUIVALENCE AND CONVERSION
- For Tostran®: 1 g of gel contains 20 mg testosterone.

CAUTIONS
- Thrombophilia—increased risk of thrombosis

SIDE-EFFECTS
- Common or very common: Hypertriglyceridaemia
- Uncommon: Flushing
- Frequency not known: Anaemia, deep vein thrombosis, electrolyte imbalance, emotional lability, hair changes, malaise, muscle cramps, musculoskeletal pain, testicular disorder.

DIRECTIONS FOR ADMINISTRATION
Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature.

TOSTRAN®: Apply gel on clean, dry, intact skin of abdomen or both inner thighs, preferably in the morning. Gently rub in with a finger until dry before dressing. Wash hands with soap and water after applying gel; avoid washing application site for at least 2 hours. Not to be applied on genital area.

TESTOGEL® 50MG/5G: Apply thin layer of gel on clean, dry, healthy skin such as shoulders, arms or abdomen, immediately after sachet is opened. Not to be applied on genital area as high alcohol content may cause local irritation. Allow to dry for 3–5 minutes before dressing. Wash hands with soap and water after applying gel; avoid shower or bath for at least 6 hours.

TESTIM®: Squeeze entire content of tube on to one palm and apply as a thin layer on clean, dry, healthy skin of shoulder or upper arm, preferably in the morning after washing or bathing (if 2 tubes required use 1 per shoulder or upper arm); rub in and allow to dry before putting on clothing to cover site; wash hands with soap after application; avoid washing application site for at least 6 hours.

TESTOGEL® 16.2MG/G: Apply thin layer of gel on clean, dry, healthy skin over right and left upper arms and shoulders. Not to be applied on genital area as high alcohol content may cause local irritation. Allow to dry for 3–5 minutes before dressing. Wash hands with soap and water after applying gel, and cover the site with clothing once gel dried; avoid shower or bath for at least 2 hours.

TESTAVAN®: Manufacturer advises apply one pump actuation of gel evenly onto clean, dry, intact skin over upper arm and shoulder using the applicator, without getting any gel on the hands—repeat on opposite upper arm and shoulder if two pump actuations are required, and repeat again on initial upper arm and shoulder if three pump actuations are required. Allow to dry completely before dressing and cover application site with clothing. Wash hands with soap and water immediately if gel was touched during application; avoid shower or bath for at least 2 hours.
Testosterone propionate

**INDICATIONS AND DOSE**

- **Androgen deficiency**
  - **By intramuscular injection**
  - Adult: 50 mg 2–3 times a week
  - **Delayed puberty in males**
  - **By intramuscular injection**
  - Adult: 50 mg once weekly
  - **Breast cancer in women**
  - **By intramuscular injection**
  - Adult: 100 mg 2–3 times a week

**SIDE-EFFECTS**

- Increased risk of thrombosis

**MEDICINAL FORMS**

- Forms available from special-order manufacturers include: solution for injection

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Testosterone undecanoate

**INDICATIONS AND DOSE**

- **Androgen deficiency**
  - Adult: 120–160 mg daily for 2–3 weeks; maintenance 40–120 mg daily
  - **Hypogonadism**
    - **By deep intramuscular injection**
    - Adult (male): 1 g every 10–14 weeks, to be given over 2 minutes, if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks.

**SIDE-EFFECTS**

- Increased risk of thrombosis

**MEDICINAL FORMS**

- Not licensed for use in breast cancer.
- **Thrombophilia** — increased risk of thrombosis

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Testosterone enantate

**INDICATIONS AND DOSE**

- **Hypogonadism**
  - **By slow intramuscular injection**
  - Adult: Initially 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks
  - **Breast cancer**
  - **By slow intramuscular injection**
  - Adult: 250 mg every 2–3 weeks

**SIDE-EFFECTS**

- Increased risk of thrombosis

**Caution**

- **With intramuscular use**
  - Hair growth increased
  - **With oral use**
  - Fluid imbalance, gastrointestinal discomfort, hepatic function abnormal, lipid metabolism change, myalgia

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Testosterone decanoate, isocaproate, phenylpropionate and propionate

The properties listed below are those particular to the combination only. For the properties of the components please consider, testosterone propionate below.

**INDICATIONS AND DOSE**

- **Androgen deficiency**
  - **By deep intramuscular injection**
  - Adult: 1 mL every 3 weeks, adjusted according to response

**DOSE EQUIVALENCE AND CONVERSION**

- Each 1 mL dose of Sustanon 250 solution for injection contains 100 mg testosterone decanoate, 60 mg testosterone isocaproate, 60 mg testosterone phenylpropionate and 30 mg testosterone propionate.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Excipients:** May contain Butylated hydroxytoluene, propylene glycol
  - Testovan (Ferring Pharmaceuticals Ltd)
  - Testim (Ferring Pharmaceuticals Ltd)
  - Testogel (Besins Healthcare (UK) Ltd)
  - Testogen 50 mg Testim 50 mg/g gel | 30 tube POM £32.00 DT = £32.00 (C4-2)
  - Testogen 16.2 mg per 1 gram Testogel 16.2 mg/g gel | 88 gram POM £31.11 DT + £31.11 (C4-2)
  - Tostran (Kyowa Kirin Ltd)
  - Testosterone 20 mg per 1 gram Tostran 2% gel | 60 gram POM £28.63 DT = £28.67 (C4-2)

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Testosterone propionate

**INDICATIONS AND DOSE**

- **Androgen deficiency**
  - **By intramuscular injection**
  - Adult: 50 mg 2–3 times a week

**SIDE-EFFECTS**

- Bone formation increased, circulatory system disorder, gastrointestinal disorder, gastrointestinal haemorrhage, hepatomegaly, hypercalcaemia, neoplasms

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Testosterone enantate (Non-proprietary)**
  - Testosterone enantate 250 mg per 1 ml Testosterone enantate 250 mg/1 ml solution for injection ampoules | 3 ampoule POM £83.74–£87.73 DT + £85.74 (C4-2)

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Testosterone undecanoate

**INDICATIONS AND DOSE**

- **Androgen deficiency**
  - Adult: 120–160 mg daily for 2–3 weeks; maintenance 40–120 mg daily

**SIDE-EFFECTS**

- Increased risk of thrombosis

**Caution**

- **With intramuscular use**
  - Hair growth increased
  - **With oral use**
  - Fluid imbalance, gastrointestinal discomfort, hepatic function abnormal, lipid metabolism change, myalgia

www.getintopharma.com
8.2a Male sex hormone antagonism

ANTI-ANDROGENS

Cyproterone acetate

- **INDICATIONS AND DOSE**
  - Hyper-sexuality in males
  - Sexual deviation in males
    - BY MOUTH
    - Adult: 50 mg twice daily, to be taken after food
  - Prevention of tumour flare with initial gonadorelin analogue therapy
    - BY MOUTH
    - Adult (male): 200 mg daily in 2–3 divided doses for 5–7 days before initiation of gonadorelin analogue, followed by 200 mg daily in 2–3 divided doses for 3–4 weeks after initiation of gonadorelin analogue; maximum 300 mg per day.
  - Long-term palliative therapy where gonadorelin analogues or orchidectomy contra-indicated, not tolerated, or where oral therapy preferred
    - BY MOUTH
    - Adult (male): 200–300 mg daily in 2–3 divided doses.
  - Hot flushes with gonadorelin analogue therapy or after orchidectomy
    - BY MOUTH
    - Adult (male): Initially 50 mg daily, then adjusted according to response to 50–150 mg daily in 1–3 divided doses.

- **CONTRA-INDICATIONS**
  - GENERAL CONTRA-INDICATIONS
    - Meningioma or history of meningioma
  - SPECIFIC CONTRA-INDICATIONS
    - When used for when used for hypersexuality
      - Dubin–Johnson syndrome
      - history of thromboembolic disorders
      - liver disease
      - malignant diseases
      - previous or existing liver tumours
      - Rotor syndrome
      - severe depression
      - severe diabetes (with vascular changes)
      - sickle-cell anaemia
      - wasting diseases
  - **CAUTIONS**
    - Diabetes mellitus
    - in prostate cancer
    - severe depression
    - in prostate cancer
    - sickle-cell anaemia
    - ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known)
  - **SIDE-EFFECTS**
    - Common or very common
      - Depressed mood
      - dyspnoea
      - fatigue
      - gynaecomastia
      - hepatic disorders
      - hot flush
      - hyperhidrosis
      - nipple pain
      - restlessness
      - weight change
    - Uncommon
      - Skin reactions
    - Rare or very rare
      - Gallerhorrhea
      - neoplasms
    - Frequency not known
      - Adrenocortical suppression
      - anaemia
      - azoospermia
      - hair changes
      - hypotrichosis
      - osteoporosis
      - sebaceous gland underactivity (may clear acne)
      - thromboembolism

**SIDE-EFFECTS, FURTHER INFORMATION**

- Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (fatalities reported, usually after several months, at dosages of 100 mg and above). If hepatotoxicity is confirmed, cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease (in which case cyproterone should be continued only if the perceived benefit exceeds the risk).
- **HEPATIC IMPAIRMENT**
  - Avoid (unless used for prostate cancer)—dose-related toxicity.
- **MONITORING REQUIREMENTS**
  - Monitor blood counts initially and throughout treatment.
  - Monitor adrenocortical function regularly.
  - Liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of hepatotoxicity occur.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
    - Fatigue and lassitude may impair performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Nebido (Bayer Plc)
  - Testosterone undecanoate 250 mg per 1 ml
  - Nebido 1000 mg/4 ml solution for injection vials | 1 vial [48](https://www.getintopharma.com) £17.11 DT = £17.11 [48](https://www.getintopharma.com)

Capsule

CAUTIONARY AND ADVISORY LABELS

21, 25

- Restandol (Merck Sharp & Dohme Ltd)
  - Testosterone undecanoate 40 mg
  - Restandol 40 mg Testocaps | 30 capsule [48](https://www.getintopharma.com) £8.55 [48](https://www.getintopharma.com) | 60 capsule [48](https://www.getintopharma.com) £17.10 DT = £17.10 [48](https://www.getintopharma.com)

9 Thyroid disorders

PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES

Thyrotropin alfa

(Recombinant human thyroid stimulating hormone; rhTSH)

**DRUG ACTION**

- Thyrotropin alfa is a recombinant form of thyrotropin (thyroid stimulating hormone).

**INDICATIONS AND DOSE**

Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients, together with serum thyroglobulin testing (with or without radiiodine imaging) to increase radio-iodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 900 micrograms every 24 hours for 2 doses, dose to be administered into the gluteal muscle, consult product literature for further information on indications and dose

**CAUTIONS**

- Presence of thyroglobulin autoantibodies may give false negative results

www.getintopharma.com
9.1 Hyperthyroidism

Antithyroid drugs

Overview

Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management. In the UK carbimazole below is the most commonly used drug. Propylthiouracil p. 772 should be reserved for patients who are intolerant of carbimazole or for those who experience sensitivity reactions to carbimazole (sensitivity is not necessarily displayed to both drugs), and for whom other treatments are inappropriate. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

Over-treatment with antithyroid drugs can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.

A combination of carbimazole with levothyroxine sodium p. 773 daily, may be used in a blocking-replacement regimen; therapy is usually given for 18 months. The blocking-replacement regimen is not suitable during pregnancy.

Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (¹³¹I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.

Propranolol hydrochloride p. 150 is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism. Propranolol hydrochloride has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propranolol hydrochloride but nadolol p. 149 is also used.

Thyrotoxic crisis (‘thyroid storm’) requires emergency treatment with intravenous administration of fluids, propranolol hydrochloride and hydrocortisone p. 676 (as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

Antithyroid drugs in pregnancy

Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen is not suitable. Carbimazole is associated with congenital defects, including aplasia cutis of the neonate, therefore propylthiouracil remains the drug of choice during the first trimester of pregnancy. In the second trimester, consider switching to carbimazole because of the potential risk of hepatotoxicity with propylthiouracil. Both propylthiouracil and carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy). See also Important safety information in the carbimazole below drug monograph.

Advanced Pharmacy Services

Patients with thyroid disorders may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Other drugs used for Hyperthyroidism Metoprolol tartrate, p. 154

ANTITHYROID DRUGS > SULFUR-CONTAINING IMIDAZOLES

Carbimazole

INDICATIONS AND DOSE

Hyperthyroidism

> BY MOUTH

Adult: 15–40 mg daily continue until the patient becomes euthyroid, usually after 4 to 8 weeks, higher doses should be prescribed under specialist supervision only, then reduced to 5–15 mg daily, reduce dose gradually, therapy usually given for 12 to 18 months

Hyperthyroidism (blocking-replacement regimen) in combination with levothyroxine

> BY MOUTH

Adult: 40–60 mg daily, therapy usually given for 18 months

DOSE EQUIVALENCES AND CONVERSION

When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

IMPORTANT SAFETY INFORMATION

NEUTROPENIA AND AGRANULOCYTOSIS

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

> Patient should be advised to report symptoms and signs suggestive of infection, especially sore throat.

A white cell count should be performed if there is any clinical evidence of infection.

Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.
Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Women of childbearing potential should use effective contraception during treatment with carbimazole. It should only be considered in pregnancy after a thorough benefit-risk assessment, and at the lowest effective dose without additional administration of thyroid hormones—close maternal, fetal, and neonatal monitoring is recommended.

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

Carbimazole should not be used in patients with a history of acute pancreatitis associated with previous treatment—re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.

MHRA/CHM ADVICE: CARBIMAZOLE: RISK OF ACUTE PANCREATITIS (FEBRUARY 2019)

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

MHRA/CHM ADVICE: CARBIMAZOLE: INCREASED RISK OF CONGENITAL MALFORMATIONS; STRENGTHENED ADVICE ON CONTRACEPTION (FEBRUARY 2019)

Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Propylthiouracil can be given but the dose may need adjusting according to response. The dose may require adjustment in cases requiring liver transplant—discontinue if significant liver-enzyme abnormalities develop.

Propylthiouracil crosses the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

Breast feeding

Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used.

CONTRA-INDICATIONS

Severe blood disorders

SIDE-EFFECTS

Rare or very rare Bone marrow disorders · haemolytic anaemia · severe cutaneous adverse reactions (SCARs) · thrombocytopenia

Frequency not known Agranulocytosis · aplasia · angiodema · dyspepsia · eosinophilia · fever · gastrointestinal disorder · generalised lymphadenopathy · haemorrhage · headache · hepatic disorders · insulin autoimmune syndrome · leucopenia · malaise · myopathy · nausea · nerve disorders · neutropenia · pancreatitis acute (discontinue permanently) · salivary gland enlargement · skin reactions · taste loss

CONCEPTION AND CONTRACEPTION

The MHRA advises that females of childbearing potential should use effective contraception during treatment.

PREGNANCY

The MHRA advises consider use only after a thorough benefit-risk assessment. See Important Safety Information and Antithyroid drugs p. 771 for further information.

BREAST FEEDING

Present in breast milk and this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used.

BREAST FEEDING

Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk probably too small to affect infant; high doses may affect neonatal thyroid function.

MHRA/CHM ADVICE: CARBIMAZOLE: INCREASED RISK OF CONGENITAL MALFORMATIONS; STRENGTHENED ADVICE ON CONTRACEPTION (FEBRUARY 2019)

Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Women of childbearing potential should use effective contraception during treatment with carbimazole. It should only be considered in pregnancy after a thorough benefit-risk assessment, and at the lowest effective dose without additional administration of thyroid hormones—close maternal, fetal, and neonatal monitoring is recommended.

MHRA/CHM ADVICE: CARBIMAZOLE: RISK OF ACUTE PANCREATITIS (FEBRUARY 2019)

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

Carbimazole should not be used in patients with a history of acute pancreatitis associated with previous treatment—re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.

MHRA/CHM ADVICE: CARBIMAZOLE: INCREASED RISK OF CONGENITAL MALFORMATIONS; STRENGTHENED ADVICE ON CONTRACEPTION (FEBRUARY 2019)

Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Women of childbearing potential should use effective contraception during treatment with carbimazole. It should only be considered in pregnancy after a thorough benefit-risk assessment, and at the lowest effective dose without additional administration of thyroid hormones—close maternal, fetal, and neonatal monitoring is recommended.

MHRA/CHM ADVICE: CARBIMAZOLE: RISK OF ACUTE PANCREATITIS (FEBRUARY 2019)

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

Carbimazole should not be used in patients with a history of acute pancreatitis associated with previous treatment—re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.

MHRA/CHM ADVICE: CARBIMAZOLE: INCREASED RISK OF CONGENITAL MALFORMATIONS; STRENGTHENED ADVICE ON CONTRACEPTION (FEBRUARY 2019)

Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Women of childbearing potential should use effective contraception during treatment with carbimazole. It should only be considered in pregnancy after a thorough benefit-risk assessment, and at the lowest effective dose without additional administration of thyroid hormones—close maternal, fetal, and neonatal monitoring is recommended.

MHRA/CHM ADVICE: CARBIMAZOLE: RISK OF ACUTE PANCREATITIS (FEBRUARY 2019)

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

Carbimazole should not be used in patients with a history of acute pancreatitis associated with previous treatment—re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.

MHRA/CHM ADVICE: CARBIMAZOLE: INCREASED RISK OF CONGENITAL MALFORMATIONS; STRENGTHENED ADVICE ON CONTRACEPTION (FEBRUARY 2019)

Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, especially in the first trimester and at high doses (daily dose of 15 mg or more).

Women of childbearing potential should use effective contraception during treatment with carbimazole. It should only be considered in pregnancy after a thorough benefit-risk assessment, and at the lowest effective dose without additional administration of thyroid hormones—close maternal, fetal, and neonatal monitoring is recommended.

MHRA/CHM ADVICE: CARBIMAZOLE: RISK OF ACUTE PANCREATITIS (FEBRUARY 2019)

Cases of acute pancreatitis have been reported during treatment with carbimazole. It should be stopped immediately and permanently if acute pancreatitis occurs.

Carbimazole should not be used in patients with a history of acute pancreatitis associated with previous treatment—re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.
VITAMINS AND TRACE ELEMENTS

Iodide with iodine
(Lugol’s Solution; Aqueous Iodine Oral Solution)

- **INDICATIONS AND DOSE**
  - **Thyrotoxicosis (pre-operative)**
    - BY MOUTH USING ORAL SOLUTION
    - Adult: 0.1–0.3 mL 3 times a day
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Doses based on the use of an aqueous oral solution containing iodine 50 mg/mL and potassium iodide 100 mg/mL.

- **CAUTIONS** Not for long-term treatment
- **SIDE-EFFECTS** Conjunctivitis • depression (long term use) • erectile dysfunction (long term use) • excessive tearing • headache • hypersensitivity • increased risk of infection • influenza like illness • insomnia (long term use) • rash • salivary gland pain
- **PREGNANCY** Neonatal goitre and hypothyroidism.
- **BREAST FEEDING** Stop breast-feeding. Danger of neonatal hypothyroidism or goitre. Appears to be concentrated in milk.
- **DIRECTIONS FOR ADMINISTRATION** For oral solution, dilute well with milk or water.
- **MEDICINAL FORMS** Forms available from special-order manufacturers include: oral solution

9.2 Hypothyroidism

**Thyroid hormones**

**Overview**
Thyroid hormones are used in hypothyroidism (myxoedema), and also in diffuse non-toxic goitre, Hashimoto’s thyroiditis (lymphadenoid goitre), and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development. Levothyroxine sodium below (thyroxine sodium) is the treatment of choice for maintenance therapy.

In infants and children with congenital hypothyroidism and juvenile myxoedema, the dose of levothyroxine sodium should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone.

Liothyronine sodium p. 774 has a similar action to levothyroxine sodium but is more rapidly metabolised and has a more rapid effect. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in severe hypothyroid states when a rapid response is desired.

Liothyronine sodium by intravenous injection is the treatment of choice in hypothyroid coma. Adjunctive therapy includes intravenous fluids, hydrocortisone p. 676, and treatment of infection; assisted ventilation is often required.

**Advanced Pharmacy Services**
Patients with thyroid disorders may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

**THYROID HORMONES**

Levothyroxine sodium
(Thyroxine sodium)

- **INDICATIONS AND DOSE**
  - **Hypothyroidism**
    - BY MOUTH
      - Adult 18–49 years: Initially 50–100 micrograms once daily; adjusted in steps of 25–50 micrograms every 3–4 weeks, adjusted according to response; maintenance 100–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication
      - Adult 50 years and over: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication
  - **Hyperthyroidism (blocking-replacement regimen) in combination with carbimazole**
    - BY MOUTH
      - Adult: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 2 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication

**CONTRA-INDICATIONS** Thyrotoxicosis

**CAUTIONS** Cardiovascular disorders • diabetes insipidus • diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased) • elderly • hypertension • long-standing hypothyroidism • myocardial infarction • myocardial insufficiency • panhypopituitarism (initiate corticosteroid therapy before starting levothyroxine) • predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine)

**SIDE-EFFECTS**

- **INFECTIONS**
  - **Long-term use**
    - Fever • malaise • myalgia • rash • skin reactions • weight decreased

**INTERACTIONS** → Appendix 1: thyroid hormones

**SIDE-EFFECTS**

- **Angina pectoris**
  - **Long-term use**
    - Angina

**DIABETES MELLITUS**

- **Initiation of antidiabetic medication**
  - **Long-term use**
    - Insulin may need to be increased

**PREGNANCY** Levothyroxine may cross the placenta. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus.

**Dose adjustments** Levothyroxine requirement may increase during pregnancy.
Monitoring Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of levothyroxine).

- **BREAST FEEDING** Amount too small to affect tests for neonatal hypothyroidism.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

**Tablet**
- **Levothyroxine sodium (Non-proprietary)**
  - Levothyroxine sodium anhydrous 22.5 microgram: Levothyroxine sodium 12.5-microgram tablets | 28 tablet (PPO) £1.20–£2.80 DT = £2.56
  - Levothyroxine sodium anhydrous 25 microgram: Levothyroxine sodium 25-microgram tablets | 28 tablet (PPO) £3.05 DT = £1.63 | 500 tablet (PPO) £41.61–£56.25
  - Levothyroxine sodium 25-microgram tablets lactose free | 100 tablet (PPO) £
  - Levothyroxine sodium anhydrous 50 microgram: Levothyroxine sodium 50-microgram tablets lactose free | 100 tablet (PPO) £
  - Levothyroxine sodium 50-microgram tablets | 28 tablet (PPO) £1.50 DT = £1.03 | 1000 tablet (PPO) £36.79–£55.71
  - Levothyroxine sodium anhydrous 75 microgram: Levothyroxine sodium 75-microgram tablets | 28 tablet (PPO) £2.10–£4.00 DT = £2.73
  - Levothyroxine sodium anhydrous 100 microgram: Levothyroxine sodium 100-microgram tablets lactose free | 100 tablet (PPO) £
  - Levothyroxine sodium 100-microgram tablets | 28 tablet (PPO) £1.50 DT = £1.03 | 1000 tablet (PPO) £36.79–£56.07
- **Eltroxin (Advanz Pharma)**
  - Levothyroxine sodium anhydrous 25 microgram: Eltroxin 25-microgram tablets | 28 tablet (PPO) £2.54 DT = £1.63
  - Levothyroxine sodium anhydrous 50 microgram: Eltroxin 50-microgram tablets | 28 tablet (PPO) £1.77 DT = £1.03
  - Levothyroxine sodium anhydrous 100 microgram: Eltroxin 100-microgram tablets | 28 tablet (PPO) £1.78 DT = £1.03

**Oral solution**
- **Levothyroxine sodium (Non-proprietary)**
  - Levothyroxine sodium anhydrous 5 microgram per 1 ml: Levothyroxine sodium 25micrograms/5ml oral solution sugar free | 100 ml (PPO) £118.63 DT = £94.98
  - Levothyroxine sodium anhydrous 10 microgram per 1 ml: Levothyroxine sodium 50micrograms/5ml oral solution sugar free sugar-free | 100 ml (PPO) £91.22 DT = £89.12
  - Levothyroxine sodium anhydrous 20 microgram per 1 ml: Levothyroxine sodium 100micrograms/5ml oral solution sugar free sugar-free | 100 ml (PPO) £165.00 DT = £164.98
  - Levothyroxine sodium anhydrous 25 microgram per 1 ml: Levothyroxine sodium 125micrograms/5ml oral solution sugar free sugar-free | 100 ml (PPO) £185.00

**Liothyronine sodium** (L-Tri-iodothyronine sodium)

- **INDICATIONS AND DOSE**

  **Hypothyroidism**
  - **BY MOUTH**
    - Adult: Initially 10–20 micrograms daily; increased to 60 micrograms daily in 2–3 divided doses, dose should be increased gradually, smaller initial doses given for the elderly.

  **Hypothyroid coma**
  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: 5–20 micrograms every 12 hours, increased to 5–20 micrograms every 4 hours if required, alternatively initially 50 micrograms for 1 dose, then 25 micrograms every 8 hours, reduced to 25 micrograms twice daily

**DOSE EQUIVALENCE AND CONVERSION**
- 20–25 micrograms of liothyronine sodium is equivalent to approximately 100 micrograms of levothyroxine sodium.
- Brands without a UK licence may not be bioequivalent and dose adjustment may be necessary.

- **CONTRA-INDICATIONS**
  - Thyrotoxicosis

- **CAUTIONS**
  - Cardiovascular disorders - diabetes insipidus - diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased) - elderly - hypertension - long-standing hypothyroidism - myocardial infarction - myocardial insufficiency - panhypopituitarism (initiate corticosteroid therapy before starting liothyronine) - predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting liothyronine)

**CAUTIONS, FURTHER INFORMATION**
- Cardiovascular disorders Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia.

- **INTERACTIONS** → Appendix 1: thyroid hormones

- **SIDE EFFECTS**

  **GENERAL SIDE-EFFECTS**
  - Rare or very rare
    - Alopecia - angina pectoris (more common at excessive dosage) - arrhythmia (more common at excessive dosage) - diarrhoea (more common at excessive dosage) - heat intolerance - muscle cramps - muscle weakness - palpitations (more common at excessive dosage) - tachycardia (more common at excessive dosage) - vomiting (more common at excessive dosage)

    - Frequency not known
      - Agitation - fever - flushing - headache - hyperhidrosis - insomnia (more common at excessive dosage) - oedema - restlessness (more common at excessive dosage) - skin reactions - tremor (more common at excessive dosage) - weight decreased

  **SPECIFIC SIDE-EFFECTS**
  - With intravenous use Menstruation irregular

  **SIDE-EFFECTS, FURTHER INFORMATION**

  **Initial dosage in patients with cardiovascular disorders**

  If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose.

- **PREGNANCY** Does not cross the placenta in significant amounts. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus.

**Dose adjustments**
- Levothyroxine requirement may increase during pregnancy.

**Monitoring** Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of levothyroxine).

- **BREAST FEEDING** Amount too small to affect tests for neonatal hypothyroidism.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching to a different brand Patients switched to a different brand should be monitored (particularly if pregnant or if heart disease present) as brands without a UK licence may not be bioequivalent. Pregnant women or those with heart disease should undergo an early review of thyroid status, and other patients should have thyroid function assessed if experiencing a significant change in symptoms. If liothyronine is continued long-term, thyroid function tests should be repeated 1–2 months after any change in brand.
MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, solution for injection

**Tablet**

- Liothyronine sodium (Non-proprietary)
  - Liothyronine sodium 20 microgram tablets | 28 tablet £245.29 DT = £206.71

- Cytomel (imported (United States))
  - Liothyronine sodium 5 microgram tablets | 100 tablet
  - Liothyronine sodium 25 microgram tablets | 100 tablet

**Powder for solution for injection**

- Liothyronine sodium (Non-proprietary)
  - Liothyronine sodium 20 microgram powder for solution for injection vials | 5 vial £1,567.50
Chapter 7
Genito-urinary system

1 Bladder and urinary disorders

1.1 Urinary frequency, enuresis, and incontinence

Urinary frequency, enuresis and incontinence

Urinary frequency and incontinence

Incontinence in adults which arises from detrusor instability is managed by combining drug therapy with conservative methods for managing urge incontinence such as pelvic floor exercises and bladder training; stress incontinence is generally managed by non-drug methods. Duloxetine p. 367 can be added and is licensed for the treatment of moderate to severe stress incontinence in women; it may be more effective when used as an adjunct to pelvic floor exercises.

Antimuscarinic drugs reduce symptoms of urgency and urge incontinence and increase bladder capacity. Oxybutynin hydrochloride p. 778 also has a direct relaxant effect on urinary smooth muscle. Side-effects limit the use of oxybutynin hydrochloride, but they may be reduced by starting at a lower dose. A modified-release preparation of oxybutynin hydrochloride is effective and has fewer side-effects; a transdermal patch is also available. The efficacy and side-effects of tolterodine tartrate p. 780 are comparable to those of modified-release oxybutynin hydrochloride. Flavoxate hydrochloride p. 778 has less marked side-effects but it is also less effective. Darifenacin p. 777, fesoterodine fumarate p. 777, propiverine hydrochloride p. 779, solifenacin succinate p. 779, and trospium chloride p. 781 are newer antimuscarinic drugs licensed for urinary frequency, urgency, and incontinence. The need for continuing antimuscarinic drug therapy should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

Propantheline bromide p. 86 and tricyclic antidepressants were used for urge incontinence but they are little used now because of their side-effects. The use of imipramine hydrochloride p. 376 is limited by its potential to cause cardiac side-effects.

Mirabegron p. 781, a selective beta_3 agonist, is licensed for the treatment of urinary frequency, urgency, and urge incontinence associated with overactive bladder syndrome. Purified bovine collagen implant (Contigen®, Bard) is indicated for urinary incontinence caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism). The implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.

See also Nocturnal enuresis in children below.

Nocturnal enuresis in children

23-May-2017

Description of condition

Nocturnal enuresis is the involuntary discharge of urine during sleep, which is common in young children. Children are generally expected to be dry by a developmental age of 5 years, and historically it has been common practice to consider children for treatment only when they reach 7 years; however, symptoms may still persist in a small proportion by the age of 10 years.

Treatment

Children under 5 years

For children under 5 years, treatment is usually unnecessary as the condition is likely to resolve spontaneously. Reassurance and advice can be useful for some families.

Non Drug Treatment

Initially, advice should be given on fluid intake, diet, toileting behaviour, and use of reward systems. For children who do not respond to this advice (more than 1–2 wet beds per week), an enuresis alarm should be the recommended treatment for motivated, well-supported children. Alarms in children under 7 years should be considered depending on the child’s maturity, motivation and understanding of the alarm. Alarms have a lower relapse rate than drug treatment when discontinued.

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Treatment using an alarm should be reviewed after 4 weeks and continued until a minimum of 2 weeks’ uninterrupted dry nights have been achieved. If complete dryness is not achieved after 3 months but the condition is still improving and the child remains motivated to use the alarm, it is recommended to continue the treatment. Combined treatment with desmopressin p. 867, or the use of desmopressin alone, is recommended if the initial alarm treatment is unsuccessful or it is no longer appropriate or desirable.

Drug Treatment
Treatment with oral or sublingual desmopressin is recommended for children over 5 years of age when alarm use is inappropriate or undesirable, or when rapid or short-term results are the priority (for example, to cover periods away from home). Desmopressin alone can also be used if there has been a partial response to a combination of desmopressin and an alarm following initial treatment with an alarm alone. Treatment should be assessed after 4 weeks and continued for 3 months if there are signs of response. Repeated courses of desmopressin can be used in responsive children who experience repeated recurrences of bedwetting, but should be withdrawn gradually at regular intervals (for 1 week every 3 months) for full reassessment.

Under specialist supervision, nocturnal enuresis associated with daytime symptoms (overactive bladder) can be managed with desmopressin alone or in combination with an antimuscarinic drug (such as oxybutynin hydrochloride p. 778 or tolterodine tartrate p. 780 [unlicensed indication]). Treatment should be continued for 3 months; the course can be repeated if necessary. The tricyclic antidepressant imipramine hydrochloride p. 376 can be considered for children who have not responded to all other treatments and have undergone specialist assessment, however relapse is common after withdrawal and children and their carers should be aware of the dangers of overdose. Initial treatment should continue for 3 months; further courses can be considered following a medical review every 3 months. Tricyclic antidepressants should be withdrawn gradually.

Useful Resources

ANTIMUSCARINICS

Antimuscarinics (systemic)

- **CONTRA-INDICATIONS** Gastro-intestinal obstruction · intestinal atony · myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases) · paralytic ileus · prostatic enlargement (in adults) · pyloric stenosis · severe ulcerative colitis · significant bladder outflow obstruction · toxic megacolon · urinary retention

- **CAUTIONS** Acute myocardial infarction (in adults) · arrhythmias (may be worsened) · autonomic neuropathy · cardiac insufficiency (due to association with tachycardia) · cardiac surgery (due to association with tachycardia) · children (increased risk of side-effects) · conditions characterised by tachycardia · congestive heart failure (may be worsened) · coronary artery disease (may be worsened) · diarrhoea · elderly (especially if frail) · gastrointestinal reflux disease · hiatus hernia with reflux oesophagitis · hypertension · hyperthyroidism (due to association with tachycardia) · individuals susceptible to angle-closure glaucoma · prostatic hyperplasia (in adults) · pyrexia · ulcerative colitis

- **SIDE-EFFECTS**
  - Common or very common Constipation · dizziness · drowsiness · dry mouth · dyspepsia · flushing · headache · nausea · palpitations · skin reactions · tachycardia · urinary disorders · vision disorders · vomiting
  - Rare or very rare Angioedema · confusion (more common in elderly)

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks Antimuscarinics can affect the performance of skilled tasks (e.g. driving).

**ANTIMUSCARINICS | URINARY**

**Darifenacin**

08-Mar-2017

- **INDICATIONS AND DOSE**
  - Urinary frequency | Urinary urgency | Incontinence
    - **BY MOUTH**
      - Adult: Initially 7.5 mg once daily, increased if necessary to 15 mg after 2 weeks

- **INTERACTIONS** → Appendix 1: darifenacin

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain · dry eye · nasal dryness
  - Uncommon Asthenia · bladder pain · cough · diarrhoea · dysphagia · erectile dysfunction · flatulence · hyperhidrosis · hypertension · increased risk of infection · injury · insomnia · oedema · oral ulceration · taste altered · thinking abnormal · urinary tract disorder

- **PREGNANCY** Manufacturer advises avoid—tobacco in animal studies.

- **BREAST FEEDING** Present in milk in animal studies—manufacturer advises caution.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment; avoid in severe impairment (risk of increased exposure).

- **Dose adjustments** Manufacturer advises maximum 7.5 mg daily in moderate impairment.

- **PRESCRIBING AND DISPENSING INFORMATION** The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>3, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emslee (Meru Labs Luxco S.A.R.L.)</td>
<td>Darifenacin (as Darifenacin hydrobromide) 7.5 mg Emslee 7.5 mg modified-release tablets</td>
</tr>
</tbody>
</table>

**Darifenacin (as Darifenacin hydrobromide) 15 mg** Emslee 15 mg modified-release tablets | 28 tablet [F38] £25.48 OT + £25.48

**Fesoterodine fumarate**

08-Feb-2019

- **INDICATIONS AND DOSE**
  - Urinary frequency | Urinary urgency | Urge incontinence
    - **BY MOUTH**
      - Adult: 4 mg once daily, increased if necessary up to 8 mg once daily

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises max. 4 mg daily with concurrent use of potent inhibitors of CYP3A4; avoid concurrent use in patients who also have hepatic or renal impairment.
  - For dose adjustments with concurrent use of moderate inhibitors of CYP3A4 in patients with hepatic or renal impairment, consult product literature.

- **INTERACTIONS** → Appendix 1: fesoterodine
Oxybutynin hydrochloride

**INDICATIONS AND DOSE**

**Urinary frequency** | **Urinary urgency** | **Urinary incontinence** | **Neurogenic bladder instability**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Child 5-11 years: Initially 2.5–3 mg twice daily, increased to 5 mg 2–3 times a day
- Child 12-17 years: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4–5 times a day
- Adult: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4–5 times a day
- Elderly: Initially 2.5–3 mg twice daily, increased if tolerated to 5 mg twice daily, adjusted according to response

**BY MOUTH USING MODIFIED-RELEASE TABLETS**

- Child 5-17 years: Initially 5 mg once daily, adjusted in steps of 5 mg every week, adjusted according to response; maximum 15 mg per day
- Adult: Initially 5 mg once daily, increased in steps of 5 mg every week, adjusted according to response; maximum 20 mg per day

**Dose equivalence and conversion**

- Patients taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of Lyrinel® XL

**SIDE-EFFECTS**

- Common or very common: Diarrhoea, dry eye, gastrointestinal discomfort, insomnia, throat complaints
- Uncommon: Cough, fatigue, gastrointestinal disorders, nasal dryness, taste altered, urinary tract infection, vertigo
- Pregnancy: Manufacturer advises caution—no information available
- Breast feeding: Manufacturer advises caution—no information available

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**Flavoxate hydrochloride**

**INDICATIONS AND DOSE**

**Urinary frequency** | **Urinary incontinence** | **Dysuria** | **Urinary urgency** | **Bladder spasm due to catheterisation, cystoscopy, or surgery**

**BY MOUTH**

- Adult: 200 mg 3 times a day

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**SIDE-EFFECTS**

- Diarrhoea, dysphagia, eosinophilia, fatigue, hyperpyrexia, hypersensitivity, leucopenia, nervousness, vertigo
- Pregnancy: Manufacturer advises caution—no information available
- Breast feeding: Manufacturer advises caution—no information available

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**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
- **Modified-release tablet**
  - **Toviaz** (Pfizer Ltd)
    - 3 mg: 28 tablet pack £25.78 DT + £25.78
    - 4 mg: 28 tablet pack £25.78 DT + £25.78

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**BNF 78**

**778 Bladder and urinary disorders**

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disorders, glaucoma, hallucination, heat stroke, hypophysiosis, mydriasis, nightmare, paranoia, phototoxicity reaction, seizure, urinary tract infection

- **PREGNANCY** Manufacturers advise avoid unless essential—toxicity in animal studies.
- **BREAST FEEDING** Manufacturers advise avoid—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
- **RENA L IMPAIRMENT** Manufacturer advises caution.

- **DIRECTIONS FOR ADMINISTRATION**
  - With transdermal use in adults Apply patches to clean, dry, unbroken skin on abdomen, hip or buttock, remove after every 3–4 days and site replacement patch on a different area (avoid using same area for 7 days).

- **PRESCRIBING AND DISPENSING INFORMATION**
  - In adults: The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.
  - In children: The need for therapy for urinary indications should be reviewed soon after it has been commenced and then at regular intervals; a response usually occurs within 6 months but may take longer.

- **PATIENT AND CARER ADVICE**
  - With transdermal use in adults: Patients or carers should be given advice on how to administer oxybutynin transdermal patches.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions:
    - With transdermal use in adults: The Scottish Medicines Consortium has advised (July 2005) that Kentera® should be reserved for use in patients who benefit from oral oxybutynin but cannot tolerate its side-effects.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

- **CAUTIONARY AND ADVISORY LABELS 3, 25**
  - Lyri nel XL (Jansen-Cilag Ltd)
    - Oxybutynin hydrochloride 5 mg Lyri nel XL 5mg tablets | 84 tablet (PDT) £25.77 / 42.71
  - Oxybutynin hydrochloride 10 mg Lyri nel XL 10mg tablets | 84 tablet (PDT) £51.54 / 85.49

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 3**
  - Oxybutynin hydrochloride (Non-proprietary)
    - Oxybutynin hydrochloride 2.5 mg Oxybutynin 2.5mg tablets | 56 tablet (PDT) £6.58 / £2.17 | 84 tablet (PDT) £3.26–£7.71
  - Oxybutynin hydrochloride 3 mg Oxybutynin 3mg tablets | 56 tablet (PDT) £15.23 / £14.44
  - Oxybutynin hydrochloride 5 mg Oxybutynin 5mg tablets | 56 tablet (PDT) £13.85 / £3.09 | 84 tablet (PDT) £4.64–£20.77
  - Cystrin (Sanofi)
    - Oxybutynin hydrochloride 5 mg Cystrin 5mg tablets | 84 tablet (PDT) £21.99
  - Ditropan (Sanofi)
    - Oxybutynin hydrochloride 2.5 mg Ditropan 2.5mg tablets | 84 tablet (PDT) £1.60
  - Oxybutynin hydrochloride 5 mg Ditropan 5mg tablets | 84 tablet (PDT) £2.99

**Oral solution**

- **CAUTIONARY AND ADVISORY LABELS 3**
  - Oxybutynin hydrochloride (Non-proprietary)
    - Oxybutynin hydrochloride 500 microgram per 1 ml Oxybutynin 2.5mg/5ml oral solution sugar free-sugar free | 150 ml (PDT) £154.50–£214.85 DT = £194.26
    - Oxybutynin hydrochloride 1 mg per 1 ml Oxybutynin 5mg/5ml oral solution sugar free-sugar free | 150 ml (PDT) £190.20–£235.53 DT = £235.53

**Propiverine hydrochloride**

- **INDICATIONS AND DOSE**
  - Urinary frequency, urgency and incontinence associated with overactive bladder
    - By mouth using immediate-release medicines
      - Adult: 15 mg 1–2 times a day, increased if necessary up to 15 mg 3 times a day
      - By mouth using modified-release capsules
        - Adult: 30 mg once daily
  - Urinary frequency, urgency and incontinence associated with neurogenic bladder instability
    - By mouth using immediate-release medicines
      - Adult: 15 mg 3 times a day

- **INTERACTIONS** → Appendix 1: propiverine

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain, fatigue
  - Uncommon: Taste altered, tremor
  - Rare or very rare: Restlessness, Frequency not known: Hallucination

- **PREGNANCY** Manufacturer advises avoid (restriction of skeletal development in animals).

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment (no information available).

- **RENA L IMPAIRMENT** Manufacturer advises caution in mild or moderate impairment.

- **Dose adjustments** Max. daily dose 30 mg if eGFR less than 30 mL/minute/1.73m².

- **PRESCRIBING AND DISPENSING INFORMATION** The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Modified-release capsule**

- **CAUTIONARY AND ADVISORY LABELS 3, 25**
  - Detrunorm XL (Advanz Pharma)
    - Propiverine hydrochloride 30 mg Detrunorm XL 30mg capsules | 28 capsule (PDT) £24.45 DT = £24.45
    - Propiverine hydrochloride 45 mg Detrunorm XL 45mg capsules | 28 capsule (PDT) £27.90 DT = £27.90

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 3**
  - Propiverine hydrochloride (Non-proprietary)
    - Propiverine hydrochloride 15 mg Propiverine 15mg tablets | 28 tablet (PDT) £18.00 DT = £18.00
    - Propiverine hydrochloride 15 mg Detrunorm 15mg tablets | 56 tablet (PDT) £18.00 DT = £18.00

**Solifenacin succinate**

- **INDICATIONS AND DOSE**
  - Urinary frequency | Urinary urgency | Urinary incontinence
    - By mouth
      - Adult: 5 mg once daily, increased if necessary to 10 mg once daily

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DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Manufacturer advises max. dose 5 mg daily with concurrent use of potent inhibitors of CYP3A4; avoid concurrent use in patients who also have moderate hepatic impairment or severe renal impairment.

CONTRA-INDICATIONS

- Narrow-angle glaucoma

CAUTIONS

- Neurogenic bladder disorder - susceptibility to QT-interval prolongation

INTERACTIONS

- Appendix 1: solifenacin

SIDE-EFFECTS

- QT-interval prolongation

RENAL IMPAIRMENT

- The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

PREGNANCY

- Manufacturer advises caution - no information available.

BREAST FEEDING

- Manufacturer advises avoid — no information available.

HEPATIC IMPAIRMENT

- Manufacturer advises caution (risk of increased exposure).

Dose adjustments

- For immediate-release medicines, manufacturer advises dose reduction to 1 mg twice daily. For modified-release capsules, manufacturer advises dose reduction to 2 mg once daily.

RENAL IMPAIRMENT

- Avoid modified-release preparations if eGFR less than 30 mL/minute/1.73m². Dose adjustments: Reduce dose to 1 mg twice daily if eGFR less than 30 mL/minute/1.73m².

PRESCRIBING AND DISPENSING INFORMATION

- The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder.

Tablet

- 30 mg:
  - Tolterodine tartrate 4 mg (Astellas Pharma Ltd) £25.03 DT = £2.21
  - Tolterodine tartrate 2 mg (Astellas Pharma Ltd) £30.56 DT = £2.34

- 1 mg:
  - Detrusitol (Pfizer Ltd) £25.03 DT = £2.21
  - Tolterodine tartrate 2 mg Detrusitol 2 mg tablets £30.56 DT = £2.34

Modified-release capsule

- Blerone XL (Zentiva)
  - Tolterodine tartrate 4 mg Blerone XL 4 mg capsules £25.78 DT = £25.78

- Detrusitol XL (Pfizer Ltd)
  - Tolterodine tartrate 4 mg Detrusitol XL 4 mg capsules £25.78 DT = £25.78

- Efflomosyl XL (Mylan)
  - Tolterodine tartrate 4 mg Efflomosyl XL 4 mg capsules £25.78 DT = £25.78

- Inconex XL (Sandoz Ltd)
  - Tolterodine tartrate 4 mg Inconex XL 4 mg capsules £25.78 DT = £25.78

- Marisoea XL (Teva UK Ltd)
  - Tolterodine tartrate 4 mg Marisoea XL 2 mg capsules £25.78 DT = £25.78

- Neditol XL (Aspire Pharma Ltd)
  - Tolterodine tartrate 2 mg Neditol XL 2 mg capsules £25.78 DT = £25.78

- Preblacon XL (Actavis UK Ltd)
  - Tolterodine tartrate 4 mg Preblacon XL 4 mg capsules £25.78 DT = £25.78

- Santizor XL (Pfizer Ltd)
  - Tolterodine tartrate 4 mg Santizor XL 4 mg capsules £25.78 DT = £25.78

Tolterodine tartrate

- Indications and dose

  - Urinary frequency / Urinary urgency / Urinary incontinence
    - By mouth using immediate-release medicines
    - Adult: 2 mg twice daily, reduced if not tolerated to 1 mg twice daily
    - By mouth using modified-release capsules
    - Adult: 4 mg once daily

  - Dose equivalence and conversion

  - Children stabilised on immediate-release tolterodine tartrate 2 mg twice daily may be transferred to modified-release tolterodine tartrate 4 mg once daily.

- Cautions

  - History of QT-interval prolongation

- Interactions

  - Appendix 1: tolterodine

SIDE-EFFECTS

- Common or very common Abdominal pain - bronchitis - chest pain - diarrhoea - dry eye - fatigue - gastrointestinal disorders - paraesthesia - peripheral oedema - vertigo - weight increased

- Uncommon Arrhythmia - heart failure - memory loss - nervousness

- Frequency not known Hallucination

- Pregnancy

  - Manufacturer advises avoid — toxicity in animal studies.

- Breast feeding

  - Manufacturer advises avoid — no information available.

- Hepatic impairment

  - Manufacturer advises caution (risk of increased exposure).

  - Dose adjustments

    - For immediate-release medicines, manufacturer advises dose reduction to 1 mg twice daily.

    - For modified-release capsules, manufacturer advises dose reduction to 2 mg once daily.

- Renal impairment

  - Avoid modified-release preparations if eGFR less than 30 mL/minute/1.73 m².

    - Dose adjustments

      - Reduce dose to 1 mg twice daily if eGFR less than 30 mL/minute/1.73 m².

- Prescribing and dispensing information

  - The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder.

Tablet

- 30 mg
  - Tolterodine tartrate 4 mg (Astellas Pharma Ltd)
  - Tolterodine tartrate 2 mg (Astellas Pharma Ltd)

- 1 mg
  - Detrusitol (Pfizer Ltd)
  - Tolterodine tartrate 2 mg Detrusitol 2 mg tablets

- Modified-release capsule

- Blerone XL (Zentiva)
  - Tolterodine tartrate 4 mg Blerone XL 4 mg capsules

- Detrusitol XL (Pfizer Ltd)
  - Tolterodine tartrate 4 mg Detrusitol XL 4 mg capsules

- Efflomosyl XL (Mylan)
  - Tolterodine tartrate 4 mg Efflomosyl XL 4 mg capsules

- Inconex XL (Sandoz Ltd)
  - Tolterodine tartrate 4 mg Inconex XL 4 mg capsules

- Marisoea XL (Teva UK Ltd)
  - Tolterodine tartrate 4 mg Marisoea XL 2 mg capsules

- Neditol XL (Aspire Pharma Ltd)
  - Tolterodine tartrate 2 mg Neditol XL 2 mg capsules

- Preblacon XL (Actavis UK Ltd)
  - Tolterodine tartrate 4 mg Preblacon XL 4 mg capsules

- Santizor XL (Pfizer Ltd)
  - Tolterodine tartrate 4 mg Santizor XL 4 mg capsules
**Trospium chloride**

*11-May-2018*

**INDICATIONS AND DOSE**

**Urinary frequency | Urinary urgency | Urge incontinence**

- Adult: 20 mg twice daily, to be taken before food
- Adult: 60 mg once daily

**INTERACTIONS** → Appendix 1: trosipium

**SIDE-EFFECTS**

- Common or very common: Abdominal pain, chest pain, diarrhoea, flatulence, nausea
- Rare or very rare: Arthralgia, asthenia, dyspnœa, myalgia

**FREQUENCY not known**

- Agitation
- Anaphylactic reaction
- Cystitis
- Dyspepsia
- Gastritis
- Hypersensitivity vasculitis
- Increased risk of infection
- Headache
- Hypertension
- Increased risk of infection
- Myalgia
- Nausea
- Pruritus
- Rash
- Severe uncontrolled hypertension
- Skin reactions
- Stevens-Johnson syndrome
- Stevens-Johnson syndrome
- Urticaria
- Vomiting
- Dyspepsia
- Dyspepsia
- Gastritis
- Gastritis
- Hypersensitivity vasculitis
- Hypersensitivity vasculitis
- Increased risk of infection
- Increased risk of infection
- Myalgia
- Myalgia
- Nausea
- Nausea
- Pruritus
- Pruritus
- Rash
- Rash
- Severe uncontrolled hypertension
- Skin reactions
- Stevens-Johnson syndrome
- Stevens-Johnson syndrome
- Urticaria
- Vomiting

**INTERACTIONS** → Appendix 1: mirabegron

**SIDE-EFFECTS**

- Common or very common: Arrhythmias, constipation, diarrhoea, dizziness, headache, joint swelling, palpitations, skin reactions, vulvovaginal pruritus
- Rare or very rare: Angioedema, eyelid oedema, increased risk of infection, nausea

**INTERACTIONS** → Appendix 1: mirabegron

**SIDE-EFFECTS**

- Common or very common: Arrhythmias, constipation, diarrhoea, dizziness, headache, increased risk of infection, nausea
- Uncommon: Cystitis, dyspepsia, gastritis, joint swelling, palpitations, skin reactions, vulvovaginal pruritus
- Rare or very rare: Angioedema, eyelid oedema, hypersensitivity vasculitis, hypertensive crisis, joint swelling, urinary retention

**FREQUENCY not known**

- Insomnia

**CONCEPTION AND CONTRACEPTION**

Contraception advised in women of child-bearing potential.

**PREGNANCY**

Avoid—toxicity in animal studies.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate to severe impairment (risk of increased exposure); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**

Use with caution. Avoid Regurin®-XL.

Dose adjustments

- Reduce dose to 20 mg once daily or 20 mg on alternate days if eGFR 10–30 mL/minute/1.73 m².
- Avoid in severe impairment (no information available).

**PRESCRIBING AND DISPENSING INFORMATION**

The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
- Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS 23, 25**

- Regurin XL (Contura Ltd)
  - Trosipium chloride 60 mg
  - 28 capsule (P.M.) £23.05 DT = £23.05

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 23
  - Trosipium chloride 20 mg
  - 60 tablet (P.M.) £8.90 DT = £8.42

- Trosipium chloride 20 mg
  - 60 tablet (P.M.) £18.20 DT = £15.42

- Regurin (Contura Ltd)
  - Trosipium chloride 20 mg
  - 60 tablet (P.M.) £26.00 DT = £25.42

- Uraplex (Contura Ltd)
  - Trosipium chloride 20 mg
  - 60 tablet (P.M.) £26.00 DT = £25.42

**BETA-3-ADRENOCEPTOR AGONISTS**

**Mirabegron**

**INDICATIONS AND DOSE**

**Urinary frequency, urgency, and urge incontinence**

- Adult: 50 mg once daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises reduce dose to 25 mg once daily in patients with mild hepatic impairment with concurrent use of potent inhibitors of CYP3A4; avoid in moderate impairment.
- Manufacturer advises reduce dose to 25 mg once daily if eGFR 30–89 mL/minute/1.73 m² with concurrent use of potent inhibitors of CYP3A4; avoid if eGFR less than 30 mL/minute/1.73 m².

**CONTRA-INDICATIONS**

- Severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg).

**CAUTIONS**

- History of QT-interval prolongation—stage 2 hypertension.

**INTERACTIONS** → Appendix 1: mirabegron

**SIDE-EFFECTS**

- Common or very common: Arrhythmias, constipation, diarrhoea, dizziness, headache, increased risk of infection, nausea
- Uncommon: Cystitis, dyspepsia, gastritis, joint swelling, palpitations, skin reactions, vulvovaginal pruritus
- Rare or very rare: Angioedema, eyelid oedema, hypersensitivity vasculitis, hypertensive crisis, joint swelling, urinary retention

**FREQUENCY not known**

- Insomnia

**CONCEPTION AND CONTRACEPTION**

Contraception advised in women of child-bearing potential.

**PREGNANCY**

Avoid—toxicity in animal studies.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate to severe impairment (risk of increased exposure); avoid in severe impairment (no information available).

**DOSE ADJUSTMENTS**

Manufacturer advises dose reduction to 25 mg once daily in moderate impairment.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 15 mL/minute/1.73 m²—no information available.

**DOSE ADJUSTMENTS**

Dose adjustments: Reduce dose to 25 mg once daily if eGFR 15–29 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Blood pressure should be monitored before starting treatment and regularly during treatment, especially in patients with pre-existing hypertension.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE decisions

- Mirabegron for treating symptoms of overactive bladder (June 2013) NICE TA290

Mirabegron is recommended as an option only for patients in whom antimuscarinic drugs are ineffective, contra-indicated, or not tolerated; patients currently receiving mirabegron who do not meet these criteria should have the option to continue until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA290

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

- CAUTIONARY AND ADVISORY LABELS 25

  - Betmiga (Astellas Pharma Ltd)
    - Mirabegron 25 mg
      - Betmiga 25mg modified-release tablets
        - 30 tablet (P.M.) £29.00 DT + £29.00
    - Mirabegron 50 mg
      - Betmiga 50mg modified-release tablets
        - 30 tablet (P.M.) £29.00 DT + £29.00

**1.2 Urinary retention**

**Urinary retention**

**Description of condition**

Urinary retention is the inability to voluntarily urinate. It may be secondary to urethral blockage, drug treatment (such as use of antimuscarinic drugs, sympathomimetics, tricyclic antidepressants), conditions that reduce detrusor contractions or interfere with relaxation of the urethra, neurogenic causes, or it may occur postpartum or postoperatively.
Acute urinary retention is a medical emergency characterised by the abrupt development of the inability to pass urine (over a period of hours). Chronic urinary retention is the gradual (over months or years) development of the inability to empty the bladder completely, characterised by a residual volume greater than one litre or associated with the presence of a distended or palpable bladder.

Urinary retention due to benign prostatic hyperplasia
The most common cause of urinary retention in men is benign prostatic hyperplasia. Men with an enlarged prostate can have lower urinary tract symptoms associated with obstruction, such as urinary retention (acute or chronic), frequency, urgency or nocturia.

Treatment
Treatment of urinary retention depends on the underlying condition. Catheterisation is used to relieve acute painful urinary retention or when no cause can be found. Surgical procedures or dilatation are often used to correct mechanical outflow obstructions.

Acute urinary retention
Acute retention is painful and requires immediate treatment by catheterisation. Before the catheter is removed an alpha-adrenoceptor blocker (such as alfuzosin hydrochloride, doxazosin p. 783, tamsulosin hydrochloride p. 785, prazosin p. 784, indoramin p. 784 or terazosin p. 786) should be given for at least two days to manage acute urinary retention.

Chronic urinary retention
In patients with chronic urinary retention, intermittent bladder catheterisation should be offered before an indwelling catheter. Catheters may be used as a long-term solution where persistent urinary retention is causing incontinence, infection, or renal dysfunction and a surgical solution is not feasible. Their use is associated with an increased risk of adverse events including recurrent urinary infections, trauma to the urethra, pain, and stone formation.

In men who have symptoms that are bothersome, drug treatment should only be offered when other conservative management options have failed. Men with moderate- to severe symptoms should be offered an alpha-adrenoceptor blocker (alfuzosin hydrochloride, doxazosin, tamsulosin hydrochloride or terazosin). Treatment should initially be reviewed after 4–6 weeks and then every 6–12 months.

The parasympathomimetic bethanechol chloride p. 786 increases detrusor muscle contraction. It is licensed for acute postoperative, postpartum and neurogenic urinary retention.

Urinary retention due to benign prostatic hyperplasia
In patients with benign prostatic hyperplasia, treatment is influenced by the severity of symptoms and their effect on the patient’s quality of life. Watchful waiting is suitable for men with symptoms that are not troublesome and in those who have not yet developed complications of benign prostatic hyperplasia such as renal impairment, urinary retention or recurrent infection.

The recommended treatment of benign prostatic hyperplasia is usually an alpha-adrenoceptor blocker. The alpha1-selective adrenoceptor blockers relax smooth muscle in benign prostatic hyperplasia producing an increase in urinary flow-rate and an improvement in obstructive symptoms.

In patients with an enlarged prostate, a raised prostate specific antigen concentration, and who are considered to be at high risk of progression (such as the elderly), a 5α-reductase inhibitor (such as finasteride p. 787 or dutasteride p. 787) should be used. A combination of an alpha-adrenoceptor blocker and a 5α-reductase inhibitor can be offered if symptoms remain a problem.

Surgery is recommended for men with more severe symptoms that do not respond to drug therapy, or who have complications such as acute urinary retention, haematuria, renal failure, bladder calculi or recurrent urinary-tract infection.

Related drugs
Other drugs used for urinary retention: neostigmine p. 1125, pyridostigmine bromide p. 1126.

Useful Resources

### ALPHA-ADRENOCEPTOR BLOCKERS

**Alfuzosin hydrochloride**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign prostatic hyperplasia</strong></td>
</tr>
<tr>
<td>• BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</td>
</tr>
<tr>
<td>• Adult: 2.5 mg 3 times a day; maximum 10 mg per day</td>
</tr>
<tr>
<td>• Elderly: Initially 2.5 mg twice daily, adjusted according to response; maximum 10 mg per day</td>
</tr>
<tr>
<td>• BY MOUTH USING MODIFIED-RELEASE MEDICINES</td>
</tr>
<tr>
<td>• Adult: 10 mg once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTRA-INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid if history micturition syncope</td>
</tr>
<tr>
<td>• Avoid if history of postural hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute heart failure • Concomitant antihypertensives (reduced dosage and specialist supervision may be required) • Discontinue if angina worsens • Elderly • History of QT-interval prolongation • Patients undergoing cataract surgery (risk of intraoperative floppy iris syndrome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTERACTIONS</th>
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</thead>
<tbody>
<tr>
<td>→ Appendix 1: alpha blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIDE-EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Common or very common</td>
</tr>
<tr>
<td>Asthenia • Diarrhoea • Dizziness • Dry mouth • Headache • Malaise • Nausea • Postural hypotension • Vertigo • Vomiting</td>
</tr>
<tr>
<td>• Uncommon</td>
</tr>
<tr>
<td>Abdominal pain • Arrhythmias • Chest pain • Drowsiness • Flushing • Oedema • Palpitations • Rhinitis • Skin reactions • Syncope • Visual impairment</td>
</tr>
<tr>
<td>• Rare or very rare</td>
</tr>
<tr>
<td>Angina pectoris • Angioedema</td>
</tr>
<tr>
<td>• Frequency not known</td>
</tr>
<tr>
<td>Cerebral ischaemia • Floppy iris syndrome • Hepatic disorders • Neutropenia • Priapism • Thrombocytopenia</td>
</tr>
</tbody>
</table>

SIDE-EFFECTS, FURTHER INFORMATION
First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

<table>
<thead>
<tr>
<th>HEPATIC IMPAIRMENT</th>
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<tbody>
<tr>
<td>For immediate-release preparations manufacturer advises caution in mild to moderate hepatic failure; avoid in severe hepatic failure (risk of increased half-life). For modified-release preparations manufacturer advises avoid in hepatic failure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>For immediate-release preparations manufacturer advises initial dose of 2.5 mg once daily, increased to 2.5 mg twice daily according to response in mild to moderate hepatic failure.</td>
</tr>
</tbody>
</table>
Doxazosin

INDICATIONS AND DOSE

Hypertension

Adult: Initially 1 mg once daily for 1–2 weeks, then increased to 2 mg once daily, then increased if necessary to 4 mg once daily; maximum 16 mg per day

Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

Benign prostatic hyperplasia

Adult: Initially 1 mg daily, dose may be doubled at intervals of 1–2 weeks according to response; usual maintenance 2–4 mg daily; maximum 8 mg per day

Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

DOSE EQUIVALENS AND CONVERSION

Tablet

Alfuzosin hydrochloride 10 mg | 30 tablet | £12.51 + £12.51
Alfuzosin hydrochloride 10 mg | 30 tablet | £11.48 + £12.51
Alfuzosin hydrochloride 10 mg | 30 tablet | £12.76 + £12.51
Alfuzosin hydrochloride 8 mg | 28 tablet | £9.98 + £9.98
Alfuzosin hydrochloride 4 mg | 28 tablet | £5.00 + £5.00
Alfuzosin hydrochloride 4 mg | 28 tablet | £5.50 + £5.50
Alfuzosin hydrochloride 4 mg | 28 tablet | £6.08 + £6.08

Table

Alfuzosin hydrochloride (Non-proprietary) 10 mg | 30 tablet | £12.51 + £12.51
Alfuzosin hydrochloride 10 mg | 30 tablet | £12.51 + £12.51
Alfuzosin hydrochloride 10 mg | 30 tablet | £14.35 + £14.35

CONTRA-INDICATIONS

History of micturition syncope (in patients with benign prostatic hypertrophy) - history of postural hypotension - monotherapy in patients with overactive bladder or anuria

CAUTIONS

Care with initial dose (postural hypotension) - cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - heart failure - pulmonary oedema due to aortic or mitral stenosis

INTERACTIONS

Common or very common Arrhythmias - asthenia - chest pain - cough - cystitis - dizziness - drowsiness - dry mouth - dyspnoea - gastrointestinal discomfort - headache - hypotension - increased risk of infection - influenza like illness - muscle complaints - nausea - oedema - pain - palpitations - skin reactions - urinary disorders - vertigo

Uncommon Angina pectoris - anxiety - appetite abnormal - arthralgia - constipation - depression - diarrhoea - gastrointestinal disorders - gout - haemorrhage - insomnia - myocardial infarction - sensation abnormal - sexual dysfunction - stroke - syncope - tinnitus - tremor - vomiting - weight increased

Rare or very rare Alopecia - bronchospasm - flushing - gynaecomastia - hepatic disorders - leucopenia - malaise - muscle weakness - thrombocytopenia - vision blurred

Frequency not known Floppy iris syndrome

SIDE-EFFECTS

PREGNANCY

No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

BREAST FEEDING

Accumulates in milk in animal studies—manufacturer advises avoid.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild to moderate impairment (limited information available); avoid in severe impairment (no information available).

PATIENT AND CARER ADVICE

Patient counselling is advised for doxazosin tablets (initial dose).

Driving and skilled tasks May affect performance of skilled tasks e.g. driving.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

Modiﬁed-release tablet

CAUTIONARY AND ADVISORY LABELS

21, 25

Benign prostatic hyperplasia

Patient should be counselled

Driving and skilled tasks

INDICATIONS AND DOSE

- Doxazosin
- Alfuzosin hydrochloride
- Alfuzosin hydrochloride 2.5 mg Tablet
- Doxazosin (as Doxazosin mesilate) 2 mg Tablet
Indoramin

30-Mar-2017

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 25 mg twice daily, increased in steps of 25–50 mg every 2 weeks, maximum daily dose should be given in divided doses; maximum 200 mg per day

**Benign prostatic hyperplasia**

- **BY MOUTH**
  - Adult: 20 mg twice daily, increased in steps of 20 mg every 2 weeks if required, increased if necessary up to 100 mg daily in divided doses
  - Elderly: 20 mg daily may be adequate, dose to be taken at night

**SIDE-EFFECTS**

- Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

**CONTRA-INDICATIONS**

- Established heart failure - history micturition syncope (when used for benign prostatic hyperplasia) - history of postural hypotension (when used for benign prostatic hyperplasia)

**CAUTIONS**

- Cataract surgery (risk of intra-operative floppy iris syndrome) - control incipient heart failure before initiating indoramin - elderly - epilepsy (convulsions in animal studies) - history of depression - Parkinson’s disease (extrapyramidal disorders reported)

**INTERACTIONS** → Appendix 1: alpha blockers

**SIDE-EFFECTS**

- Rare or very rare Parkinson’s disease exacerbated
- Frequency not known Depression - dizziness - drowsiness - dry mouth - ejaculation failure - fatigue - headache - nasal congestion - weight increased
- **PREGNANCY** No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.
- **BREAST FEEDING** No information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution.
- **RENAL IMPAIRMENT** Manufacturer advises caution.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

**MEDIcINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Indoramin (non-proprietary)**
  - Indoramin (as Indoramin hydrochloride) 20 mg | Indoramin 20mg tablets | 60 tablet (P6) £61.00 DT = £7.96
  - Indoramin (as Indoramin hydrochloride) 25 mg | Indoramin 25mg tablets | 84 tablet (P6) £60.26 DT = £60.26
  - Doralese Tiltab (Chemix Pharma Ltd)
    - Indoramin (as Indoramin hydrochloride) 20 mg | Doralese Tiltab 20mg tablets | 60 tablet (P6) £11.44 DT = £7.96

**Prazosin**

**INDICATIONS AND DOSE**

**Hypertension**

- **BY MOUTH**
  - Adult: Initially 500 micrograms 2–3 times a day for 3–7 days, the initial dose should be taken on retiring to bed at night to avoid collapse, increased to 1 mg 2–3 times a day for a further 3–7 days, then increased if necessary up to 20 mg daily in divided doses

**Congestive heart failure (rarely used)**

- **BY MOUTH**
  - Adult: 500 micrograms 2–4 times a day, initial dose to be taken at bedtime, then increased to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

**Raynaud’s syndrome (but efficacy not established)**

- **BY MOUTH**
  - Adult: Initially 500 micrograms twice daily, initial dose to be taken at bedtime, dose may be increased after 3–7 days, then increased if necessary to 1–2 mg twice daily

**Benign prostatic hyperplasia**

- **BY MOUTH**
  - Adult: Initially 500 micrograms twice daily for 3–7 days, subsequent doses should be adjusted according to response, maintenance 2 mg twice daily, initiate with lowest possible dose in elderly patients

**SIDE-EFFECTS**

- Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

**CONTRA-INDICATIONS**

- History of micturition syncope - history of postural hypotension - not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)

**CAUTIONS**

- Cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - first dose hypotension

**INTERACTIONS** → Appendix 1: alpha blockers

**SIDE-EFFECTS**

- Common or very common Asthenia - constipation - depression - diarrhoea - dizziness - dry mouth - dyspnoea - headache - nasal congestion - nausea - nervousness - oedema - palpitations - postural hypotension - sexual dysfunction - skin reactions - syncope - urinary disorders - vertigo - vision blurred - vomiting
- Uncommon Angina pectoris - arrhythmias - arthralgia - cataract surgery (risk of intra-operative floppy iris syndrome) - dizziness - epistaxis - eye pain - eye redness - gastrointestinal discomfort - hyperhidrosis - paraesthesia - sleep disorders - tinnitus
- Rare or very rare Alopecia - fever - flushing - gynaecomastia - hallucination - hepatic function abnormal - pain - pancreatitis - vasculitis
- **PREGNANCY** No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.
- **BREAST FEEDING** Present in milk, amount probably too small to be harmful; manufacturer advises use with caution.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution (no information available).

**RENAL IMPAIRMENT**

- Manufacturer advises initial dose reduction to 500 micrograms daily; increased with caution.

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- History of micturition syncope - postural hypotension - not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required.

**DADE**

- Established heart failure - history micturition syncope (when used for benign prostatic hyperplasia) - history of postural hypotension (when used for benign prostatic hyperplasia)
Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS 25**

- **Tamsulosin hydrochloride (Non-proprietary)**
  - Tamsulosin hydrochloride 400 microgram
    - Tamsulosin 400 microgram modified-release capsules | 30 capsule [P] £3.87–£5.07 DT = £3.87
  - **Contífluo** (Ranbaxy (UK) Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Contífluo XL 400 microgram capsules | 30 capsule [P] £7.44 DT = £3.87
  - **Diffúndox XL** (Zentiva)
    - Tamsulosin hydrochloride 400 microgram
      - Diffúndox XL 400 microgram capsules | 30 capsule [P] £9.55 DT = £3.87
  - **Flomax MR** (Sanofi)
    - Tamsulosin hydrochloride 400 microgram
  - **Losinate MR** (Consilient Health Ltd)
    - Tamsulosin hydrochloride 400 microgram
  - **Pamsvax XL** (Actavis UK Ltd, Almus Pharmaceuticals Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Pamsvax XL 400 microgram capsules | 30 capsule [P] £1.28 DT = £3.87
  - **Peyme MR** (Teva UK Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Peyme 400 microgram MR capsules | 30 capsule [P] £4.06 DT = £3.87
  - **Pineexel PR** (Wockhardt UK Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Pineexel PR 400 microgram capsules | 30 capsule [P] £2.50 DT = £3.87
  - **Tabpyn MR** (Genus Pharmaceuticals Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Tabpyn MR 400 microgram capsules | 30 capsule [P] £4.45 DT = £3.87
  - **Tamfrex XL** (Milpharm Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Tamfrex XL 400 microgram capsules | 30 capsule [P] £28.51 DT = £3.87
  - **Tamsumac** (Macleods Pharma UK Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Tamsumac 0.4mg modified-release capsules | 30 capsule [P] £3.87 DT = £3.87
  - **Tamurex** (Sornex Pharma)
    - Tamsulosin hydrochloride 400 microgram
      - Tamurex 400 microgram modified-release capsules | 30 capsule [P] £3.50 DT = £1.87

Tamsulosin with dutasteride

The properties listed below are those particular to the combination only. For the properties of the components please consider, tamsulosin hydrochloride above, dutasteride p. 787.

**INDICATIONS AND DOSE**

**Benign prostatic hyperplasia**

**BY MOUTH**

- Adult (male): 1 capsule daily.

**INTERACTIONS** → Appendix 1: alpha blockers · dutasteride

**PATIENT AND CARER ADVICE**

Driving and skilled tasks May affect performance of skilled tasks e.g. driving.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 25**

- **Cositam XL** (Consilient Health Ltd)
  - Tamsulosin hydrochloride 400 microgram
    - Cositam XL 400 microgram tablets | 30 tablet [P] £8.89 DT = £10.47
  - **Faramsil** (Sanofi)
    - Tamsulosin hydrochloride 400 microgram
      - Faramsil 400 microgram modified-release tablets | 30 tablet [P] £8.89 DT = £10.47
  - **Flectone XL** (Teva UK Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Flectone XL 400 microgram tablets | 30 tablet [P] £9.95 DT = £10.37
  - **Flomaxtra XL** (Astellas Pharma Ltd)
    - Tamsulosin hydrochloride 400 microgram
      - Flomaxtra XL 400 microgram tablets | 30 tablet [P] £10.47 DT = £10.47

**Tamsulosin hydrochloride**

**INDICATIONS AND DOSE**

**Benign prostatic hyperplasia**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 400 micrograms once daily

**CONTRA-INDICATIONS**

- History of micturition syncope · history of postural hypotension

**CAUTIONS**

- Cataract surgery (risk of intra-operative floppy iris syndrome) · concomitant antihypertensives (reduced dosage and specialist supervision may be required) · elderly

**INTERACTIONS** → Appendix 1: alpha blockers

**SIDE-EFFECTS**

- Common or very common Dizziness · sexual dysfunction
  - Uncommon Asthenia · constipation · diarrhea · headache · nausea · palpitations · postural hypotension · rhinitis · skin reactions · vomiting
  - Rare or very rare Angioedema · Stevens-Johnson syndrome · syncope
  - Frequency not known Dry mouth · epistaxis · vision disorders

**HEPATIC IMPAIRMENT**

Manufacturer advises avoid in severe impairment.

**RENAL IMPAIRMENT**

Use with caution if eGFR less than 10 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Driving and skilled tasks May affect performance of skilled tasks e.g. driving.

**EXCEPTIONS TO LEGAL CATEGORY**

Tamsulosin hydrochloride 400 microgram capsules can be sold to the public for the treatment of functional symptoms of benign prostatic hyperplasia in men aged 45–75 years to be taken for up to 6 weeks before clinical assessment by a doctor.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 25**

- **Cositam XL** (Consilient Health Ltd)
  - Tamsulosin hydrochloride 400 microgram
    - Cositam XL 400 microgram tablets | 30 tablet [P] £8.89 DT = £10.47
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    - Tamsulosin hydrochloride 400 microgram
      - Flomaxtra XL 400 microgram tablets | 30 tablet [P] £10.47 DT = £10.47

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Tamsulosin with solifenacin

The properties listed below are those particular to the combination only. For the properties of the components please consider, tamsulosin hydrochloride p. 785, solifenacin succinate p. 779.

**INDICATIONS AND DOSE**

Moderate to severe urinary frequency, urgency, and obstructive symptoms associated with benign prostate hyperplasia when monotherapy ineffective

- **BY MOUTH**
- Adult (male): 1 tablet daily.

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

- Manufacturer advises max. 1 Vesomni® tablet daily with concurrent use of potent inhibitors of CYP3A4; avoid concurrent use in patients who also have moderate hepatic impairment, severe renal impairment, are poor metabolisers of CYP2D6, or in patients also taking a potent inhibitor of CYP2D6.

**INTERACTIONS**

- Appendix 1: alpha blockers - solifenacin
- Appendix 1: cholinesterase inhibitors - solifenacin

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment; avoid in severe impairment (no information available).

**DOSE ADJUSTMENTS**

Manufacturer advises max. 1 Vesomni® tablet daily in moderate impairment.

**RENAI IMPAIRMENT**

Dose adjustments Max. 1 Vesomni® tablet daily if eGFR less than 30 ml/minute/1.73 m².

**MEDIACIAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

- Vesomni (Astellas Pharma Ltd)
- Tamsulosin hydrochloride 400 microgram, Solifenacin succinate 6 mg Vesomni 6mg/0.4mg modified-release tablets | 30 tablet (Pos) £27.62 DT = £27.62

**Terazosin**

**INDICATIONS AND DOSE**

Mild to moderate hypertension

- **BY MOUTH**
- Adult: 1 mg daily for 7 days, then increased if necessary to 2 mg daily, dose should be taken at bedtime; maintenance 2–10 mg once daily, doses above 20 mg rarely improve efficacy.

Benign prostatic hyperplasia

- **BY MOUTH**
- Adult: Initially 1 mg daily, dose should be taken at bedtime, if necessary dose may be doubled at intervals of 1–2 weeks according to response; maintenance 5–10 mg daily; maximum 10 mg per day

**CONTRA-INDICATIONS**

History of micturition syncope (in benign prostatic hyperplasia) - history of postural hypotension (in benign prostatic hyperplasia)

**CAUTIONS**

Cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - first dose

**CAUTIONS, FURTHER INFORMATION**

First dose First dose may cause collapse due to hypotension within 30–90 minutes, therefore should be taken on retiring to bed; may also occur with rapid dose increase.

**INTERACTIONS**

Appendix 1: alpha blockers

**SIDE-EFFECTS**


**PREGNANCY**

No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

**BREAST FEEDING**

No information available.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for terazosin tablets (initial dose).

First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

**Driving and skilled tasks**

May affect performance of skilled tasks e.g. driving.

**CHOLINE ESTERS**

**Bethanechol chloride**

**INDICATIONS AND DOSE**

Urinary retention

- **BY MOUTH**
- Adult: 10–25 mg 3–4 times a day, to be taken 30 minutes before food

**CONTRA-INDICATIONS**

Bradyxemia - cardiovascular disorders - conditions where increased motility of the gastro-intestinal tract could be harmful - conditions where increased motility of the urinary tract could be harmful - epilepsy - heart block - hyperthyroidism - hypotension - intestinal obstruction - obstructive airways disease - parkinsonism - peptic ulcer - recent myocardial infarction - urinary obstruction

**CAUTIONS**

Autonomic neuropathy (use lower initial dose)

**SIDE-EFFECTS**

Abdominal discomfort - hyperhidrosis - nausea - vomiting

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid; gastrointestinal disturbances in infant reported.

**LESS SUITABLE FOR PRESCRIBING**

Less suitable for prescribing.

www.getintopharma.com
Finasteride

**DRUG ACTION** A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

**INDICATIONS AND DOSE**

- **Benign prostatic hyperplasia**
  - **BY MOUTH**
  - Adult: 5 mg daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained)

**SIDE-EFFECTS**

- **Adult:**
  - **Obstructive uropathy**
  - **Common or very common** Sexual dysfunction
  - **Uncommon** Breast abnormality
  - **Frequency not known** Angioedema; depressed mood; hypersensitivity; localised oedema; skin reactions; testicular disorders

**CONCEPT AND CONTRACEPTION**

- Finasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.
- Finasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

**IMPORTANT SAFETY INFORMATION**

- **MHRA/CHM ADVICE: RARE REPORTS OF DEPRESSION AND SUICIDAL THOUGHTS (MAY 2017)**
  - The MHRA has received reports of depression and, in rare cases, suicidal thoughts in men taking finasteride (Propecia®) for male pattern hair loss; depression is also associated with Proscar® for benign prostatic hyperplasia. Patients should be advised to stop finasteride immediately and inform a healthcare professional if they develop depression.

**CAUTIONS**

- Obstructive uropathy
- **SIDE-EFFECTS**
  - **Adult:**
  - **Common or very common** Sexual dysfunction
  - **Uncommon** Breast abnormalities
  - **Frequency not known** Angioedema; depression; infertility

**HANDLING AND STORAGE**

- Women of childbearing potential should avoid handling crushed or broken tablets of finasteride.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Finasteride is not prescribable in NHS primary care for the treatment of androgenetic alopecia in men.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Finasteride**
  - **Finasteride 1 mg** Finasteride 1mg tablets | 28 tablet £8.36
  - **Finasteride 5 mg** Finasteride 5mg tablets | 28 tablet £11.85
  - **Aindeem** (Actavis UK Ltd)
  - **Finasteride 1 mg** Aindeem 1mg tablet | 28 tablet £33.68
  - **Finasteride 5 mg** Aindeem 5mg tablet | 84 tablet £88.40
  - **Propecia** (Merck Sharp & Dohme Ltd)
  - **Finasteride 1 mg** Propecia 1mg tablets | 28 tablet £33.68
  - **Finasteride 5 mg** Proscar 5mg tablets | 28 tablet £13.94

**Combination available:** Tamsulosin with dutasteride, p. 785

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**Mepostrone**

**DRUG ACTION** A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

**INDICATIONS AND DOSE**

- **Prostate hyperplasia**
  - **BY MOUTH**
  - Adult: 0.5 mg daily

**SIDE-EFFECTS**

- **Adult:**
  - **Obstructive uropathy**
  - **Common or very common** Sexual dysfunction
  - **Uncommon** Breast abnormalities

**CONCEPT AND CONTRACEPTION**

- Mepostrone is not prescribed in the UK.

**HANDLING AND STORAGE**

- Women of childbearing potential should avoid handling crushed or broken tablets of mepostrone.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Mepostrone is not prescribable in NHS primary care for the treatment of androgenetic alopecia in men.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Mepostrone**
  - **Mepostrone 0.5 mg** Mepostrone 0.5mg tablets | 28 tablet £22.56

**Combination available:** Tamsulosin with dutasteride, p. 785

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**Progesterone**

**DRUG ACTION** A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

**INDICATIONS AND DOSE**

- **Breast cancer**
  - **BY MOUTH**
  - Adult: 0.5 mg daily

**SIDE-EFFECTS**

- **Adult:**
  - **Obstructive uropathy**
  - **Common or very common** Sexual dysfunction
  - **Uncommon** Breast abnormalities

**CONCEPT AND CONTRACEPTION**

- Progesterone is not prescribed in the UK.

**HANDLING AND STORAGE**

- Women of childbearing potential should avoid handling crushed or broken tablets of progesterone.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Progesterone is not prescribable in NHS primary care for the treatment of androgenetic alopecia in men.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **Progesterone**
  - **Progesterone 0.5 mg** Progesterone 0.5mg tablets | 28 tablet £22.56

**Combination available:** Tamsulosin with dutasteride, p. 785
1.3 Urolithiasis

Renal and ureteric stones 03-Apr-2019

Description of condition
Renal and ureteric stones are crystalline calculi that may form anywhere in the upper urinary tract. They are often asymptomatic but may cause pain when they move or obstruct the flow of urine. Most stones are composed of calcium salts (calcium oxalate, calcium phosphate or both). The rest are composed of struvite, uric acid, cystine and other substances. Patients are susceptible to stone formation when there is a decrease in urine volume and/or an excess of stone forming substances in the urine.

The following are risk factors that have been associated with stone formation: dehydration, change in urine pH, males aged between 40–60 years, positive family history, obesity, urinary anatomical abnormalities, and excessive dietary intake of oxalate, urate, sodium, and animal protein. Certain diseases which alter urinary volume, pH, and concentrations of certain ions (such as calcium, phosphate, oxalate, sodium, and uric acid) may also increase the risk of stone formation. Certain drugs such as calcium or vitamin D supplements, protease inhibitors, or diuretics may also increase the risk of stone formation.

Symptoms of acute renal or ureteric stones can include an abrupt onset of severe unilateral abdominal pain radiating to the groin (known as renal colic) that may be accompanied with nausea, vomiting, haematuria, increased urinary frequency, dysuria and fever (if concomitant urinary infection is present).

Stones can pass spontaneously and will depend on a number of factors, including the size of the stone (stones greater than 6 mm have a very low chance of spontaneous passage), the location (distal ureteral stones are more likely to pass than proximal ureteral stones), and the degree of obstruction.

Aims of treatment
- The aim of treatment is to improve the detection, clearance and prevention of renal and ureteric stones thereby reducing pain and improving quality of life.

Non-drug treatment
- Consider watchful waiting for asymptomatic renal stones if they are less than 5mm in diameter. If they are larger; the risk and benefit of this option should be discussed with the patient.
- Options for surgical stone removal should be discussed by the specialist hospital team depending on severity of obstruction, patient factors, size and site of stone. Options include shockwave lithotripsy, percutaneous nephrolithotomy and ureteroscopy.
- Consider stone analysis and measure serum calcium in patients with recurring renal or ureteric stones.
- Along with maintaining a healthy lifestyle, advise patients to drink 2.5–3 litres of water a day with the addition of fresh lemon juice and to avoid carbonated drinks. Maintain a normal daily calcium intake of 700–1200mg and salt intake of no more than 6g a day. For patients with recurrent calcium stones avoid excessive intake of oxalate-rich products, such as rhubarb, spinach, cocoa, tea, nuts, soy products, strawberries, and wheat bran. For patients with recurrent uric acid stones, avoid excessive dietary intake of urate rich products, such as liver, kidney, calf thymus, poultry skin, and certain fish (herring with skin, sardines and anchovies).

Pain Management
- Offer NSAIDs as first line treatment for the management of pain associated with suspected renal colic or renal and ureteric stones. If NSAIDs are contra-indicated or not sufficiently controlling the pain, consider intravenous paracetamol. Subsequently, opioids can be used if both paracetamol and NSAIDs are contra-indicated or not sufficiently controlling the pain. Do not offer antispasmodics to patients with suspected renal colic.

Medical Expulsive Therapy
- Consider alpha-adrenoceptor blockers for patients with distal ureteric stones less than 10mm in diameter. Alpha-adrenoceptor blockers may also be considered as adjunctive therapy for patients having shockwave lithotripsy for ureteric stones less than 10mm.

Prevention of recurrence of stones
- Alongside lifestyle advice, consider potassium citrate [unlicensed] in patients with recurrent stones composed of at least 50% calcium oxalate. Thiazides [unlicensed] may be given if patients also have hypercalciuria after restricting their sodium intake to no more than 6g a day.

1.4 Urological pain

Urological pain 03-Apr-2019

Treatment
- Lidocaine hydrochloride gel is a useful topical application in urethral pain or to relieve the discomfort of catheterisation.
- For information on the management of pain in renal and ureteric stones, see Renal and ureteric stones above.

Alkalisation of urine
- Alkalisation of urine can be undertaken with potassium citrate. The alkalising action may relieve the discomfort of cystitis caused by lower urinary tract infections. Sodium bicarbonate p. 1038 is used as a urinary alkalising agent in some metabolic and renal disorders.

ALKALISING DRUGS

<table>
<thead>
<tr>
<th>Citric acid with potassium citrate</th>
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### INDICATIONS AND DOSE
- **Relief of discomfort in mild urinary-tract infections**
- **Alkalisation of urine**
  - **By mouth using oral solution**
    - Adult: 10 mL 3 times a day, diluted well with water

### CAUTIONS
- Cardiac disease – elderly

### INTERACTIONS
- Appendix 1: potassium citrate

### SIDE EFFECTS
- Hyperkalaemia - nausea, vomiting

### RENAL IMPAIRMENT
- Avoid in severe impairment.

Monitoring
- Close monitoring required in renal impairment—high risk of hyperkalaemia.

### PRESCRIBING AND DISPENSING INFORMATION
- When prepared extemporaneously, the BP states Potassium Citrate Mixture BP consists of potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillaia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K+/10 mL

### EXCEPTIONS TO LEGAL CATEGORY
- Proprietary brands of potassium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections.
Sodium citrate

**INDICATIONS AND DOSE**

**Bladder washouts**
- Adult: (consult product literature)

**Relief of discomfort in mild urinary-tract infections**
- **BY MOUTH**
  - Adult: 6 ml for 1 dose

**Microlax®**

**Constipation**
- **BY RECTUM**
  - Child 3–7 years: 5–10 ml for 1 dose
  - Adult: 5–10 ml for 1 dose

**Relaxit®**

**Constipation**
- **BY RECTUM**
  - Child 3–7 years: 5 ml for 1 dose
  - Adult: 5 ml for 1 dose

**CONTRA-INDICATIONS**
- With rectal use: Acute gastro-intestinal conditions

**CAUTIONS**
- With oral use: Cardiac disease (in adults) · elderly · hypertension (in adults) · patients on a sodium-restricted diet (in adults)
- With rectal use: Debilitated patients (in adults) · sodium and water retention in susceptible individuals

**INTERACTIONS**
- Appendix 1: sodium citrate

**SIDE-EFFECTS**
- Polypuria

**PREGNANCY**
- With oral use in adults: Use with caution.

**RENAL IMPAIRMENT**
- With oral use: In patients with fluid retention, avoid antacids containing large amounts of sodium.

**PRESCRIBING AND DISPENSING INFORMATION**
- Sodium citrate 300 mmol/litre (88.2 mg/ml) oral solution is licensed for use before general anaesthesia for caesarean section (available from Viridian).

**EXCEPTIONS TO LEGAL CATEGORY**
- Proprietary brands of sodium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

Oral solution

**CAUTIONARY AND ADVISORY LABELS**
- Note: Sodium citrate may cause fluid and sodium retention in susceptible individuals.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Granules**
- **Sodium citrate (Non-proprietary)**
  - Sodium citrate 4 gram
  - Sodium citrate 4g oral granules sachets
  - 6 sachet (£1.28)
- Brands may include CanesOasis, Cymalon (sodium citrate), Cystocalm

**Oral solution**
- **Sodium citrate (Non-proprietary)**
  - Sodium citrate 8.23 mg per ml
  - Sodium citrate 0.3M oral solution
  - 30 ml (£1.50) 4.50 DT = £4.50

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**Powder**
- **Sodium citrate (Non-proprietary)**
  - Sodium citrate 4 gram
  - Sodium citrate 4g oral powder sachets
  - 6 sachet (£1.65) 1.65 DT = £1.65

**Irrigation solution**
- **Sodium citrate (Non-proprietary)**
  - Sodium citrate 3% irrigation solution
  - 1 litre bags

**Enema**
- **Micolette Micro-enema** (Pinewood Healthcare)
  - Sodium citrate 90 mg per ml
  - Micolette Micro-enema 5ml
  - 12 enema (£1.45)
- **Micralax Micro-enema** (RPH Pharmaceuticals AB)
  - Sodium citrate 90 mg per ml
  - Micralax Micro-enema 5ml
  - 12 enema (£1.87)

**HEPARINOID**

Pentosan polysulfate sodium

**INDICATIONS AND DOSE**

**Bladder pain syndrome**
- **BY MOUTH**
  - Adult: 100 mg 3 times a day, review treatment after 6 months and discontinue if no response

**CONTRA-INDICATIONS**
- Active bleeding

**CAUTIONS**
- Patients at increased risk of bleeding

**SIDE-EFFECTS**
- Common or very common: Anemia · asthenia · back pain · diarrhoea · dizziness · gastrointestinal discomfort · haemorrhage · headache · increased risk of infection · nausea · pelvic pain · peripheral oedema·
- Uncommon: Amylobia · anemia · appetite decreased · arthralgia · constipation · depression · dyspnoea · emotional lability · excessive tearing · flatulence · hyperhidrosis · hyperkinesia · insomnina · leucopenia · melanoctytic naevus size increased · myalgia · oral ulceration · paraesthesia · photosensitivity reaction · skin reactions · thrombocytopenia · tinnitus · vomiting · weight changes
- Frequency not known: Coagulation disorder · hepatic function abnormal

**PREGNANCY**
- Manufacturer advises avoid—no information available.

**BREAST FEEDING**
- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution—evidence of hepatic involvement in elimination.

**RENAL IMPAIRMENT**
- Manufacturer advises caution—evidence of renal involvement in elimination.

**MONITORING REQUIREMENTS**
- Manufacturer advises careful monitoring in patients with history of heparin or pentosan polysulfate sodium induced thrombocytopenia.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**
- Note: Pentosan polysulfate sodium may cause fluid and sodium retention in susceptible individuals.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Anethol with borneol, camphene, cineole, fenchone and pinene**

**INDICATIONS AND DOSE**

**Urolithiasis for the expulsion of calculi**
- **BY MOUTH**
  - Adult: 1–2 capsules 3–4 times a day, to be taken before food

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www.getintopharma.com
Bladder instillations and urological surgery

Bladder instillations and urological surgery

Bladder infection

Various solutions are available as irrigations or washouts. Aqueous chlorhexidine p. 1211 can be used in the management of common infections of the bladder but it is ineffective against most Pseudomonas spp. Solutions containing chlorhexidine 1 in 5000 (0.02%) are used but they may irritate the mucosa and cause burning and haematuria (in which case they should be discontinued); sterile sodium chloride solution 0.9% p. 1040 (physiological saline) is usually adequate and is preferred as a mechanical irrigant.

Continuous bladder irrigation with amphotericin 50 micrograms/mL p. 593 may be of value in mycotic infections in adults.

Dissolution of blood clots

Clot retention is usually treated by irrigation with sterile sodium chloride solution 0.9% but sterile sodium citrate solution for bladder irrigation 3% p. 789 may also be helpful.

Bladder cancer

Bladder instillations of doxorubicin hydrochloride p. 901 and mitomycin p. 919 are used for recurrent superficial bladder tumours. Such instillations reduce systemic side-effects; adverse effects on the bladder (e.g. micturition disorders and reduction in bladder capacity) may occur.

Instillation of epirubicin hydrochloride p. 902 is used for treatment and prophylaxis of certain forms of superficial bladder cancer; instillation of doxorubicin hydrochloride is also used for some papillary tumours.

Instillation of BCG (Bacillus Calmette-Guérin p. 958), a live attenuated strain derived from Mycobacterium bovis is licensed for the treatment of primary or recurrent bladder carcinoma in-situ and for the prevention of recurrence following transurethral resection.

Urological surgery

Glycine below irrigation solution 1.5% is the irrigant of choice for transurethral resection of the prostate gland and bladder tumours; sterile sodium chloride solution 0.9% (physiological saline) is used for percutaneous renal surgery.

Maintenance of indwelling urinary catheters

The deposition which occurs in catheterised patients is usually chiefly composed of phosphate and to minimise this the catheter (if latex) should be changed at least as often as every 6 weeks. If the catheter is to be left for longer periods a silicone catheter should be used together with the appropriate use of catheter maintenance solutions. Repeated blockage usually indicates that the catheter needs to be changed.

ANTISEPTICS AND DISINFECTANTS

Chlorhexidine with lidocaine

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1211, lidocaine hydrochloride p. 103.

INDICATIONS AND DOSE

Urethral sounding and catheterisation

BY URETHRAL APPLICATION

Adult: 6–11 mL

Cystoscopy

BY URETHRAL APPLICATION

Adult: 11 mL, then 6–11 mL if required

INTERACTIONS

Appendix 1: antiarrhythmics

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gel

EXCipients: May contain Hydroxybenzoates (parabens)

Instillagel (CliniMed Ltd)

Chlorhexidine gluconate 500 microgram per 1 mL, Lidocaine hydrochloride 20 mg per 1 mL Instillagel gel | 60 mL £14.05 DT + £14.05 | 110 mL £15.76 DT + £15.76

IRRIGATING SOLUTIONS

Glycine

INDICATIONS AND DOSE

Bladder irrigation during urological surgery | Irrigation for transurethral resection of the prostate gland and bladder tumours

Adult: (consult product literature)

CAUTIONs

Urological surgery There is a high risk of fluid absorption from the irrigant used in endoscopic surgery within the urinary tract.

SIDE-EFFECTS

Cardiovascular disorder - electrolyte depletion - fluid overload - pulmonary disorder - seizure - vision blurred

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Irrigation solution

Glycine (Non-proprietary)

Glycine 1.5% irrigation solution 3 litre Flowfusor bottles | 1 bag £0.05

Glycine 1.5% irrigation solution 1 litre Easyflow bags | 1 bag £0.05

Glycine 1.5% irrigation solution 2 litre Flowfusor bottles | 1 bottle

Catheter maintenance solutions

CATHETER MAINTENANCE SOLUTIONS

OptiFlo G citric acid 3.23% catheter maintenance solution (Bard Ltd)

50 mL - NHS indicative price = £3.66 - Drug Tariff (Part Ixa)100 mL - NHS indicative price = £3.66 - Drug Tariff (Part Ixa)

OptiFlo R citric acid 6% catheter maintenance solution (Bard Ltd)

50 mL - NHS indicative price = £3.66 - Drug Tariff (Part Ixa)100 mL - NHS indicative price = £3.66 - Drug Tariff (Part Ixa)

Uro-Tainer PHMB polihexanide 0.02% catheter maintenance solution (B.Braun Medical Ltd)

100 mL - NHS indicative price = £3.46 - Drug Tariff (Part Ixa)

Uro-Tainer Twin Soluto R citric acid 6% catheter maintenance solution (B.Braun Medical Ltd)

60 mL - NHS indicative price = £4.89 - Drug Tariff (Part Ixa)
3 Contraception

Contraceptives, hormonal

Overview
The Fraser Guidelines (Department of Health Guidance (July 2004): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health, available at www.tinyurl.com/bpg) should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use (available at www.fsrh.org) is published by the Faculty of Sexual and Reproductive Healthcare; it categorises the risks of using contraceptive methods with pre-existing medical conditions.

Hormonal contraception is the most effective method of fertility control, but can have major and minor side-effects, especially for certain groups of women. Hormonal contraception should only be used by adolescents after menarche.

Intra-uterine devices are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irrespective of parity, but are less appropriate for those with an increased risk of pelvic inflammatory disease.

Barrier methods alone (condoms, diaphragms, and caps) are less effective but can be reliable for well-motivated couples if used in conjunction with a spermicide. Occasionally sensitivity reactions occur. A female condom (Femidom®) is also available; it is pre-lubricated but does not contain a spermicide.

Combined hormonal contraceptives
Oral contraceptives containing an oestrogen and a progestogen (‘combined oral contraceptives’) are effective preparations for general use. Advantages of combined oral contraceptives include:
- reliable and reversible;
- reduced dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual tension;
- less symptomatic fibroids and functional ovarian cysts;
- less benign breast disease;
- reduced risk of ovarian and endometrial cancer;
- reduced risk of pelvic inflammatory disease.

Combined oral contraceptives containing a fixed amount of an oestrogen and a progestogen in each active tablet are termed ‘monophasic’; those with varying amounts of the two hormones are termed ‘phasic’. A transdermal patch and a vaginal ring, both containing an oestrogen with a progestogen, are also available.

<table>
<thead>
<tr>
<th>Oestrogen content</th>
<th>Progestogen content</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (as hemihydrate) 1.5 mg</td>
<td>Norethisterone acetate 2.5 mg</td>
<td>Zoely®</td>
</tr>
<tr>
<td>Estradiol 30 micrograms</td>
<td>Norethisterone 150 micrograms</td>
<td>Microgynon® 30 ED</td>
</tr>
<tr>
<td>Estradiol 35 micrograms</td>
<td>Norethisterone 1 mg</td>
<td>Norinyl®-1®</td>
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<td>Estradiol 35 micrograms</td>
<td>Norethisterone acetate 1.5 mg</td>
<td>Loestrin® ED</td>
</tr>
<tr>
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<td>Norethisterone acetate 2.5 mg</td>
<td>Loestrin®-30</td>
</tr>
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<td>Estradiol 30 micrograms</td>
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<td>Estradiol 30 micrograms</td>
<td>Norethisterone acetate 2.5 mg</td>
<td>Loestrin®-30</td>
</tr>
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Combined Oral Contraceptives Monophasic

21-day preparations

<table>
<thead>
<tr>
<th>Oestrogen content</th>
<th>Progestogen content</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Desogestrel 150 micrograms</td>
<td>Gedarel® 20/150</td>
</tr>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Desogestrel 150 micrograms</td>
<td>Mercilon®</td>
</tr>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Gestodene 75 micrograms</td>
<td>Femodette®</td>
</tr>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Gestodene 75 micrograms</td>
<td>Millinette® 20/75</td>
</tr>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Gestodene 75 micrograms</td>
<td>Sunya® 20/75</td>
</tr>
<tr>
<td>Ethinylestradiol 20 micrograms</td>
<td>Norethisterone acetate 1 mg</td>
<td>Loestrin® 20</td>
</tr>
<tr>
<td>Ethinylestradiol 30 micrograms</td>
<td>Desogestrel 150 micrograms</td>
<td>Gedarel® 30/150</td>
</tr>
<tr>
<td>Ethinylestradiol 30 micrograms</td>
<td>Desogestrel 150 micrograms</td>
<td>Marvicol®</td>
</tr>
<tr>
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<td>Drosiprenal 3 mg</td>
<td>Yasmin®</td>
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<td>Rigevon®</td>
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<td>Norgestimate 250 micrograms</td>
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<td>Norethisterone 500 micrograms</td>
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<td>Ethinylestradiol 35 micrograms</td>
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<td>Norinyl-1®</td>
</tr>
<tr>
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</tr>
<tr>
<td>OptiFlo S saline 0.9% catheter maintenance solution (Bard Ltd) Sodium chloride 9 mg per 1 ml 50 ml • NHS indicative price = £3.45 • Drug Tariff (Part Ixa)100 ml • NHS indicative price = £3.45 • Drug Tariff (Part Ixa)</td>
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</tbody>
</table>
Genito-urinary system

The content of combined oral contraceptives ranges from 30 to 40 micrograms. Generally a preparation with the lowest ethinylestradiol is chosen. It is recommended that combined hormonal contraceptives are not continued beyond 50 years of age since more suitable alternatives exist.

- Low strength preparations (containing ethinylestradiol 30 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable.
- Standard strength preparations (containing ethinylestradiol 40 micrograms) are appropriate for standard use. Phased preparations are generally reserved for women who either do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.

The progestogens ethinylestradiol with desogestrel p. 798, ethinylestradiol with drospirenone p. 798, and ethinylestradiol with gestodene p. 799 may be considered for women who have side-effects (such as acne, headache, depression, breast symptoms, and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous.

Dienogest with estradiol valerate p. 797 is in the combined oral contraceptive Qlaira®. Nomegestrol is the progestogen contained in the combined oral contraceptive Zoely®, in combination with estradiol.

The progestogen norelgestromin is combined with ethinylestradiol in a transdermal patch (Evra®). The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol (NavarRing®).

Surgery

Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A progestogen-only contraceptive may be offered as an alternative and the oestrogen-containing contraceptive restarted after mobilisation. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with unfractionated or low molecular weight heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives.

Reason to stop immediately

Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg; (in adolescents stop if blood pressure very high);
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment.

Progestogen-only contraceptives

Oral progestogen-only contraceptives

Oral progestogen-only preparations alter cervical mucus to prevent sperm penetration and may inhibit ovulation in some women; oral desogestrel-only preparations consistently inhibit ovulation and this is their primary mechanism of action. There is insufficient clinical trial evidence to compare the efficacy of oral progestogen-only contraceptives with each other or with combined hormonal contraceptives.
contraceptives. Progestogen-only contraceptives offer a suitable alternative to combined hormonal contraceptives when oestrogens are contra-indicated (including those with venous thrombosis or a past history or predisposition to venous thrombosis, heavy smokers, those with hypertension above systolic 160 mmHg or diastolic 55 mmHg, valvular heart disease, diabetes mellitus with complications, and migraine with aura).

Parenteral progestogen-only contraceptives
Medroxyprogesterone acetate p. 810 (Depo-Provera®, SAYANA PRESS®) is a long-acting progestogen given by injection; it is at least as effective as the combined oral preparations but because of its prolonged action it should never be given without full counselling backed by the patient information leaflet. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Troublesome bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium; delaying the first injection until 6 weeks after birth may minimise bleeding problems. If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of troublesome bleeding may be increased).

- In adolescents, medroxyprogesterone acetate (Depo-Provera®, SAYANA PRESS®) should be used only when other methods of contraception are inappropriate;
- in all women, the benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against the risks;
- in women with risk factors for osteoporosis, a method of contraception other than medroxyprogesterone acetate should be considered.

Norethisterone enantate (Noristerat®) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

An etonogestrel-releasing implant (Neplanon®) is also available. It is a highly effective long-acting contraceptive, consisting of a single flexible rod that is inserted subdermally into the lower surface of the upper arm and provides contraception for up to 3 years. The manufacturer advises that in heavier women, blood–etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third year; they advise that earlier replacement may be considered in such patients—however, evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of etonogestrel is rapidly reversed on removal of the implant.

Intra-uterine progestogen-only device
The progestogen-only intra-uterine systems Mirena®, Jaydess® and Levovsert® release levonorgestrel p. 806 directly into the uterine cavity. Mirena® is licensed for use as a contraceptive, for the treatment of primary menorrhagia and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. Jaydess® and Levovsert® are licensed for contraception, and Levovsert® is additionally licensed for the treatment of menorrhagia. These may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogenic activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete.

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhoea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time.

Surgery
All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Contraceptives, non-hormonal
Spermicidal contraceptives
Spermicidal contraceptives are useful additional safeguards but do not give adequate protection if used alone unless fertility is already significantly diminished. They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however, spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted infections (including HIV); high frequency use of the spermicide nonoxinol ‘9’ p. 811 has been associated with genital lesions, which may increase the risk of acquiring these infections.

Contraceptive devices
Intra-uterine devices
The intra-uterine device (IUD) is a suitable contraceptive for women of all ages irrespective of parity; however, it is less appropriate for those with an increased risk of pelvic inflammatory disease e.g. women under 25 years.

The most effective intra-uterine devices have at least 380 mm² of copper and have banded copper on the arms. Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper.

Fertility declines with age and therefore a copper intra-uterine device which is fitted in a woman over the age of 40, may remain in the uterus until menopause.

A frameless, copper-bearing intra-uterine device (Gyne Fi®) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus.

Caution with oil-based lubricants
Products such as petroleum jelly (Vaseline®), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections (including HIV).
Emergency contraception

Overview
Emergency contraception is intended for occasional use, to reduce the risk of pregnancy after unprotected sexual intercourse. It does not replace effective regular contraception.

Women who do not wish to conceive should be offered emergency contraception after unprotected sexual intercourse that has taken place on any day of a natural menstrual cycle. Emergency contraception should also be offered after unprotected intercourse from day 21 after childbirth (unless criteria for lactational amenorrhea are met), and from day 5 after abortion, miscarriage, ectopic pregnancy or uterine evacuation for gestational trophoblastic disease.

Emergency contraception should also be offered to women if their regular contraception has been compromised or has been used incorrectly.

Emergency contraceptive methods
Copper intra-uterine devices

Insertion of a copper intra-uterine device (see intra-uterine contraceptive devices (copper) p. 802) is the most effective form of emergency contraception and should be offered (if appropriate) to all women who have had unprotected sexual intercourse and do not want to conceive. A copper intra-uterine contraceptive device can be inserted up to 120 hours (5 days) after unprotected intercourse or up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation), regardless of the number of episodes of unprotected intercourse earlier in the cycle. Antibacterial cover should be considered for copper intra-uterine contraceptive device insertion if there is a significant risk of sexually transmitted infection that could be associated with ascending pelvic infection.

A copper intra-uterine device is not known to be affected by body mass index (BMI) or body-weight or by other drugs.

Hormonal methods

Hormonal emergency contraception (includes levonorgestrel p. 806 and ulipristal acetate p. 804) should be offered as soon as possible after unprotected intercourse if a copper intra-uterine device is not appropriate or is not acceptable to the patient; either drug should be taken as soon as possible after unprotected intercourse to increase efficacy. Hormonal emergency contraception administered after ovulation is ineffective.

Levonorgestrel is effective if taken within 72 hours (3 days) of unprotected intercourse and may also be used between 72 and 96 hours after unprotected intercourse (unlicensed use), but efficacy decreases with time. Ulipristal acetate is effective if taken within 120 hours (5 days) of unprotected intercourse. Ulipristal acetate has been demonstrated to be more effective than levonorgestrel for emergency contraception. It is possible that a higher body-weight or BMI could reduce the effectiveness of oral emergency contraception, particularly levonorgestrel; if BMI is greater than 26 kg/m² or body-weight is greater than 70 kg, it is recommended that either ulipristal acetate or a double dose of levonorgestrel [unlicensed indication] (see Emergency contraception under levonorgestrel) is given. It is unknown which is more effective.

Ulipristal acetate should be considered as the first-line hormonal emergency contraceptive for a woman who has had unprotected intercourse 96–120 hours ago (even if she has also had unprotected intercourse within the last 96 hours). It should also be considered first line for a woman who has had unprotected sexual intercourse within the last 5 days if it is likely to have taken place during the 5 days before the estimated day of ovulation.

Hormonal emergency contraception interactions
See Contraceptives, interactions below.

Starting hormonal contraception after emergency hormonal contraception

Emergency hormonal contraception methods do not provide ongoing contraception. After taking levonorgestrel, women should start suitable hormonal contraception immediately. They must use condoms reliably or abstain from intercourse until contraception becomes effective.

Women should wait 5 days after taking ulipristal acetate before starting suitable hormonal contraception. Women must use condoms reliably or abstain from intercourse during the 5 day waiting period and also until their contraceptive method is effective.

The copper intra-uterine device immediately provides effective ongoing contraception.

Useful Resources

Contraceptives, interactions

Overview
The effectiveness of combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, and emergency hormonal contraception can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. carbamazepine p. 311, eslicarbazepine acetate, nevirapine p. 645, oxcarbazepine p. 321, phenytoin p. 323, phenobarbital p. 335, primidone p. 336, rifonavir p. 659, St John’s Wort, topiramate p. 331, and, above all, rifabutin p. 578 and rifampicin p. 582), and possibly also griseofulvin p. 601. A condom together with a long-acting method (such as an injectable contraceptive) may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with antiretroviral drugs should be sought from HIV specialists.

Combined hormonal contraceptive interactions

Women using combined hormonal contraceptive patches, vaginal rings or oral tablets who require enzyme-inducing drugs or griseofulvin should be advised to change to a reliable contraceptive method that is unaffected by enzyme-inducers, such as some parenteral progesteron-only contraceptives (medroxyprogesterone acetate p. 810 and norethisterone p. 764) or intra-uterine devices (levonorgestrel p. 806; see also Contraceptives, non-hormonal p. 793). This should be continued for the duration of treatment and for four weeks after stopping. If a change in contraceptive method is undesirable or inappropriate the following options should be discussed:

Short course (2 months or less) of an enzyme-inducing drug

Containing the combined hormonal contraceptive method may be appropriate if used in combination with consistent and careful use of condoms for the duration of treatment and for four weeks after stopping the enzyme-inducing drug.

Long-term course (over 2 months) of an enzyme-inducing drug (except rifampicin or rifabutin) or a course of griseofulvin

Use a monophasic combined oral contraceptive at a dose of ethinylestradiol p. 759 50 micrograms or more daily [unlicensed use] and use either an extended or a “tricycling” regime (i.e. taking three packets of monophasic tablets without a break followed by a shortened tablet-free interval of four days [unlicensed use]); continue for the duration of
treatment with the interacting drug and for four weeks after stopping. If breakthrough bleeding occurs (and all other causes are ruled out) it is recommended that the dose of ethinylestradiol is increased by increments of 10 micrograms up to a maximum of 70 micrograms daily [unlicensed use] on specialist advice, or to use additional precautions, or to change to a method unaffected by the interacting drugs.

Use of contraceptive patches and vaginal rings (including concurrent use of two patches or two vaginal rings) is not recommended for women taking enzyme-inducing drugs over a long period.

**Long-term contraception (over 2 months) of rifampicin or rifabutin**

An alternative method of contraception (such as an IUD) is always recommended because they are such potent enzyme-inducing drugs; the alternative method of contraception should be continued for four weeks after stopping the enzyme-inducing drug.

**Antibacterials that do not induce liver enzymes**

It is recommended that no additional contraceptive precautions are required when combined oral contraceptives, contraceptive patches or vaginal rings are used with antibacterials that do not induce liver enzymes, unless diarrhoea or vomiting occur. These recommendations should be discussed with the woman.

There had been concerns that some antibacterials that do not induce liver enzymes (e.g. ampicillin p. 550, doxycycline p. 564) reduce the efficacy of combined oral contraceptives by impairing the bacterial flora responsible for recycling ethinylestradiol from the large bowel. However, there is a lack of evidence to support this interaction.

**Oral progestogen-only contraceptives interactions**

Effectiveness of oral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs or griseofulvin and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with an interacting drug and for at least 4 weeks afterwards.

For a short course of an enzyme-inducing drug (less than two months), continuing the progestogen-only oral method may be appropriate if used in combination with consistent and careful use of condoms for the duration of treatment and for four weeks after stopping the enzyme-inducing drug.

**Parenteral progestogen-only contraceptives interactions**

Effectiveness of parenteral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The effectiveness of intramuscular norethisterone injection and intramuscular and subcutaneous medroxyprogesterone acetate injections is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs.

Effectiveness of the etonogestrel-releasing implant p. 809 may be reduced by enzyme-inducing drugs or griseofulvin and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the interacting drug and for at least 4 weeks after stopping.

For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, continued contraception with the implant may be appropriate if used in combination with consistent and careful use of condoms for the duration of treatment and for 4 weeks after stopping the enzyme-inducing drug.

**Hormonal emergency contraception interactions**

The effectiveness of levonorgestrel and ulipristal acetate p. 804 is reduced in women taking enzyme-inducing drugs or griseofulvin (and for at least 4 weeks after stopping). A copper intra-uterine device can be offered instead. If the copper intra-uterine device is declined or unsuitable, the dose of levonorgestrel should be increased (See *Dose adjustments due to interactions* under levonorgestrel). There is no need to increase the dose for emergency contraception if the patient is taking antibiotics that are not enzyme inducers.

The effectiveness of ulipristal acetate for emergency contraception in women using drugs that increase gastric pH has not been studied. Levonorgestrel or a copper intra-uterine device should be considered as alternatives.

**Hormonal contraception should not be newly initiated in a patient until five days after administration of ulipristal acetate as emergency hormonal contraception**—the contraceptive effect of ulipristal acetate will be reduced. Consistent and careful use of condoms is recommended. Ulipristal acetate can be used as emergency hormonal contraception more than once in the same cycle. Conversely, manufacturer advises that use of levonorgestrel as emergency contraception more than once in the same cycle is not advisable due to increased risk of side-effects (such as menstrual irregularities).

**Useful Resources**


### 3.1 Contraception, combined

**OESTROGENS COMBINED WITH PROGESTOGENS**

**Combined hormonal contraceptives**

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 - gallstones - heart disease associated with pulmonary hypertension or risk of embolus - history during pregnancy of cholestatic jaundice - history during pregnancy of choledocholithiasis - history of breast cancer (but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable) - history of haemolytic jaundice syndrome - migraine with aura - personal history of venous or arterial thrombosis - sclerosing treatment for varicose veins - severe or multiple risk factors for arterial disease - severe or multiple risk factors for venous thromboembolism - systemic lupus erythematosus with (or unknown) antiphospholipid antibodies - transient ischaemic attacks without headaches - undiagnosed vaginal bleeding

- **CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration) — seek specialist advice - Crohn’s disease - gene mutations associated with breast cancer (e.g. BRCA 1) - history of severe depression especially if induced by hormonal contraceptive - hyperprolactinaemia (seek specialist advice) - inflammatory bowel disease - migraine - personal or family history of hypertriglyceridaemia
Risk factors for venous thromboembolism

There is an increased risk of venous thromboembolic disease in users of combined hormonal contraceptives particularly during the first year and possibly after restarting combined hormonal contraceptives following a break of four weeks or more. This risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100,000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors, such as obesity. The risk also varies depending on the type of progestogen.

Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Combined hormonal contraceptives also slightly increase the risk of arterial thromboembolism; however, there is no evidence to suggest that this risk varies between different preparations.

Risk factors for venous thromboembolism

Use with caution if any of the following factors present but avoid if two or more factors present:

- family history of venous thromboembolism in first-degree relative aged under 45 years (avoid if atherogenic lipid profile);
- diabetes mellitus (avoid if diabetes complications present);
- hypertension; blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (in adolescents, avoid if blood pressure very high);
- smoking (avoid if smoking 40 or more cigarettes daily);
- age over 35 years (avoid if over 50 years);
- obesity (avoid if body mass index \( \geq 35 \text{ kg/m}^2 \) unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
- migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).

Combined hormonal contraceptives should be stopped (pending investigation and treatment), if serious neurological effects occur, including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dizziness or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body.

SIDE-EFFECTS

- Common or very common Acne, fluid retention, headaches, metrorrhagia, nausea, weight increased
- Uncommon Alopecia, hypertension
- Rare or very rare Venous thromboembolism

Combined Hormonal Contraception and Risk of Venous Thromboembolism

Progestogen in Combined Hormonal Contraceptive

<table>
<thead>
<tr>
<th>Progestogen in Combined Hormonal Contraceptive</th>
<th>Estimated incidence per 10 000 women per year of use</th>
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<tr>
<td>Non-pregnant, not using combined hormonal contraception</td>
<td>2</td>
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<tr>
<td>Levonorgestrel</td>
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<tr>
<td>Norgestimate</td>
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<tr>
<td>Norethisterone</td>
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<td>Etonogestrel</td>
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<td>Norelgestromin</td>
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<td>Gestrone</td>
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<td>Drospirenone</td>
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<td>Dienogest</td>
<td>Not known—insufficient data</td>
</tr>
<tr>
<td>Nomegestrol</td>
<td>Not known—insufficient data</td>
</tr>
</tbody>
</table>

Combined with ethinyloestradiol

- Risk factors for arterial disease Use with caution if any one of the following factors present but avoid if two or more factors present:
- family history of arterial disease in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
- diabetes mellitus (avoid if diabetes complications present);
- hypertension; blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (in adolescents, avoid if blood pressure very high);
- smoking (avoid if smoking 40 or more cigarettes daily);
- age over 35 years (avoid if over 50 years);
- obesity (avoid if body mass index \( \geq 35 \text{ kg/m}^2 \) unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative).

- Cryptococcal meningitis
- Mediaeval fever
- Malaria
- Meningoencephalitis
- Molluscum contagiosum
- Mumps
- Pneumocystis carinii pneumonia
- Puerperal sepsis
- Rhematogenous meningitis
- Rickettsial disease
- Typhoid fever
- Typhus fever
- Tuberculosis
- Unclassified infection
- Urinary tract infection
- Venereal disease
- Visceral leishmaniasis
- Visceral tuberculosis
- Warts
- Yaws
- Zoonoses

- Risk factors for venous thromboembolism
- family history of venous thromboembolism in first-degree relative aged under 45 years (avoid if atherogenic lipid profile);
- diabetes mellitus (avoid if diabetes complications present);
- hypertension; blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (in adolescents, avoid if blood pressure very high);
- smoking (avoid if smoking 40 or more cigarettes daily);
- age over 35 years (avoid if over 50 years);
- obesity (avoid if body mass index \( \geq 35 \text{ kg/m}^2 \) unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
- migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).

Combination hormone contraceptives should be stopped (pending investigation and treatment), if serious neurological effects occur, including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dizziness or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body.

SIDE-EFFECTS

Common or very common Acne, fluid retention, headaches, metrorrhagia, nausea, weight increased

Uncommon Alopecia, hypertension

Rare or very rare Venous thromboembolism

Combination hormone contraceptives should be stopped (pending investigation and treatment), if serious neurological effects occur, including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dizziness or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body.

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SIDE-EFFECTS

Common or very common Acne, fluid retention, headaches, metrorrhagia, nausea, weight increased

Uncommon Alopecia, hypertension

Rare or very rare Venous thromboembolism
reasonably certain woman is not pregnant, first course can be
started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days. Every day (ED) combined preparations, 1 active tablet daily for 21 days, followed by 1 inactive tablet daily for 7 days; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets being taken); if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days.

Changing to combined preparation containing different progestogen If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start the first active tablet of new brand immediately. See individual monographs for requirements of specific preparations. Changing from progestogen-only tablet If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start new brand immediately, additional precautions (barrier methods) necessary for first 7 days. Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days (9 days for Qlaira ®). After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days (9 days for Qlaira ®). After abortion or miscarriage Start same day.

■ PATIENT AND CARER ADVICE

Travel Women taking oral contraceptives or using the patch or vaginal ring are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery. Diarrhoea and vomiting Vomiting and severe diarrhoea can interfere with the absorption of combined oral contraceptives. The FSRH advises following the instructions for missed pills if vomiting occurs within 3 hours of taking a combined oral contraceptive or severe diarrhoea occurs for more than 24 hours. Use of non-oral contraception should be considered if diarrhoea or vomiting persist.

Missed doses The critical time for loss of contraceptive protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late. If a woman misses only one pill, she should take an active pill as soon as she remembers and then resume normal pill-taking. No additional precautions are necessary. If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday (ED) pills, omitting the 7 inactive tablets).

Emergency contraception is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet.

Dienogest with estradiol valerate

■ INDICATIONS AND DOSE

Contraception with 28-day combined preparations | Menstrual symptoms with 28-day combined preparations

■ BY MOUTH

• Females of childbearing potential: 1 active tablet daily for 26 days, followed by 1 inactive tablet daily for 2 days, to be started on day 1 of cycle with first active tablet (withdrawal bleeding may occur during the 2-day interval of inactive tablets); subsequent courses repeated without interval

■ INTERACTIONS ➔ Appendix 1: combined hormonal contraceptives

■ SIDE-EFFECTS

→ Common or very common Breast abnormalities • gastrointestinal discomfort • increased risk of infection • menstrual cycle irregularities

→ Uncommon Appetite increased • cervical abnormalities • crying • depression • diaphragm • dizziness • fatigue • haemorrhage • hot flush • hyperhidrosis • mood altered • muscle spasms • neoplasms • oedema • ovarian and fallopian tube disorders • painful sexual intercourse • pelvic disorders • sexual dysfunction • skin reactions • sleep disorders • uterine cramps • vomiting • vulvovaginal disorders • weight decreased

→ Rare or very rare Aggression • anxiety • arterial thrombocytopenia • asthma • chest pain • cholecystitis • chronic • concentration impaired • constipation • contact lens intolerance • dry eye • dry mouth • dyspnoea • eye swelling • fever • galactorrhoea • gastrointestinal reflux disease • genital discharge • hair changes • hypertriglyceridaemia • hypotension • lymphadenopathy • malaise • myocardial infarction • pain • palpitations • paraesthesia • seborrhoea • sensation of pressure • urinary tract pain • vascular disorders • vertigo

■ DIRECTIONS FOR ADMINISTRATION

Changing to Qlaira ® Start the first active Qlaira ® tablet on the day after taking the last active tablet of the previous brand.

■ PATIENT AND CARER ADVICE

Diarrhoea and vomiting In cases of persistent vomiting or severe diarrhoea lasting more than 12 hours in women taking Qlaira ®, refer to product literature. Missed doses A missed pill for a patient taking Qlaira ® can be taken if started no later than 12 hours of the end of the packet, or repeated without interval on the previous cycle.

■ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

• Qlaira (Bayer Plc)
  Qlaira tablets  84 tablet  £25.18

Estradiol with nomegestrol

■ INDICATIONS AND DOSE

Contraception

■ BY MOUTH

• Females of childbearing potential: 1 active tablet daily for 24 days, followed by 1 inactive tablet daily for 4 days, to be started on day 1 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval
Ethinylestradiol with drospirenone

**INDICATIONS AND DOSE**

**Contraception with 21-day combined preparations**

**Menstrual symptoms with 21-day combined preparations**

- **BY MOUTH**
  - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval

**SIDE-EFFECTS**

- Common or very common  
  - Breast abnormalities • depressed mood • increased risk of infection • menstrual disorder • vaginal discharge
- Uncommon  
  - Diarrhoea • hypotension • sexual dysfunction • skin reactions • vomiting • weight decreased
- Rare or very rare  
  - Arterial thromboembolism • asthma • erythema nodosum • hearing impairment

**PATIENT AND CARER ADVICE**

Pill-free interval Withdrawal bleeding can occur during the 7-day tablet-free interval.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Dretine (Theramex HJ UK Ltd)
  - Ethinylestradiol 30 microgram, Drospirenone 3 mg
  - Dretine 0.03mg/3mg tablets | 63 tablet | £6.33 DT = £4.70
- Eloine (Bayer Plc)
  - Ethinylestradiol 20 microgram, Drospirenone 3 mg
  - Eloine 0.02mg/3mg tablets | 84 tablet | £4.70 DT = £14.70
- Lucette (Consilient Health Ltd)
  - Ethinylestradiol 30 microgram, Drospirenone 3 mg
  - Lucette 0.03mg/3mg tablets | 63 tablet | £3.35 DT = £14.70
- Yacella (Morningside Healthcare Ltd)
  - Ethinylestradiol 30 microgram, Drospirenone 3 mg
  - Yacella 0.03mg/3mg tablets | 63 tablet | £3.30 DT = £14.70
- Yasmin (Bayer Plc)
  - Ethinylestradiol 30 microgram, Drospirenone 3 mg
  - Yasmin tablets | 63 tablet | £4.70 DT = £14.70
- Yázinel (Lupin Healthcare (UK) Ltd)
  - Ethinylestradiol 30 microgram, Drospirenone 3 mg
  - Yázinel 0.03mg/3mg tablets | 63 tablet | £8.30 DT = £14.70

**INTERACTIONS**

→ Appendix 1: combined hormonal contraceptives

**PATIENT AND CARER ADVICE**

Diarrhoea and vomiting. In cases of persistent vomiting or severe diarrhoea lasting more than 12 hours in women taking Zoely®, refer to product literature.

- Missed doses A missed pill for a patient taking Zoely® is one that is 12 hours or more late; for information on how to manage missed pills in women taking Zoely®, refer to product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Zoely (Merck Sharp & Dohme Ltd)
  - Estradiol (as Estradiol hemihydrate) 1.5 mg, Nomegestrol acetate 2.5 mg Zoely 2.5mg/1.5mg tablets | 84 tablet | £9.80 DT = £19.80

**Ethinylestradiol with desogestrel**

**INDICATIONS AND DOSE**

Contraception with 21-day combined preparations

- BY MOUTH
  - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval

**SIDE-EFFECTS**

- Common or very common  
  - Breast abnormalities • depression • menstrual cycle irregularities • mood altered • pelvic pain • sexual dysfunction
- Uncommon  
  - Abdominal distension • appetite abnormal • galactorrhea • hot flush • hyperhidrosis • oedema • painful sexual intercourse • seborrhoea • sensation of pressure • skin reactions • uterine cramps • vulvovaginal disorders
- Rare or very rare  
  - Cerebrovascular insufficiency • concentration impaired • contact lens intolerance • dry eye • dry mouth • gallbladder disorders • hypertrichosis

**PREGNANCY**

Toxicity in animal studies.

**DIRECTIONS FOR ADMINISTRATION**

Zoely® (every day (ED) combined (monophasic) preparation), 1 active tablet daily for 24 days, followed by 1 inactive tablet daily for 4 days, starting on day 1 of cycle with first active tablet; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets are being taken). Changing to Zoely® Start the first active Zoely® tablet on the day after taking the last active tablet of the previous brand or, at the latest, the day after the tablet-free or inactive tablet interval of the previous brand.

**PATIENT AND CARER ADVICE**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Alenvona (Teva UK Ltd)
  - Ethinylestradiol 30 microgram, Desogestrel 150 microgram Alenvona 150microgram/30microgram tablets | 63 tablet | £6.33 DT = £4.19
- Bimizza (Morningside Healthcare Ltd)
  - Ethinylestradiol 20 microgram, Desogestrel 150 microgram Bimizza 150microgram/20microgram tablets | 63 tablet | £5.04 DT = £5.08

**INTERACTIONS**

→ Appendix 1: combined hormonal contraceptives

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Cimizt (Morningside Healthcare Ltd)
  - Ethinylestradiol 30 microgram, Desogestrel 150 microgram Cimizt 30microgram/150microgram tablets | 63 tablet | £3.80 DT = £4.19
- Gedarel (Consilient Health Ltd)
  - Ethinylestradiol 20 microgram, Desogestrel 150 microgram Gedarel 20microgram/150microgram tablets | 63 tablet | £5.08 DT = £5.08
- Ethinylestradiol 30 microgram, Desogestrel 150 microgram Gedarel 30microgram/150microgram tablets | 63 tablet | £4.19 DT = £4.19
- Marvelon (Merck Sharp & Dohme Ltd)
  - Ethinylestradiol 20 microgram, Desogestrel 150 microgram Marvelon tablets | 63 tablet | £10.70 DT = £4.19
- Mercilon (Merck Sharp & Dohme Ltd)
  - Ethinylestradiol 20 microgram, Desogestrel 150 microgram Mercilon 150microgram/20microgram tablets | 63 tablet | £8.44 DT = £5.08
- Munalea (Lupin Healthcare (UK) Ltd)
  - Ethinylestradiol 20 microgram, Desogestrel 150 microgram Munalea 150microgram/20microgram tablets | 63 tablet | £5.07 DT = £5.08
- Ethinylestradiol 30 microgram, Desogestrel 150 microgram Munalea 150microgram/30microgram tablets | 63 tablet | £4.18 DT = £4.19

www.getintopharma.com
**Ethinylestradiol with etonogestrel**

**INDICATIONS AND DOSE**

**Contraception** | Menstrual symptoms
- **BY VAGINA**
- Females of childbearing potential: 1 unit, insert the ring into the vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring free interval (during which withdrawal bleeding occurs).
- **INTERACTIONS** | Appendix 1: combined hormonal contraceptives

**DIRECTIONS FOR ADMINISTRATION**

Changing method of contraception to vaginal ring
Changing from combined hormonal contraception: Insert ring at the latest on the day after the usual tablet-free, patch-free, or inactive-tablet interval. If previous contraceptive used correctly, or pregnancy can reasonably be excluded, can switch to ring on any day of cycle.
Changing from progestogen-only method: From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when next injection due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

**PATIENT AND CARER ADVICE**
Patients or carers should be given advice on how to administer vaginal ring. Counselling: The presence of the ring should be checked regularly.

**Missed doses**
Expulsion, delayed insertion or removal, or broken vaginal ring
If the vaginal ring is expelled for less than 3 hours, rinse the ring with cool water and reinsert immediately; no additional contraception is needed.
If the ring remains outside the vagina for more than 3 hours or if the user does not know when the ring was expelled, contraceptive protection may be reduced:
- If ring expelled during week 1 or 2 of cycle, rinse ring with cool water and reinsert; use additional precautions (barrier methods) for next 7 days;
- If ring expelled during week 3 of cycle, either insert a new ring to start a new cycle or allow a withdrawal bleed and insert a new ring no later than 7 days after ring was expelled; latter option only available if ring was used continuously for at least 7 days before expulsion.
If insertion of a new ring at the start of a new cycle is delayed, contraceptive protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered.

No additional contraception is required if removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring.
If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle.

**INTERACTIONS** | Appendix 1: combined hormonal contraceptives

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, breast abnormalities, depression, dizziness, increased risk of infection, menstrual cycle irregularities, mood swings, nervousness, vaginal discharge
- **Uncommon** Appetite abnormal, diarrhoea, hirsutism, hypertri glycaemia, sexual dysfunction, skin reactions, vomiting
- **Rare or very rare** Angioedema, chorea exacerbated, ear disorders, embolism and thrombosis, erythema nodosum, eye irritation, gallbladder disorders, gastrointestinal disorders, haemolytic uraemic syndrome, hepatic disorders, hypersensitivity, inflammatory bowel disease, neonatal depression, optic neuritis, pancreatitis, systemic lupus erythematosus exacerbated, varicose veins exacerbated, weight decreased

**MEDICINAL FORMS**

Contraception, combined | 799

**Vaginal delivery system**
- **NuvaRing** (Merck Sharp & Dohme Ltd)
  - Ethinylestradiol 2.7 mg, Etonogestrel 11.7 mg
  - NuvaRing 0.12mg/0.015mg per day vaginal delivery system | 3 system
  - £29.70 DT + £29.70
- **SyreniRing** (Crescent Pharma Ltd)
  - Ethinylestradiol 2.7 mg, Etonogestrel 11.7 mg
  - SyreniRing 0.12mg/0.015mg per day vaginal delivery system | 3 system
  - £23.76 DT + £29.70

**Ethinylestradiol with gestodene**

**INDICATIONS AND DOSE**

**Contraception with 21-day combined preparations** | Menstrual symptoms with 21-day combined preparations
- **BY MOUTH**
- Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.

**INTERACTIONS** | Appendix 1: combined hormonal contraceptives

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, breast abnormalities, depression, dizziness, increased risk of infection, menstrual cycle irregularities, mood swings, nervousness, vaginal discharge
- **Uncommon** Appetite abnormal, diarrhoea, hirsutism, hypertri glycaemia, sexual dysfunction, skin reactions, vomiting
- **Rare or very rare** Angioedema, chorea exacerbated, ear disorders, embolism and thrombosis, erythema nodosum, eye irritation, gallbladder disorders, gastrointestinal disorders, haemolytic uraemic syndrome, hepatic disorders, hypersensitivity, inflammatory bowel disease, neonatal depression, optic neuritis, pancreatitis, systemic lupus erythematosus exacerbated, varicose veins exacerbated, weight decreased

**MEDICINAL FORMS**

Contraception, combined | 799

**Tablet**
- **Ethinylestradiol with gestodene (Non-proprietary)**
  - Ethinylestradiol 30 microgram, Gestodene
  - 50 microgram Ethinylestradiol 30 microgram / Gestodene
  - 50microgram tablets | 18 tablet
- **Ethinylestradiol 40 microgram, Gestodene**
  - 70 microgram Ethinylestradiol 40 microgram / Gestodene
  - 70microgram tablets | 15 tablet
Ethinylestradiol 30 microgram, Gestodene
100 microgram Ethinylestradiol 30 microgram / Gestodene 100 microgram tablets | 30 tablet (P) N
- Aidulan (Lupin Healthcare (UK) Ltd)
- Femodette (Bayer Plc)
- Millinette (Actavis UK Ltd)
- Indications and Dose
  Contraceptive with 21-day combined preparations
  Menstrual symptoms with 21-day combined preparations
    - By mouth
      - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.
  Contraception with 28-day combined preparations
  Menstrual symptoms with 28-day combined preparations
    - By mouth
      - Females of childbearing potential: 1 active tablet once daily for 21 days, followed by 1 inactive tablet once daily for 7 days, withdrawal bleeding occurs during the 7-day interval of inactive tablets being taken, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day. Subsequent courses repeated without interval.

Ethinylestradiol with levonorgestrel

- Contraception with 21-day combined preparations
- Menstrual symptoms with 21-day combined preparations
  - By mouth
    - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle— if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day. Subsequent courses repeated without interval.

Ethinylestradiol with norelgestromin

- Contraception
- Menstrual symptoms
  - By transdermal application
    - Females of childbearing potential: Apply 1 patch once weekly for 3 weeks, apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle, subsequent courses repeated after a 7-day patch-free interval (during which withdrawal bleeding occurs)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
- Ethinylestradiol with levonorgestrel (Non-proprietary)
  Ethinylestradiol 30 microgram, Levonorgestrel 50 microgram Ethinylestradiol 30 microgram / Levonorgestrel 50 microgram tablets | 6 tablet (P) N
  Ethinylestradiol 40 microgram, Levonorgestrel 75 microgram Ethinylestradiol 40 microgram / Levonorgestrel 75 microgram tablets | 5 tablet (P) N
  Ethinylestradiol 30 microgram, Levonorgestrel 125 microgram Ethinylestradiol 30 microgram / Levonorgestrel 125 microgram tablets | 10 tablet (P) N
  Elevin (MedRx Licences Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Elevin 150 microgram / 30 microgram tablets | 63 tablet (P) £29.25 DT = £2.82
  Leandra (Genesis Pharmaceuticals Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Leandra 30 microgram / 150 microgram tablets | 63 tablet (P) £2.82 DT = £2.82
  Levest (Morningside Healthcare Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Levest 150/30 tablets | 21 tablet (P) £0.85
  Maxen (Lupin Healthcare (UK) Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Maxen 150 microgram / 30 microgram tablets | 63 tablet (P) £1.88 DT = £2.82
  Microgynon 30 (Bayer Plc)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Microgynon 30 tablets | 63 tablet (P) £2.82 DT = £2.82
  Ovranette (Pier Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Ovranette 150 microgram / 30 microgram tablets | 63 tablet (P) £2.20 DT = £2.82
  Rigevidon (Consilient Health Ltd)
  Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram Rigevidon tablets | 63 tablet (P) £1.89 DT = £2.82

INTERACTIONS
- Appendix 1: combined hormonal contraceptives

SIDE-EFFECTS
- Common or very common: Anxiety, breast abnormalities, diarrhoea, dizziness, fatigue, gastrointestinal discomfort, increased risk of infection, malaise, menstrual cycle irregularities, mood altered, muscle spasms, skin reactions, uterine cramps, vaginal haemorrhage, vomiting, vulvovaginal disorders.
- Uncommon: Appetite increased, dyslipidaemia, insomnia, lactation disorders, oedema, photosensitivity reaction, sexual dysfunction.
- Rare or very rare: Embolism and thrombosis, gallbladder disorders, genital discharge, neoplasms, stroke, swelling.
- Frequency not known: Anger, angioedema, cervical dysplasia, colitis, contact lens intolerance, erythema nodosum, hepatic disorders, hyperglycaemia, intracranial haemorrhage, myocardial infarction, pulmonary artery thrombosis, taste altered.

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**DIRECTIONS FOR ADMINISTRATION**

Adhesives or bandages should not be used to hold patch in place. If no longer sticky do not reapply but use a new patch.

**Changing to a transdermal combined hormonal contraceptive**

**Changing from combined oral contraception**

Apply patch on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last active tablet, rule out pregnancy before applying first patch. Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days.

**Changing from progestogen-only method**

- from an implant, apply first patch on the day implant is removed
- from an injection, apply first patch when next injection is due
- from oral progestogen, first patch may be applied on any day after stopping pill

For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

**After childbirth (not breast-feeding)**

Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days.

**After abortion or miscarriage**

Before 20 weeks’ gestation start immediately; no additional contraception required if started immediately. After 20 weeks’ gestation start on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days after applying the patch.

**PATIENT AND CARER ADVICE**

Patients and carers should be given advice on how to administer patches. Travel Women using patches are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

**Missed doses**

**Delayed application or detached patch**

If a patch is partly detached for less than 24 hours, reapply to the same site or replace with a new patch immediately; no additional contraception is needed and the next patch should be applied on the usual ‘change day’. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached, then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new ‘Day 1’; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch should be applied as soon as remembered giving a new ‘Day 1’; additional non-hormonal methods of contraception should be used for the first 7 days of the new cycle. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch ‘change day’ remains the same and no additional contraception is required;
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new ‘Day 1’; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual ‘change day’, the day after day 28; no additional contraception is required.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 48/03

The Scottish Medicines Consortium has advised (September 2003) that Evra™ patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Transdermal patch**

- Evra (Janssen-Cillag Ltd)
- Ethinylestradiol 33.9 microgram per 24 hour, Norelgestromin 203 microgram per 24 hour Evra transdermal patches | 9 patch (PO) £13.51 DT + £13.51

**Ethinylestradiol with norethisterone**

**INDICATIONS AND DOSE**

Contraception with 21-day combined preparations

- Menstrual symptoms with 21-day combined preparations
  - BY MOUTH
    - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.

**INTERACTIONS**

Appendix 1: combined hormonal contraceptives

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Ethinylestradiol with norethisterone (Non-proprietary)
- Ethinylestradiol 35 microgram, Norethisterone 500 microgram Ethinylestradiol 35 microgram / Norethisterone 500 microgram tablets | 5 tablet (PO) N
- Ethinylestradiol 35 microgram, Norethisterone 750 microgram Ethinylestradiol 35 microgram / Norethisterone 750 microgram tablets | 21 tablet (PO) N
- Ethinylestradiol 35 microgram, Norethisterone 1 mg Ethinylestradiol 35 microgram / Norethisterone 1 mg tablets | 9 tablet (PO) N
- Brevinor (Pfizer Ltd)
  - Ethinylestradiol 35 microgram, Norethisterone 500 microgram Brevinor 500 microgram tablets | 63 tablet (PO) £1.99 DT + £1.99
- Loestrin 20 (Galen Ltd)
  - Ethinylestradiol 20 microgram, Norethisterone acetate 1 mg Loestrin 20 tablets | 63 tablet (PO) £2.70 DT + £2.70
- Loestrin 30 (Galen Ltd)
  - Ethinylestradiol 30 microgram, Norethisterone acetate 1.5 mg Loestrin 30 tablets | 63 tablet (PO) £3.90 DT + £3.90
- Norinon (Pfizer Ltd)
  - Ethinylestradiol 35 microgram, Norethisterone 1 mg Norinon 1 mg tablets | 63 tablet (PO) £2.28 DT + £2.28

**Ethinylestradiol with norgestimrate**

**INDICATIONS AND DOSE**

Contraception with 21-day combined preparations

- Menstrual symptoms with 21-day combined preparations
  - BY MOUTH
    - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.
802 Contraception

The 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day

- **INTERACTIONS** → Appendix 1: combined hormonal contraceptives
- **SIDE-EFFECTS**
  - **Common or very common** Anxiet... palpitations... vertigo
  - **Rare or very rare** Hepatic disorders... photosensitivity reaction... vertigo
  - **Frequency not known** Angioedema... anxiety... dyspepsia... depression... vertigo
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Cilest (Janssen-Cilag Ltd)
      - 250 microgram tablet
    - Cilique (Consilient Health Ltd)
      - 250 microgram tablet
    - Lizina (Morningside Healthcare Ltd)
      - 250 microgram tablet

Norethisterone with mestranol

- **INDICATIONS AND DOSE**
  - Contraception | Menstrual symptoms
    - **By Mouth**
      - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding can occur during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at the same time each day
- **INTERACTIONS** → Appendix 1: combined hormonal contraceptives
- **SIDE-EFFECTS** Appetite change... dizziness... gastrointestinal disorder... libido disorder... metabolic disorders... uterine leiomyoma exacerbated
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Norinyl-1 (Pfizer Ltd)
      - Mestranol 50 microgram, Norethisterone 1 mg tablet

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3.2 Contraception, devices

Other drugs used for Contraception, devices

Levonorgestrel, p. 806

CONTRACEPTIVE DEVICES

**Intra-uterine contraceptive devices (copper)**

- **INDICATIONS AND DOSE**
  - Contraception
    - **By intra-uterine administration**
      - Females of childbearing potential: (consult product literature)
  - **IMPORTANT SAFETY INFORMATION**
    - MHRA/CHM advice (June 2015) INTRA-UTERINE CONTRACEPTION: UTERINE PERFORATION—UPDATED INFORMATION ON RISK FACTORS
      - Uterine perforation most often occurs during insertion, but might not be detected until sometime later. The risk of uterine perforation is increased when the device is inserted up to 36 weeks postpartum or in patients who are breastfeeding. Before inserting an intra-uterine contraceptive device, inform patients that perforation occurs in approximately 1 in every 1000 insertions and symptoms include:
        - severe pelvic pain after insertion (worse than period cramps);
        - pain or increased bleeding after insertion which continues for more than a few weeks;
        - sudden changes in periods;
        - pain during intercourse;
        - unable to feel the threads.
      - Patients should be informed on how to check their threads and to arrange a check-up if threads cannot be felt, especially if they also have significant pain. Partial perforation may occur even if the threads can be seen; consider this if there is severe pain following insertion and perform an ultrasound.

- **CONTRA-INDICATIONS** Active trophoblastic disease (until return to normal of urine and plasma-gonadotrophin concentration) · distorted uterine cavity · established or marked immunosuppression · genital malignancy · medical diathesis · pelvic inflammatory disease · recent sexually transmitted infection (if not fully investigated and treated) · severe anaemia · small uterine cavity · unexplained uterine bleeding · Wilson’s disease
- **CAUTIONS** Anaemia · anticoagulant therapy (avoid if possible) · diabetes · disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression) · drug-induced immunosuppression (risk of infection—avoid if marked immunosuppression) · endometriosis · epilepsy (risk of seizure at time of insertion) · fertility problems · history of pelvic inflammatory disease · increased risk of expulsion if inserted before uterine involution · menorrhagia (progestogen intra-uterine system might be preferable) · nulliparity · severe cervical stenosis · severe primary dysmenorrhoea · severely scarred uterus (including after endometrial resection) · young age

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**Contraception, devices**

Levonorgestrel, p. 806
and the intra-uterine device is removed after day 3 of the menstrual cycle.

- **Risk of infection** The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:
  - they are under 25 years old or
  - they are over 25 years old and
    - have a new partner or
    - have had more than one partner in the past year or
    - their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, *Neisseria gonorrhoeae*) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days.

- **SIDE-EFFECTS** Device complications - epilepsy (on insertion) - haemorrhage (on insertion) - hypersensitivity - menstrual cycle irregularities - pain (on insertion) - pelvic infection exacerbated - pre-sycope (on insertion) - uterine injuries

**SIDE-EFFECTS, FURTHER INFORMATION** Advise the patient to seek medical attention promptly in case of significant symptoms—very small risk of uterine perforation, ectopic pregnancy and pelvic inflammatory disease.

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if patient has a copper allergy.

- **PREGNANCY** If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Remove device; if pregnancy occurs, increased likelihood that it may be ectopic.

- **BREAST FEEDING** Not known to be harmful.

- **MONITORING REQUIREMENTS** Gynaecological examination before insertion, 6–8 weeks after insertion, then annually.

- **DIRECTIONS FOR ADMINISTRATION** The timing and technique of fitting an intra-uterine device are critical for its subsequent performance. The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling backed, where available, by the patient information leaflet. Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - **TT380® SLIMLINE** For uterine length 6.5–9 cm; replacement every 10 years.
  - **LOAD® 375** For uterine length over 7 cm; replacement every 5 years.
  - **NOVAPLUS T 380® AG ‘Mini’** size for minimum uterine length 5 cm; ‘Normal’ size for uterine length 6.5–9 cm; replacement every 5 years.
  - **MULTILOAD® CU375** For uterine length 6–9 cm; replacement every 5 years.
  - **GYNEFLEX®** Suitable for all uterine sizes; replacement every 5 years.
  - **UT380 STANDARD®** For uterine length 6.5–9 cm; replacement every 5 years.
  - **UT380 SHORT®** For uterine length 5–7 cm; replacement every 5 years.
  - **MULTI-SAFE® 375** For uterine length 6–9 cm; replacement every 5 years.
  - **ANCORA® 375 CU** For uterine length over 6.5 cm; replacement every 5 years.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Intra-uterine contraceptive device**

- **Intra-uterine contraceptive devices** (R.F. Medical Supplies Ltd, Farla Medical Ltd, Durbin Plc, Williams Medical Supplies Ltd, Bayer Plc, Organon Laboratories Ltd)
- Copper T380 A intra-uterine contraceptive device | 1 device £8.95
- Steriload intra-uterine contraceptive device | 1 device £8.65
- Load 375 intra-uterine contraceptive device | 1 device £8.52
- Novaplus T 380 Ag intra-uterine contraceptive device mini | 1 device £12.50
- T-Safe 380A QL intra-uterine contraceptive device | 1 device £10.55
- UT380 Standard intra-uterine contraceptive device | 1 device £11.22
- Novaplus T 380 intra-uterine contraceptive device | 1 device £15.20
- Flexi-T 380 intra-uterine contraceptive device | 1 device £10.06
- Mini TT380 Slimline intra-uterine contraceptive device | 1 device £12.46
- Flexi-T 300 intra-uterine contraceptive device | 1 device £9.47
- Multi-Safe 375 intra-uterine contraceptive device | 1 device £8.96
- Multiload Cu375 intra-uterine contraceptive device | 1 device £9.24
- Optima Tcu 380A intra-uterine contraceptive device | 1 device £9.65
- Novaplus T 380 Ag intra-uterine contraceptive device normal | 1 device £12.50
- GyneFix intra-uterine contraceptive device | 1 device £27.11
- Novaplus T 380 Cu intra-uterine contraceptive device mini | 1 device £10.95
- TT380 Slimline intra-uterine contraceptive device | 1 device £12.46
- Ancora 375 Cu intra-uterine contraceptive device | 1 device £7.95
- Novaplus T 380 Cu intra-uterine contraceptive device normal | 1 device £10.95
- Neo-Safe T380 intra-uterine contraceptive device | 1 device £13.40
- UT380 Short intra-uterine contraceptive device | 1 device £11.22

**Silicone contraceptive pessaries**

- **SILICONE CONTRACEPTIVE PESSARIES**
  - FemCap 22mm (Durbin Plc)
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part IXa)
  - FemCap 26mm (Durbin Plc)
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part IXa)
  - FemCap 30mm (Durbin Plc)
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part IXa)

**Other drugs used for Contraception, emergency**

**Intra-uterine contraceptive devices (copper)**, p. 802
- Levonorgestrel, p. 806
PROGESTERONE RECEPTOR MODULATORS

Ulipristal acetate

**DRUG ACTION** Ulipristal acetate is a progesterone receptor modulator with a partial progesterone antagonist effect.

**INDICATIONS AND DOSE**
- Pre-operative treatment of moderate to severe symptoms of uterine fibroids (initiated by a specialist)
  - **BY MOUTH**
  - Adult: 5 mg once daily for up to 3 months starting during the first week of menstruation
- Intermittent treatment of moderate to severe symptoms of uterine fibroids if surgery not appropriate (initiated by a specialist)
  - **BY MOUTH**
  - Adult: 5 mg once daily for up to 3 months starting during the first week of menstruation, treatment course may be repeated if necessary; re-treatment should start no sooner than during the first week of the second menstruation following completion of the previous course; maximum 4 courses

**EMERGENCY CONTRACEPTION**
- **BY MOUTH**
- Females of childbearing potential: 30 mg for 1 dose, to be taken as soon as possible after coitus, but no later than after 120 hours

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: ESMYA® (ULIPRISTAL ACETATE) FOR SYMPTOMS OF UTERINE FIBROIDS: RESTRICTIONS TO USE AND REQUIREMENT TO CHECK LIVER FUNCTION BEFORE, DURING AND AFTER TREATMENT (AUGUST 2018)

Rare but serious cases of liver injury, including cases of hepatic failure requiring liver transplantation, have been reported worldwide in women treated with **Esmya**® for the symptoms of uterine fibroids. An EU review of the available data concluded that **Esmya**® may have contributed to the onset of some of the cases of serious liver injury and has now finalised with a number of measures to minimise this risk. In particular, more than one treatment course is now authorised only in women who are not eligible for surgery, and liver function monitoring is to be carried out in all women treated with **Esmya**®. See Monitoring requirements for further information.

**CONTRA-INDICATIONS**
- When used for uterine fibroids Breast cancer - cervical cancer - ovarian cancer - undiagnosed vaginal bleeding - uterine cancer - vaginal bleeding not caused by uterine fibroids

**CAUTIONS**
- Uncontrolled severe asthma

**INTERACTIONS** → Appendix 1: ulipristal

**SIDE-EFFECTS**
- Common or very common Back pain; breast tenderness; dizziness; fatigue; gastrointestinal discomfort; headaches; menstrual cycle irregularities; mood altered; myalgia; nausea; pelvic pain; vomiting
- Uncommon Anxiety; appetite disorder; chills; concentration impaired; diarrhoea; drowsiness; dry mouth; fever; flatulence; hot flush; increased risk of infection; insomnia; libido disorder; malaise; skin reactions; vision disorders; vulvovaginal disorders
- Rare or very rare Abnormal sensation in eye; disorientation; dry throat; eye erythema; genital pruritus; ovarian cyst ruptured; painful sexual intercourse; syncope; taste altered; thirst; tremor; vertigo
- Frequency not known Hepatic disorders

**CONCEPTION AND CONTRACEPTION** When ulipristal is given for uterine fibroids non-hormonal contraceptive methods (barrier methods or intra-uterine device) should be used both during treatment and for 12 days after stopping, if required.

**PREGNANCY**
- When used for Emergency contraception Limited information available—if pregnancy occurs, manufacturer advises report to the ellaOne® pregnancy registry.
- When used for Uterine fibroids Manufacturer advises avoid—limited information available.

**BREAST FEEDING**
- When used for Emergency contraception Manufacturer advises avoid for 1 week after administration—present in milk.
- When used for Uterine fibroids Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- When used for Emergency contraception Manufacturer advises avoid in severe impairment (no information available).
- When used for Uterine fibroids Manufacturer advises avoid (no information available).

**RENAI IMPAIRMENT**
- When used for Uterine fibroids Manufacturer advises avoid in severe impairment unless patient is closely monitored—no information available.

**MONITORING REQUIREMENTS**
- When used for Uterine fibroids Manufacturer advises perform liver function tests before treatment initiation—do not initiate if transaminases exceed 2 times the upper limit of normal. During the first 2 treatment courses, monitor liver function monthly; for further treatment courses, perform liver function tests once before each new treatment course and when clinically indicated. At the end of each treatment course, perform liver function tests after 2–4 weeks. Discontinue treatment if serum transaminases exceed 3 times the upper limit of normal and closely monitor patient. Manufacturer advises periodic monitoring of the endometrium following repeated intermittent treatment.

**PRESCRIBING AND DISPENSING INFORMATION** The manufacturer of **Esmya**® has provided a Physician’s Guide to Prescribing **Esmya**®.

**PATIENT AND CARER ADVICE**
- When used for Emergency contraception When prescribing or supplying hormonal emergency contraception, manufacturer advises women should be told:
  - if vomiting occurs within 3 hours of taking a dose, a replacement dose should be taken;
  - that their next period may be early or late;
  - to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy.
- The Faculty of Sexual and Reproductive Healthcare also advises women should be told:
  - that a barrier method of contraception needs to be used—see Emergency contraception p. 794 for further information;
  - that a pregnancy test should be performed if the next menstrual period is delayed by more than 7 days, is lighter than usual, or is associated with abdominal pain that is not typical of the woman’s usual dysmenorrhoea;
  - that a pregnancy test should be performed if hormonal contraception is started soon after use of emergency contraception even if they have bleeding; bleeding associated with the contraceptive method may not represent menstruation.
- When used for Uterine fibroids Before initiation of **Esmya**®, the MHRA advises that women are informed of the rare risk of liver damage and the need for liver function testing. Women should also be advised to seek urgent medical attention if they develop any symptoms or signs of liver injury (such as unusual tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
3.4 Contraception, oral progestogen-only

Other drugs used for Contraception, oral progestogen-only
Norethisterone, p. 764

PROGESTOGENS
Desogestrel

INDICATIONS AND DOSE
Contraception
BY MOUTH
Females of childbearing potential: 75 micrograms daily, dose to be taken at the same time each day, starting on day 1 of cycle then continuously, if administration delayed for 12 hours or more it should be regarded as a 'missed pill'.

CONTRA-INDICATIONS
Acute porphyrias p. 1058, history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable, severe arterial disease, undiagnosed vaginal bleeding

CAUTIONS
Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice, arterial disease, functional ovarian cysts, history of jaundice in pregnancy—malabsorption syndromes, past ectopic pregnancy, sex-steroid dependent cancer, systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

CAUTIONS, FURTHER INFORMATION
Other conditions The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.

INTERACTIONS
Appendix 1: desogestrel

SIDE-EFFECTS
Common or very common
Breast abnormalities—depressed mood—headache—libido decreased—menstrual cycle irregularities—mood altered—nausea—skin reactions—weight increased

Uncommon
Allopia—contact lens intolerance—fatigue—ovarian cyst—vomiting—vulvovaginal infection

Rare or very rare
Erythema nodosum

Frequency not known
Angioedema—embolism and thrombosis—neoplasms

SIDE-EFFECTS, FURTHER INFORMATION
The benefits of using progestogen-only contraceptives (POCs), such as desogestrel, should be weighed against the possible risks for each individual woman.

There is a small increase in the risk of having breast cancer diagnosed in women using a combined oral contraceptive pill (COC); this relative risk may be due to an earlier diagnosis, biological effects of the pill or a combination of both. This increased risk is related to the age of the woman using the COC rather than the duration of use and disappears gradually within 10 years after discontinuation.

The risk of breast cancer in users of POCs is possibly of similar magnitude as that associated with COCs, however the evidence is less conclusive.

Available evidence does not support an association between the use of a progestogen-only contraceptive pill and breast cancer. Any increased risk is likely to be small and reduces gradually during the 10 years after stopping; there is no excess risk 10 years after stopping. The older age at which the contraceptive is stopped appears to have a greater influence on increased risk rather than the duration of use.

PREGNANCY
Not known to be harmful.

BREAST FEEDING
Progestogen-only contraceptives do not affect lactation.

HEPATIC IMPAIRMENT
Caution in severe liver disease and recurrent cholestatic jaundice. Avoid in liver tumour.

PATIENT AND CARER ADVICE
Surgery All progestogen-only contraceptives are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Starting routine
One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 12 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if desogestrel is started up to and including day 5 of the menstrual cycle; if started after this time, additional contraceptive precautions are required for 2 days.

Changing from a combined oral contraceptive Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth
Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

Diarrhoea and vomiting
Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking desogestrel, another pill should be taken as soon as possible. If a replacement pill is not taken within 12 hours of the normal time for taking desogestrel, or in cases of persistent vomiting or severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

Missed doses
The following advice is recommended: ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 12 hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days’.

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more tablets are missed or taken more than 12 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.
Levonorgestrel

29-Oct-2018

INDICATIONS AND DOSE

Emergency contraception

BY MOUTH

- Females of childbearing potential: 1.5 mg for 1 dose, taken as soon as possible after coitus, preferably within 12 hours and no later than after 72 hours (may also be used between 72–96 hours after coitus but efficacy decreases with time), alternatively 3 mg for 1 dose, taken as soon as possible after coitus, preferably within 12 hours and no later than after 72 hours (may also be used between 72–96 hours after coitus but efficacy decreases with time). Higher dose should be considered for patients with body-weight over 70 kg or BMI over 26 kg/m².

Contraception

BY MOUTH

- Females of childbearing potential: 30 micrograms daily starting on day 1 of the cycle then continuously, dose is to be taken at the same time each day, if administration delayed for 3 hours or more it should be regarded as a ‘missed pill’.

BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement (additional precautions (e.g. barrier methods) advised for at least 7 days before), or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately following termination of pregnancy below 24 weeks’ gestation; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years.

BY INTRA-UTERINE DEVICES

BY INTRA-UTERINE DEVICE

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement (additional precautions (e.g. barrier methods) advised for at least 7 days before), or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately following termination of pregnancy below 24 weeks’ gestation; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years.

PREVENTION OF ENDOMETRIAL HYPERPLASIA DURING OESTROGEN REPLACEMENT THERAPY

- Females of childbearing potential: Insert during last days of menstruation or withdrawal bleeding or at any time if amenorrhoeic; effective for 4 years.

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- When used orally as an emergency contraceptive, the effectiveness of levonorgestrel is reduced in women taking enzyme-inducing drugs (and for up to 4 weeks after stopping); a copper intra-uterine device should preferably be used instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose; pregnancy should be excluded following use, and medical advice sought if pregnancy occurs.
- There is no need to increase the dose for emergency contraception if the patient is taking antibiotics that are not enzyme inducers.
- With the progesterone-only intra-uterine device, levonorgestrel is released close to the site of the main

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SNC No. 36/03

The Scottish Medicines Consortium has advised (September 2003) that Cerazette® should be restricted for use in women who cannot tolerate oestrogen-containing contraceptives or in whom such preparations are contra-indicated.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Desogestrel (Non-proprietary)
  - Desogestrel 75 microgram: Desogestrel 75microgram tablets, 84 tablet [PPI] £3.50 DT = £2.44
  - Alaza (Besins Healthcare (UK) Ltd)
  - Desogestrel 75 microgram: Alaza 75microgram tablets, 84 tablet [PPI] £5.21 DT = £2.44
  - Cerazette (Merck Sharp & Dohme Ltd)
  - Desogestrel 75 microgram: Cerazette 75microgram tablets, 84 tablet [PPI] £9.55 DT = £2.44
  - Cereill (Consilent Health Ltd)
  - Desogestrel 75 microgram: Cereill 75microgram tablets, 84 tablet [PPI] £3.50 DT = £2.44
  - Desogestrel 75 microgram: Desogestrel 75microgram tablets, 84 tablet [PPI] £6.50 DT = £2.44
  - Desorex (Somex Pharma)
  - Desogestrel 75 microgram: Desorex 75microgram tablets, 84 tablet [PPI] £2.99 DT = £2.44
  - Feanolla (Lupin Healthcare (UK) Ltd)
  - Desogestrel 75 microgram: Feanolla 75microgram tablets, 84 tablet [PPI] £3.42 DT = £2.44
  - Moonia (Stragen UK Ltd)
  - Desogestrel 75 microgram: Moonia 75microgram tablets, 84 tablet [PPI] £6.50 DT = £2.44 (Hospital only)
  - Zellera (Morningside Healthcare Ltd)
  - Desogestrel 75 microgram: Zellera 75microgram tablets, 84 tablet [PPI] £2.98 DT = £2.44

Contraception

BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement (additional precautions (e.g. barrier methods) advised for at least 7 days before), or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately following termination of pregnancy below 24 weeks’ gestation; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years.

BY INTRA-UTERINE DEVICES

KYLEENA® 19.5MG INTRA-UTERINE DEVICE

Contraception

- BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement (additional precautions (e.g. barrier methods) advised for at least 7 days before), or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately following termination of pregnancy below 24 weeks’ gestation; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years.

LEVOSERT® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE

Contraception

- BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement (additional precautions (e.g. barrier methods) advised for at least 7 days before), or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately following termination of pregnancy below 24 weeks’ gestation; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 4 years.

MIRENA® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE

Contraception

- BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert during last days of menstruation or withdrawal bleeding or at any time if amenorrhoeic; effective for 4 years.

PREVENTION OF ENDOMETRIAL HYPERPLASIA DURING OESTROGEN REPLACEMENT THERAPY

- BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert during last days of menstruation or withdrawal bleeding or at any time if amenorrhoeic; effective for 4 years.

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- When used orally as an emergency contraceptive, the effectiveness of levonorgestrel is reduced in women taking enzyme-inducing drugs (and for up to 4 weeks after stopping); a copper intra-uterine device should preferably be used instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose; pregnancy should be excluded following use, and medical advice sought if pregnancy occurs.

- There is no need to increase the dose for emergency contraception if the patient is taking antibiotics that are not enzyme inducers.

- With the progesterone-only intra-uterine device, levonorgestrel is released close to the site of the main

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contraceptive action (on cervical mucus and endometrium) and therefore progestogenic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen–only intra-uterine system and additional contraceptive precautions are not required.

- **UNLICENSED USE**
  - With intra-uterine use The Faculty of Sexual and Reproductive Healthcare (FSRH) advises levonorgestrel is used as detailed below, although these situations are considered unlicensed:
    - Insertion at any time if reasonably certain the woman is not pregnant or at risk of pregnancy;
    - Additional precautions (e.g. barrier methods) for at least 7 days before replacement even if immediate replacement is intended;
    - Insertion immediately following termination of pregnancy below 24 weeks’ gestation;
    - Postpartum insertions 4 weeks after delivery.
  - With oral use The FSRH advises levonorgestrel is used as detailed below, although these situations are considered unlicensed:
    - Higher dose option for emergency contraception in patients with body-weight over 70 kg or BMI over 26 kg/m²;
    - Use for emergency contraception between 72–96 hours after coitus.
  - With intra-uterine use or oral use in children Consult product literature for licensing status of individual preparations.

- **IMPORTANT SAFETY INFORMATION**
  **MHRA/CHM ADVICE (JUNE 2015) INTRA-UTERINE CONTRACEPTION: UTERINE PERFORATION—UPDATED INFORMATION ON RISK FACTORS**
  Uterine perforation most often occurs during insertion, but might not be detected until sometime later. The risk of uterine perforation is increased when the device is inserted up to 36 weeks postpartum or in patients who are breastfeeding. Before inserting an intra-uterine contraceptive device, inform patients that perforation occurs in approximately 1 in every 1000 insertions and signs and symptoms include:
  - Severe pelvic pain after insertion (worse than period cramps);
  - Pain or increased bleeding after insertion which continues for more than a few weeks;
  - Sudden changes in periods;
  - Pain during intercourse;
  - Unable to feel the threads.
  Patients should be informed on how to check their threads and to arrange a check-up if threads cannot be felt, especially if they also have significant pain. Partial perforation may occur even if the threads can be seen; consider this if there is severe pain following insertion and perform an ultrasound.

- **CONTRA-INDICATIONS**
  - With intra-uterine use Active porphyrias p. 1058
  - When used for contraception with oral use for contraception history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable - severe arterial disease - undiagnosed vaginal bleeding

- **CAUTIONS**
  **GENERAL CAUTIONS** Risk factors for ectopic pregnancy (including previous ectopic pregnancy, tubal surgery or pelvic infection)
  **SPECIFIC CAUTIONS**
  - With intra-uterine use Disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression) - acute venous thromboembolism (consider removal) - anemia - anticoagulant therapy (avoid if possible) - diabetes - drug-induced immunosuppression (risk of infection—avoid if marked immunosuppression) - endometriosis - epilepsy - risk of seizure at time of insertion) - fertility problems - history of pelvic inflammatory disease - increased risk of expulsion if inserted before uterine involution - jaundice (consider removal) - marked increase of blood pressure (consider removal) - migraine (consider removal) - nulliparity - severe arterial disease (consider removal) - severe cervical stenosis - severe headache (consider removal) - severe primary dysmenorrhea - severely scarred uterus (including after endometrial resection) - young age
  - When used for contraception with oral use for contraception active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - arterial disease - functional ovarian cysts - history of jaundice in pregnancy - malabsorption syndromes - past ectopic pregnancy - sex-steroid dependent cancer - systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies
  - When used for emergency contraception with oral use for emergency contraception active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - arterial disease - functional ovarian cysts - history of jaundice in pregnancy - malabsorption syndromes - past ectopic pregnancy - sex-steroid dependent cancer - systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

- **CAUTIONS, FURTHER INFORMATION**
  - With intra-uterine use The Faculty of Sexual and Reproductive Healthcare advises intercourse should be avoided or another method of contraception used for at least 7 days before removal of intra-uterine device—emergency contraception may need to be considered if recent intercourse has occurred and the intra-uterine device is removed.
  - Risk of infection with intra-uterine devices The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:
    - They are under 25 years old or
    - They are over 25 years old and
    - Have a new partner or
    - Have had more than one partner in the past year or
    - Their regular partner has other partners.
  In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days.
  - Use as a contraceptive in co-morbidities
  - With oral use The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.
MIRENA® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE
Advanced uterine atrophy

INTERACTIONS
Appendix 1: levonorgestrel

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Common or very common: Gastrointestinal discomfort, headaches, menstrual cycle irregularities, nausea, skin reactions.

SPECIFIC SIDE-EFFECTS
- Common or very common:
  - With intra-uterine use: Back pain, breast abnormalities, depression, device expulsion, hirsutism, increased risk of infection, libido decreased, nervousness, ovarian cyst, pelvic disorders, uterine haemorrhage (on insertion), vaginal haemorrhage (on insertion), vulvovaginal disorders, weight increased.
  - With oral use: Breast tenderness, diarrhoea, dizziness, fatigue, haemorrhage, vomiting.
- Uncommon:
  - With intra-uterine use: Alopecia, endometritis, oedema, uterine rupture.
- Rare or very rare:
  - With oral use: Face oedema, pelvic pain.
- Frequency not known:
  - With oral use: Cerebrovascular insufficiency, depressed mood, diabetes mellitus, embolism and thrombosis, neoplasms, sexual dysfunction, weight changes.

SIDE-EFFECTS, FURTHER INFORMATION

Breast cancer: There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 6 months.

With intra-uterine use: There is no evidence of an association between the levonorgestrel intra-uterine system and breast cancer. The levonorgestrel intra-uterine system should be avoided in patients with a history of breast cancer; any consideration of its use should be by a specialist in contraception and in consultation with the patients cancer specialist.

Patients should be informed about the device that has been inserted and when it should be removed or replaced (including referring them to a patient information leaflet and other sources of information).

Patients may experience irregular, prolonged or infrequent menstrual bleeding in the 3–6 months following insertion; bleeding pattern improves with time but persists in some patients.

Progestogenic side-effects resolve with time (after the first few months).

PREGNANCY
- With oral use: Not known to be harmful.
- With intra-uterine use: If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Avoid; if pregnancy occurs remove intra-uterine system.

BREAST FEEDING
Progestogen-only contraceptives do not affect lactation.

HEPATIC IMPAIRMENT
- With intra-uterine use or oral use for Contraception in adults: Manufacturer advises avoid in liver tumour.
- With oral use for Contraception or Emergency contraception: Manufacturer advises avoid in severe impairment.
- With intra-uterine use: Manufacturer advises avoid in severe impairment—no information available; avoid in acute hepatic disease.

MONITORING REQUIREMENTS
- With intra-uterine use: Gynaecological examination before insertion, 4–6 weeks after insertion, then annually.

DIRECTIONS FOR ADMINISTRATION
- With intra-uterine use: The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

PRESCRIBING AND DISPENSING INFORMATION
- With intra-uterine use: Levonorgestrel-releasing intra-uterine devices vary in licensed indication, duration of use and insertion technique—the MHRA recommends to prescribe and dispense by brand name to avoid inadvertent switching.

PATIENT AND CARER ADVICE

Diarrhoea and vomiting with use as an oral contraceptive: Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

Starting routine:
- With oral use for Contraception: One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not required if levonorgestrel is started up to and including day 5 of the menstrual cycle; if started after this time, additional contraceptive precautions are required for 2 days. Changing from a combined oral contraceptive: Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth: Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

With oral use for Emergency contraception: When prescribing or supplying hormonal emergency contraception, manufacturer advises women should be told:
- if vomiting occurs within 3 hours, a replacement dose should be taken;
- that their next period may be early or late;
- to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy.

The Faculty of Sexual and Reproductive Healthcare also advises women should be told:
- that a barrier method of contraception needs to be used—see Emergency contraception p. 794 for further information;
- that a pregnancy test should be performed if the next menstrual period is delayed by more than 7 days, is lighter than usual, or is associated with abdominal pain that is not typical of the woman’s usual dysmenorrhoea;
- that a pregnancy test should be performed if hormonal contraception is started soon after use of emergency contraception even if they have bleeding; bleeding associated with the contraceptive method may not represent menstruation.
- With intra-uterine use: Counsel women on the signs, symptoms and risks of perforation and ectopic pregnancy.

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Missed doses When used as an oral contraceptive, the following advice is recommended: ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days’.

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

- NATIONAL FUNDING/ACCESS DECISIONS
  - Scottish Medicines Consortium (SMC) decisions
    - SMC No. 1299/18
      - The Scottish Medicines Consortium has advised (February 2018) that levonorgestrel (Kyleena\textsuperscript{®}) is accepted for use within NHS Scotland as a contraceptive device for up to 5 years.
    - All Wales Medicines Strategy Group (AWMSG) decisions
      - AWMSG No. 3582
      - The All Wales Medicines Strategy Group has advised (September 2018) that levonorgestrel (Kyleena\textsuperscript{®}) is recommended as an option for use within NHS Wales for contraception for up to five years.

- EXCEPTIONS TO LEGAL CATEGORY
  - Levonelle\textsuperscript{®} One Step can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Intra-uterine device
    - Jaydess (Bayer Plc)
      - Levonorgestrel 15.5 mg
      - Kyleena (Bayer Plc)
        - Levonorgestrel 19.5 mg
      - Levonorgestrel 20 microgram per 24 hour
        - Levonorgestrel 20 microgram per 24 hour
          - Mirena (Bayer Plc)

- Tablet
  - Levonorgestrel (Non-proprietary)
    - Levonorgestrel 1.5 mg
      - Levonorgestrel 1.5mg tablets
      - Emeress (Morningside Healthcare Ltd)
        - Levonorgestrel 1.5 mg
          - Ezinelle (Mylan)
            - Ezinelle 1.5mg tablets

- PROGESTOGENS
  - Etonogestrel
    - INDICATIONS AND DOSE
      - Contraception (no hormonal contraceptive use in previous month)
        - BY SUBDERMAL IMPLANTATION
          - Females of childbearing potential: 1 implant inserted during first 5 days of cycle, implant should be removed within 3 years of insertion
      - Contraception (postpartum)
        - BY SUBDERMAL IMPLANTATION
          - Females of childbearing potential: 1 implant to be inserted 21–28 days after delivery (delay until 28 days postpartum if breast-feeding), implant should be removed within 3 years of insertion
      - Contraception following abortion or miscarriage in the second trimester
        - BY SUBDERMAL IMPLANTATION
          - Females of childbearing potential: 1 implant to be inserted 21–28 days after abortion or miscarriage, implant should be removed within 3 years of insertion
      - Contraception following abortion or miscarriage in the first trimester
        - BY SUBDERMAL IMPLANTATION
          - Females of childbearing potential: 1 implant to be inserted within 5 days after abortion or miscarriage, implant should be removed within 3 years of insertion
      - Contraception (changing from other hormonal contraceptive)
        - BY SUBDERMAL IMPLANTATION
          - Females of childbearing potential: Implant should be removed within 3 years of insertion (consult product literature)

- UNLICENSED USE
  - Nexplanon\textsuperscript{®} not licensed for use in females outside of the age range 18–40 years.

- IMPORTANT SAFETY INFORMATION
  - MHRA/CHM ADVICE (JUNE 2016): NEXPLANON\textsuperscript{®} (ETONOGESTREL) CONTRACEPTIVE IMPLANTS: REPORTS OF DEVICE IN VASCULATURE AND LUNG
    - There have been rare reports of Nexplanon\textsuperscript{®} implants reaching the lung via the pulmonary artery. An implant that cannot be palpated at its insertion site should be located and removed as soon as possible; if unable to locate implant within the arm, the MHRA recommends using chest imaging. Correct subdermal insertion reduces the risk of these events.

- CONTRA-INDICATIONS
  - Acute porphyrias p. 1058 - history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable - severe arterial disease - undiagnosed vaginal bleeding

- CAUTIONS
  - Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - arterial disease - disturbances of lipid metabolism - history during pregnancy of deterioration of otosclerosis - history during pregnancy of pruritus - history of jaundice in pregnancy

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malabsorption syndromes - possible risk of breast cancer - sex-steroi dependent cancer - systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

- **INTERACTIONS** → Appendix 1: etonogestrel
- **SIDE-EFFECTS**
  - Common or very common Abdominal pain - alopecia - anxiety - appetite increased - breast abnormalities - depressed mood - dizziness - emotional lability - fatigue - flatulence - headaches - hot flush - increased risk of infection - influenza like illness - libido decreased - menstrual cycle irregularities - nausea - ovarian cyst - pain - skin reactions - weight changes
  - Uncommon Arthralgia - constipation - diarrhoea - drowsiness - dysuria - fever - galactorrhoea - genital abnormalities - hypertrichosis - insomnia - myalgia - oedema - vomiting - vulvovaginal discomfort
  - Frequency not known Abscess - angioedema - embolism and thrombosis - haemorrhage - insulin resistance - neoplasms - paraesthesia - seborrhoea

**SIDE EFFECTS, FURTHER INFORMATION**
The benefits of using progestogen-only contraceptives (POCs), such as etonogestrel, should be weighed against the possible risks for each individual woman.

There is a small increase in the risk of having breast cancer diagnosed in women using a combined oral contraceptive pill (COC); this relative risk may be due to an earlier diagnosis, biological effects of the pill or a combination of both. This increased risk is related to the age of the woman using the COC rather than the duration of use and disappears gradually within 10 years after discontinuation.

The risk of breast cancer in users of POCs is possibly of similar magnitude as that associated with COCs, however the evidence is less conclusive.

- **PREGNANCY** Not known to be harmful, remove implant if pregnancy occurs.
- **BREAST FEEDING** Progestogen-only contraceptives do not affect lactation.
- **DIRECTIONS FOR ADMINISTRATION** The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.
- **PATIENT AND CARER ADVICE** Full counselling backed by patient information leaflet required before administration.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Implant**
- Nexplanon (Merck Sharp & Dohme Ltd)
  - Etonogestrel 68 mg Nexplanon 68mg implant | 1 device
  - £83.43 DT = £83.43

**Medroxyprogesterone acetate**

- **INDICATIONS AND DOSE**
  - **Dysfunctional uterine bleeding**
    - **BY MOUTH**
    - Adult: 2.5–10 mg daily for 5–10 days, repeated for 2 cycles, begin treatment on day 16–21 of cycle
  - **Secondary amenorrhoea**
    - **BY MOUTH**
    - Adult: 2.5–10 mg daily for 5–10 days, repeated for 3 cycles, begin treatment on day 16–21 of cycle
  - **Mild to moderate endometriosis**
    - **BY MOUTH**
    - Adult: 10 mg 3 times a day for 90 consecutive days, begin treatment on day 1 of cycle

- **Progestogenic opposition of oestrogen HRT**
  - **BY MOUTH**
  - Adult: 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

- **Endometrial cancer | Renal cell cancer**
  - **BY MOUTH**
  - Adult: 200–600 mg daily

- **Breast cancer**
  - **BY MOUTH**
  - Adult: 0.4–1.5 g daily

- **Contraception**
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Females of childbearing potential: 150 mg, to be administered within the first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)
  - **BY SUBCUTANEOUS INJECTION**
    - Females of childbearing potential: 104 mg, to be administered within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding), injected into anterior thigh or abdomen, dose only suitable if no hormonal contraceptive use in previous month

- **Long-term contraception**
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Females of childbearing potential: 150 mg every 12 weeks, first dose to be administered within the first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)
  - **BY SUBCUTANEOUS INJECTION**
    - Females of childbearing potential: 104 mg every 13 weeks, first dose to be administered within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding), injected into anterior thigh or abdomen, dose only suitable if no hormonal contraceptive use in previous month

- **Contraception (when patient changing from other hormonal contraceptive)**
  - **BY SUBCUTANEOUS INJECTION**
    - Females of childbearing potential: (consult product literature)

- **Hot flushes caused by long-term androgen suppression in women with prostate cancer**
  - **BY MOUTH**
  - Adult: 20 mg once daily initially for 10 weeks, evaluate effect at the end of the treatment period

**UNLICENSED USE**

- Medroxyprogesterone acetate is used for the treatment of hot flushes caused by long-term androgen suppression in men, but it is not licensed for this indication.

**CONTRA-INDICATIONS**

- **GENERAL CONTRA-INDICATIONS**
  - Acute porphyrias p. 1058 - severe arterial disease - undiagnosed vaginal bleeding

- **SPECIFIC CONTRA-INDICATIONS**
  - With intramuscular use or subcutaneous use history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable
  - With oral use breast cancer (unless progestogens are being used in the management of this condition) - genital cancer (unless progestogens are being used in the management of this condition) - history of liver tumours

**CAUTIONS**

- **GENERAL CAUTIONS** Possible risk of breast cancer

- **SPECIFIC CAUTIONS** With intramuscular use or subcutaneous use history during pregnancy in disturbances of lipid metabolism - history

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during pregnancy of deterioration of otosclerosis - history during pregnancy of pruritus

- With oral use: Asthma, cardiac dysfunction, conditions that may worsen with fluid retention: diabetes (progestogens can decrease glucose tolerance—monitor patient closely), epilepsy, history of depression, hypertension, migraine, susceptibility to thromboembolism (particular caution with high dose)

- INTERACTIONS → Appendix 1: medroxyprogesterone

- SIDE-EFFECTS

  GENERAL SIDE-EFFECTS

  - Common or very common: Alopecia, breast abnormalities, depression, dizziness, fluid retention, insomnia, menstrual cycle irregularities, nausea, sexual dysfunction, skin reactions, weight changes.


  SPECIFIC SIDE-EFFECTS

  - Common or very common: With oral use, Appetite increased, cervical abnormalities, constipation, fatigue, headache, hyperhidrosis, hypersensitivity, nervousness, oedema, tremor, vomiting.

  - With parenteral use: Anxiety, asthena, gastrointestinal discomfort, headaches, mood altered, pain, vulvovaginal infection.

  - Uncommon: With oral use, Congestive heart failure, corticoid-like effects, diabetes mellitus exacerbated, diarrhoea, dry mouth, euphoric mood, hypercalcaemia.

  - With parenteral use: Appetite abnormal, arthralgia, hot flush, hypertension, ovarian cyst, painful sexual intercourse, uterine haemorrhage, varicose veins, vertigo, vulvovaginal disorders.

  - Rare or very rare: With oral use, Cerebral infarction, jaundice, malaise, myocardial infarction.

  - With parenteral use: Breast cancer, lipodystrophy.

  - Frequency not known: With oral use, Adrenergic-like effects, cataract diabetic, concentration impaired, confusion, glycosuria, palpitations, visual impairment (discontinue if papilloedema or retinal vascular lesions).

  - With parenteral use: Hepatic disorders, osteoporosis, osteoporotic fractures, seizure.

  SIDE-EFFECTS, FURTHER INFORMATION

  - With oral use: In general, side effects may be more common with high doses such as those used in malignant disease.

  - With parenteral use: Reduction in bone mineral density is greater with increasing duration of use. The loss is mostly recovered on discontinuation.

- CONCEPTION AND CONTRACEPTION

  - With intramuscular use: If interval between dose is greater than 12 weeks and 5 days (in long-term contraception), rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection.

  - With subcutaneous use: If interval between dose is greater than 13 weeks and 7 days (in long-term contraception), rule out pregnancy before next injection.

- PREGNANCY

  - With oral use: Avoid—genital malformations and cardiac defects reported.

  - With intramuscular use or subcutaneous use: Not known to be harmful.

- BREAST FEEDING

  - Present in milk—no adverse effects reported. Progestogen-only contraceptives do not affect lactation.

  - With intramuscular use or subcutaneous use: The manufacturers advise that in women who are breast-feeding, the first dose should be delayed until 6 weeks after birth; however, evidence suggests no harmful effect to infant if given earlier. The benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks.

- HEPATIC IMPAIRMENT

  - Avoid in liver tumour.

  - With oral use: Avoid in hepatic impairment.

  - With intramuscular use or subcutaneous use: Caution in severe liver disease and recurrent cholestatic jaundice.

- RENAL IMPAIRMENT

  - When used for mild to moderate endometriosis or Progestogen opposition of oestrogen HRT or Dysfunctional uterine bleeding or Secondary amenorrhea: Use with caution.

- PATIENT AND CARER ADVICE

  - With intramuscular use or subcutaneous use: Full counselling backed by patient information leaflet required before administration—likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility.

- MEDICINAL FORMS

  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

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## 3.6 Contraception, spermicidal

### SPERMICIDALS

#### Nonoxinol

- **INDICATIONS AND DOSE**

  Spermicidal contraceptive in conjunction with barrier methods of contraception such as diaphragms or caps

  - **BY VAGINA**

    - Females of childbearing potential: (consult product literature)

  - **SIDE-EFFECTS**

    Genital erosion, increased risk of HIV infection, pain - paraesthesia - skin reactions - vaginal redness

  **SIDE-EFFECTS, FURTHER INFORMATION**

  High frequency use of the spermicide nonoxinol-9 has been associated with genital lesions, which may increase the risk of acquiring sexually transmitted infections.
4 Erectile and ejaculatory conditions

4.1 Erectile dysfunction

Description of condition
Erectile dysfunction (impotence) is the persistent inability to attain and maintain an erection that is sufficient to permit satisfactory sexual performance. It can have physical or psychological causes. Erectile dysfunction can also be a side-effect of drugs such as antihypertensives, antidepressants, antipsychotics, cytotoxic drugs and recreational drugs (including alcohol).

Risk factors for erectile dysfunction include sedentary lifestyle, obesity, smoking, hypercholesterolaemia and metabolic syndrome. Erectile dysfunction increases the risk of cardiovascular disease. All men with unexplained erectile dysfunction should be evaluated for the presence of cardiovascular risk factors and any identified risk should be addressed.

Drug treatment

The recommended approach for the management of erectile dysfunction is a combination of drug treatment and lifestyle changes (including regular exercise, reduction in body mass index, Smoking cessation p. 497, and reduced alcohol consumption).

An oral phosphodiesterase type-5 inhibitor is the first-line drug treatment for erectile dysfunction, regardless of the cause. These drugs act by increasing the blood flow to the penis. They do not initiate an erection—sexual stimulation is required.

The choice of oral phosphodiesterase type-5 inhibitor depends on the frequency of intercourse and response to treatment. Avanafil below, sildenafil p. 813 and vardenafil p. 816 are short-acting drugs and are suitable for occasional use as required. Tadalafil p. 814 is a longer-acting drug. It can be used as required, but can also be used as a regular lower daily dose to allow for spontaneous (rather than scheduled) sexual activity or in those who have frequent sexual activity. A patient with erectile dysfunction should receive six doses of an individual phosphodiesterase type-5 inhibitor at the maximum dose (with sexual stimulation) before being classified as a non-responder. Patients who fail to respond to the maximum dose of at least two different phosphodiesterase type-5 inhibitors should be referred to a specialist.

Intracavernosal, intraurethral or topical application of alprostadil (prostaglandin E1) p. 816 is recommended as second-line therapy under careful medical supervision. Intracavernosal or intraurethral preparations can also be used to aid diagnosis.

Priapism associated with alprostadil
Manufacturers advise that patients should seek medical help if a prolonged erection lasting four hours or more occurs; application of an ice pack to the upper-inner thigh (alternating between the left and right thighs every two minutes for up to ten minutes) may result in reflex opening of the venous valves. If priapism has lasted more than six hours, treatment should not be delayed; manufacturer advises management as follows:

- Initial therapy by penile aspiration: using aseptic technique, 20–50 mL of blood should be aspirated using a 19–21 gauge butterfly needle inserted into the corpus cavernosum; if necessary the procedure may be repeated on the opposite side;
- Lavage: if initial aspiration is unsuccessful, a second 19–21 gauge butterfly needle can be inserted into the opposite corpus cavernosum; sterile physiological saline can be injected through the first needle and drained through the second;
- If aspiration and lavage of are unsuccessful, intracavernosal injection of a sympathomimetic with action on alpha-adrenergic receptors can be given, with continuous monitoring of blood pressure and pulse—see phentolamine mesilate p. 819 [unlicensed indication], adrenaline/epinephrine p. 818 [unlicensed indication], and metaraminol p. 187 [unlicensed indication]. Extreme caution is required in patients with coronary heart disease, hypertension, cerebral ischaemia and in patients taking a monoamine–oxidase inhibitor (facilities for managing hypertensive crisis should be available when administered to patients taking MAOIs);
- If necessary the sympathomimetic injections can be followed by further aspiration of blood through the same butterfly needle;
- If administration of a sympathomimetic drug is unsuccessful, urgent referral for surgical management is required.

Prescribing on the NHS
Some drug treatments for erectile dysfunction may only be prescribed on the NHS under certain circumstances; for details see the criteria listed in part XVIII of the Drug Tariff (Part XIB of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Health and Personal Social Services for Northern Ireland Drug Tariff: www.hscbusiness.hscni.net/services/2034.htm
Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

Related drugs
Other drugs used for Erectile dysfunction: aviptadil with phenolamine mesilate p. 820.

PHOSPHODIESTERASE TYPE-5 INHIBITORS

Avanafil

- INDICATIONS AND DOSE
  - Erectile dysfunction
    - BY MOUTH
      - Adult: Initially 100 mg, to be taken approximately 15–30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day

www.getintopharma.com
Erectile dysfunction in patients on alpha-blocker therapy

- **BY MOUTH**
- Adult: Initially 50 mg, to be taken approximately 15–30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day

**Dose Adjustments due to Interactions**
- Manufacturer advises max. 100 mg once every 48 hours with concurrent use of moderate inhibitors of CYP3A4.

**Contra-Indications**
- Avoid if systolic blood pressure below 90 mmHg (no information available) - blood pressure >170/100 mmHg - hereditary degenerative retinal disorders - history of non-arteritic anterior ischaemic optic neuropathy - life-threatening arrhythmia in previous 6 months - mild to severe heart failure - patients in whom vasodilatation or sexual activity are inadvisable - recent history of myocardial infarction - recent history of stroke - recent unstable angina

**Caution**
- Active peptic ulceration - anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) - bleeding disorders - cardiovascular disease - left ventricular outflow obstruction - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)

**Interactions**
- Appendix 1: phosphodiesterase type-5 inhibitors

**Side-Effects**
- Common or very common
  - Headaches
  - Nasal complaints
  - Vasodilation
- Uncommon
  - Asthenia
  - Dizziness
  - Drowsiness
  - Dyspnoea
  - Exertional angina
  - Headaches
  - Hypotension
  - Migraine
  - Muscle cramps

**Hepatic Impairment**
- Manufacturer advises avoid in severe impairment.

Dose Adjustments
- Manufacturer advises use lowest effective initial dose in mild to moderate impairment and adjust according to tolerance.

**Renal Impairment**
- Avoid if eGFR less than 30 ml/minute/1.73 m².

**Patient and Carer Advice**
- Onset of effect may be delayed if taken with food.

**National Funding/Access Decisions**

Scottish Medicines Consortium (SMC) decisions
- SMC No. 980/14
  - The Scottish Medicines Consortium has advised (September 2015) that avanafil (Spedra®) is not recommended for use within NHS Scotland, for treatment of erectile dysfunction in men as the clinical and economic analysis presented was not sufficiently robust.

All Wales Medicines Strategy Group (AWMSG) decisions
- AWMSG No. 1261
  - The All Wales Medicines Strategy Group has advised (July 2015) that avanafil (Spedra®) is recommended as an option for use within NHS Wales for the treatment of erectile dysfunction in men.

NHS Restrictions
- Spedra® is not prescribable in NHS primary care for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIIB of the Drug Tariff. The prescription must be endorsed ‘SLS’.

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**Sildenafil**

- **Indications and Dose**
  - Pulmonary arterial hypertension (initiated under specialist supervision)
    - **By Mouth**
      - Adult: 20 mg 3 times a day
    - **By Intravenous Injection**
      - Adult: 10 mg 3 times a day, use intravenous route when the oral route is not appropriate
  - Erectile dysfunction
    - **By Mouth**
      - Adult: Initially 50 mg, to be taken approximately 1 hour before sexual activity, adjusted according to response to 25–100 mg (max. per dose 100 mg) as required, to be taken as a single dose; maximum 1 dose per day

**Digital Ulcers [Associated with Systemic Sclerosis]**
- **By Mouth**
  - Adult: 25 mg 3 times a day, increased to 50 mg 3 times a day

**Dose Adjustments due to Interactions**
- When used for Erectile dysfunction
  - Manufacturer advises a starting dose of 25 mg with concurrent use of moderate and potent inhibitors of CYP3A4. Manufacturer advises if concurrent use of ritonavir is unavoidable, the max. dose should not exceed 25 mg within 48 hours.
  - With oral use for Pulmonary arterial hypertension
    - Manufacturer advises reduce dose to 20 mg twice daily with concurrent use of moderate inhibitors of CYP3A4.
    - Manufacturer advises reduce dose to 20 mg once daily with concurrent use of some potent inhibitors of CYP3A4 (avoid with ketoconazole, itraconazole and ritonavir).
  - With intravenous use for Pulmonary arterial hypertension
    - Manufacturer advises reduce dose to 10 mg twice daily with concurrent use of moderate inhibitors of CYP3A4.
    - Manufacturer advises reduce dose to 10 mg once daily with concurrent use of some potent inhibitors of CYP3A4 (avoid with ketoconazole, itraconazole and ritonavir).

**Unlicensed Use**
- Sildenafil is used for the treatment of digital ulcer, but is not licensed for this indication.

**Contra-Indications**
- General Contra-Indications
  - Hereditary degenerative retinal disorders - history of non-arteritic anterior ischaemic optic neuropathy - recent history of myocardial infarction - recent history of stroke

**Specific Contra-Indications**
- When used for erectile dysfunction
  - Avoid if systolic blood pressure below 90 mmHg (no information available) - patients in whom vasodilatation or sexual activity are inadvisable - recent unstable angina

**Caution**
- General Caution
  - Active peptic ulceration - bleeding disorders - cardiovascular disease - left ventricular outflow obstruction
814 Erectile and ejaculatory conditions

SPECIFIC CAUTIONS
- When used for erectile dysfunction: Anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, Peyronie’s disease) - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukemia)
- When used for pulmonary arterial hypertension: Anatomical deformation of the penis - autonomic dysfunction - hypotension (avoid if systolic blood pressure below 90 mmHg) - intravascular volume depletion - predisposition to priapism - pulmonary veno-occlusive disease

INTERACTIONS
- Appendix A: phosphodiesterase type-5 inhibitors

SIDE-EFFECTS
- When used for pulmonary arterial hypertension
- When used for erectile dysfunction

RARE OR VERY RARE
- Acute coronary syndrome - arteriosclerotic retinopathy - cerebrovascular insufficiency - glaucoma - haematoxylin - hearing impairment - irritability - optic neuropathy (discontinue if sudden visual impairment occurs) - oral hypoaesthesia - priapism - retinal occlusion - scleral discoloration - seizure - severe cutaneous adverse reactions (SCARs) - sudden cardiac death - syncope - throat tightness

PREGNANCY
- Use only if potential benefit outweighs risk—no evidence of harm in animal studies.

BREAST FEEDING
- Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT
- Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

Dose adjustments
- With intravenous use for Pulmonary arterial hypertension: Manufacturer advises if usual dose not tolerated, consider dose reduction to 10 mg twice daily in mild to moderate impairment.
- With oral use for Pulmonary arterial hypertension: Manufacturer advises if usual dose not tolerated, consider dose reduction to 20 mg twice daily in mild to moderate impairment.
- When used for Erectile dysfunction: Manufacturer advises consider initial dose reduction to 25 mg in mild to moderate impairment; adjust according to response.

RENAL IMPAIRMENT
- Dose adjustments: Use initial dose of 25 mg in erectile dysfunction if eGFR less than 30 mL/minute/1.73 m².
- In pulmonary hypertension, if usual dose not tolerated, reduce oral dose to 20 mg twice daily and intravenous dose to 10 mg twice daily.

TREATMENT CESSATION
- When used for Pulmonary arterial hypertension: Consider gradual withdrawal.

PATIENT AND CARER ADVICE
- When used for Erectile dysfunction: Onset of effect may be delayed if taken with food.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (February 2010) that sildenafil tablets (Revatio®) is accepted for restricted use within NHS Scotland and should be initiated for patients with pulmonary arterial hypertension only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

The Scottish Medicines Consortium has advised (March 2011) that sildenafil injection (Revatio®) is accepted for restricted use within NHS Scotland for patients with pulmonary arterial hypertension who are currently prescribed oral sildenafil and are temporarily unable to take oral medicine, and should be prescribed only on the advice of specialists in the Scottish Pulmonary Vascular Unit or the Scottish Adult Congenital Cardiac Service.

NHS restrictions
- Viagra® is not prescribable in NHS primary care for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII of the Drug Tariff (Part XIB of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use the BNF.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
- Sildenafil (Non-proprietary)
  - Sildenafil (as Sildenafil citrate) 20 mg: Sildenafil 20 mg tablets | 90 tablet (P) £46.33 DT = £46.33
  - Sildenafil (as Sildenafil citrate) 25 mg: Sildenafil 25 mg tablets | 4 tablet (P) £16.59 DT = £10.72 | 8 tablet (P) £69.96-£33.19
  - Sildenafil (as Sildenafil citrate) 50 mg: Sildenafil 50 mg tablets | 4 tablet (P) £21.27 DT = £10.71 | 8 tablet (P) £110.64–£42.54
  - Sildenafil (as Sildenafil citrate) 100 mg: Sildenafil 100 mg tablets | 4 tablet (P) £23.50 DT = £10.80 | 8 tablet (P) £144.69–£46.39
  - 12 tablet (P) £39
- Granipiram (Accord Healthcare Ltd)
  - Sildenafil (as Sildenafil citrate) 20 mg: Granipiram 20 mg tablets | 90 tablet (P) £424.01 DT = £464.33

Sildenafil (as Sildenafil citrate) 100 mg: Sildenafil 100 mg tablets | 12 tablet (P) £39
- Myslecard (Mylan)
  - Sildenafil (as Sildenafil citrate) 20 mg: Myslecard 20 mg tablets | 90 tablet (P) £379.38 DT = £464.33

- Revatio (Pfizer Ltd)
  - Sildenafil (as Sildenafil citrate) 20 mg: Revatio 20 mg tablets | 90 tablet (P) £46.33 DT = £46.33
  - Viagia (Pfizer Ltd, Pfizer Consumer Healthcare Ltd)
  - Sildenafil (as Sildenafil citrate) 25 mg: Viagia 25 mg tablets | 4 tablet (P) £16.59 DT = £10.72 | 8 tablet (P) £69.96–£33.19
  - Sildenafil (as Sildenafil citrate) 50 mg: Viagia 50 mg tablets | 4 tablet (P) £21.27 DT = £10.71 | 8 tablet (P) £110.64–£42.54
  - Sildenafil (as Sildenafil citrate) 100 mg: Viagia 100 mg tablets | 4 tablet (P) £23.50 DT = £10.80 | 8 tablet (P) £144.69
  - Vizarsin (Consilient Health Ltd)
  - Sildenafil (as Sildenafil citrate) 25 mg: Vizarsin 25 mg tablets | 4 tablet (P) £13.10 DT = £10.72
  - Sildenafil (as Sildenafil citrate) 50 mg: Vizarsin 50 mg tablets | 4 tablet (P) £18.07 DT = £10.71
  - Sildenafil (as Sildenafil citrate) 100 mg: Vizarsin 100 mg tablets | 4 tablet (P) £19.97 DT = £10.80

Solution for injection
- Revatio (Pfizer Ltd)
  - Sildenafil (as Sildenafil citrate).8 mg per 1 mL: Revatio 10mg/12.5ml solution for injection vials | 1 vial (P) £45.28 (Hospital only)

Oral suspension
- Revatio (Pfizer Ltd)
  - Sildenafil (as Sildenafil citrate) 10 mg per 1 mL: Revatio 10 mg/ml oral suspension sugar-free | 112 ml (P) £186.75 DT = £186.75

Tadalafil

INDICATIONS AND DOSE
- Pulmonary arterial hypertension (initiated under specialist supervision)
  - BY MOUTH
  - Adult: 40 mg once daily

www.getintopharma.com
Erectile dysfunction

BY MOUTH
Adult: Initially 10 mg (max. per dose 20 mg), to be taken at least 30 minutes before sexual activity, subsequent doses adjusted according to response, the effect of intermittent dosing may persist for longer than 24 hours, continuous daily use not recommended; maximum 1 dose per day.

Erectile dysfunction: for patients who anticipate sexual activity at least twice a week
BY MOUTH
Adult: 5 mg once daily, reduced to 2.5 mg once daily, adjusted according to response.

Benign prostatic hyperplasia
BY MOUTH
Adult: 5 mg once daily.

CONTRA-INDICATIONS
GENERAL CONTRA-INDICATIONS
History of non-arteritic anterior ischaemic optic neuropathy
SPECIFIC CONTRA-INDICATIONS
When used for benign prostatic hyperplasia hypotension (avoid if systolic blood pressure below 90 mmHg) - mild to severe heart failure - myocardial infarction - patients in whom vasodilatation or sexual activity are inadvisable - recent stroke - uncontrolled arrhythmias - uncontrolled hypertension - unstable angina
When used for erectile dysfunction hypotension (avoid if systolic blood pressure below 90 mmHg) - mild to severe heart failure - myocardial infarction - patients in whom vasodilatation or sexual activity are inadvisable - recent stroke - uncontrolled arrhythmias - uncontrolled hypertension - unstable angina
When used for pulmonary arterial hypertension acute myocardial infarction in past 90 days

CAUTIONS
When used for benign prostatic hyperplasia anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) - cardiovascular disease - left ventricular outflow obstruction - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)
When used for erectile dysfunction anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) - cardiovascular disease - left ventricular outflow obstruction - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)
When used for pulmonary arterial hypertension Anatomical deformation of the penis - aortic and mitral valve disease - congestive cardiomyopathy - coronary artery disease - hereditary degenerative retinal disorders - hypotension (avoid if systolic blood pressure below 90 mmHg) - left ventricular dysfunction - life-threatening arrhythmias - pericardial constriction - predisposition to priapism - pulmonary veno-occlusive disease - uncontrolled hypertension

INTERACTIONS → Appendix 1: phosphodiesterase type-5 inhibitors

SIDE-EFFECTS
Common or very common: Flushing - gastrointestinal discomfort - headache - myalgia - nasal congestion - pain
Rare or very rare: Acute coronary syndrome - angioedema - cerebrovascular insufficiency - eye erythema - eye swelling - haematoma/permia - hyperhidrosis - memory loss - optic neuropathy (discontinue if sudden visual impairment occurs) - priapism - retinal occlusion - seizure - Stevens-Johnson syndrome - sudden cardiac death - sudden hearing loss (discontinue drug and seek medical advice) - syncope

PREGNANCY Manufacturer advises avoid.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
When used for Pulmonary arterial hypertension Manufacturer advises caution in mild to moderate impairment (limited information available); avoid in severe impairment (no information available).
When used for Benign prostatic hyperplasia or Erectile dysfunction Manufacturer advises caution for regular once-daily dosing (no information available), and in severe impairment for intermittent use (limited information available).

Dose adjustments
When used for Pulmonary arterial hypertension Manufacturer advises consider initial dose reduction to 20 mg once daily in mild to moderate impairment.
When used for Erectile dysfunction Manufacturer advises dose of 10 mg for intermittent use (no information available for higher doses).

RENAL IMPAIRMENT
When used for Pulmonary arterial hypertension Manufacturer advises avoid in severe impairment.
When used for Erectile dysfunction or Benign prostatic hyperplasia Manufacturer advises avoid regular once-daily dosing in severe impairment.

Dose adjustments
When used for Pulmonary arterial hypertension Manufacturer advises initial dose of 20 mg once daily in mild-to-moderate impairment; dose may be increased to 40 mg once daily if tolerated.
When used for Erectile dysfunction Manufacturer advises maximum dose of 10 mg for intermittent use in severe impairment.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (July 2012) that tadalafil (Adcirca®) is accepted for restricted use within NHS Scotland for adults with pulmonary arterial hypertension and should be initiated only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland.
NHS restrictions Clinals® is not prescribable in NHS primary care for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIb of the Drug Tariff (Part Xib of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use the BNF.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Tadalafil (Non-proprietary)
Tadalafil 2.5 mg 28 tablet £54.99 DT = £54.99
Tadalafil 5 mg 28 tablet £54.99 DT = £23.99
Tadalafil 10 mg 28 tablet £28.88 DT = £1.93
Tadalafil 20 mg 28 tablet £1.95 | 8 tablet £3.90-£109.98 | 56 tablet £375.11-£466.66
Adcirca (Eli Lilly and Company Ltd)
Tadalafil 20 mg 28 tablet £491.22
Clinals (Eli Lilly and Company Ltd)
Tadalafil 2.5 mg 28 tablet £54.99 DT = £54.99
Vardenafil

20-Jul-2017

INDICATIONS AND DOSE

Erectile dysfunction

By mouth using tablets

Adult: Initially 10 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day.

By mouth using orodispersible tablet

Adult: 10 mg, to be taken approximately 25–60 minutes before sexual activity; maximum 10 mg per day.

Erectile dysfunction (patients on alpha-blocker therapy)

By mouth using tablets

Adult: Initially 5 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day.

DOSE EQUIVALENCE AND CONVERSION

Levi® 10 mg orodispersible tablets and Levitra® 10 mg film-coated tablets are not bioequivalent.

CONTRA-INDICATIONS

Avoid if systolic blood pressure below 90 mmHg - hereditary degenerative renal disorders - myocardial infarction - patients in whom vasodilation or sexual activity is inadvisable - previous history of non-arteritic anterior ischaemic optic neuropathy - recent stroke - unstable angina.

CAUTIONS

Active peptic ulceration - anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) - bleeding disorders - cardiovascular disease - elderly - left ventricular outflow obstruction - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia) - susceptibility to prolongation of QT interval.

INTERACTIONS

Appendix 1: phosphodiesterase type-5 inhibitors.

SIDE-EFFECTS

Common or very common

Dizziness - flushing - gastrointestinal discomfort - headache - nasal congestion.

Uncommon


Rare or very rare


Frequency not known

Haematopsia - optic neuropathy (discontinue if sudden visual impairment occurs) - QT interval prolongation - sudden hearing loss.

HEPATIC IMPAIRMENT

For film-coated tablets, manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

For orodispersible tablets, manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

Dose adjustments

Film-coated tablets, manufacturer advises initial dose reduction to 5 mg in mild to moderate impairment, increase according to response; max. 10 mg in moderate impairment.

For orodispersible tablets, manufacturer advises initial dose reduction to 5 mg using film-coated tablets in mild impairment, increase according to response.

RENAL IMPAIRMENT

Orodispersible tablets not suitable if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments

Initial dose 5 mg if eGFR less than 30 mL/minute/1.73 m².

PRESCRIBING AND DISPENSING INFORMATION

Orodispersible tablets not suitable for initiation of therapy in patients taking alpha-blockers.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (October 2011) that vardenafil orodispersible tablets (Levitra®) are accepted for restricted use within NHS Scotland for treatment of erectile dysfunction in men for whom an orodispersible tablet is an appropriate formulation.

NHS restrictions

Levitra® is not prescribable in NHS primary care for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIb of the Drug Tariff (Part XIII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SL’. For more information see Prices in the BNF, under How to use the BNF.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Orodispersible tablet

EXCIPIENTS: May contain Aspartame

Levitra® (Bayer Plc)

Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra® 10 mg orodispersible tablets sugar-free 4 tablet pack £13.67 DT = £13.67

Tablet

Vardenafil (as Vardenafil hydrochloride trihydrate) 5 mg Levitra® 5 mg tablets 4 tablet pack £6.24–£12.04 DT = £8.31 | 8 tablet pack £14.97–£24.08

Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra® 10 mg tablets 4 tablet pack £11.09–£21.41 DT = £14.77 | 8 tablet pack £26.61–£42.82

Vardenafil (as Vardenafil hydrochloride trihydrate) 20 mg Levitra® 20 mg tablets 4 tablet pack £18.23–£35.20 DT = £24.29 | 8 tablet pack £42.52–£70.40

Levitra® (Bayer Plc)

Vardenafil (as Vardenafil hydrochloride trihydrate) 5 mg Levitra® 5 mg tablets | 4 tablet pack £8.32 DT = £8.31

Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra® 10 mg tablets | 4 tablet pack £14.78 DT = £14.77 | 8 tablet pack £29.57

Vardenafil (as Vardenafil hydrochloride trihydrate) 20 mg Levitra® 20 mg tablets | 4 tablet pack £24.30 DT = £24.29 | 8 tablet pack £48.60

PROSTAGLANDINS AND PROSTAMIDIES

Alprostadil

20-Jul-2017

INDICATIONS AND DOSE

Erectile dysfunction (initiated under specialist supervision)

By urethral application

Adult: Initially 250 micrograms, adjusted according to response; usual dose 0.125–1 mg; maximum 2 doses per day; maximum 7 doses per week.
Erectile dysfunction

Erectile dysfunction associated with neurological dysfunction

➤ By intracavernosal injection
- Adult: Initially 1.25 micrograms for 1 dose (first dose), then 2.5 micrograms for 1 dose (second dose), then 5 micrograms for 1 dose (third dose), increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection lasting not more than 1 hour; if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 5–20 micrograms (max. per dose 60 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections

Aid to diagnosis
- By intracavernosal injection
- Adult: 10–20 micrograms for 1 dose (consult product literature)

Virdal ® Duo

Neurogenic erectile dysfunction

➤ By intracavernosal injection
- Adult: Initially 1.25 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

Erectile dysfunction

➤ By intracavernosal injection
- Adult: Initially 2.5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

Contra-indications

General Contra-indications
Not for use in patients with penile implants or when sexual activity medically inadvisable (e.g. orthostatic hypotension, myocardial infarction, and syncope) · not for use with other agents for erectile dysfunction · predisposition to prolonged erection (as in thrombocytopenia, polycythemia, sickle cell anemia, multiple myeloma or leukaemia) · urethral application contra-indicated in balanitis · urethral application contra-indicated in severe curvature · urethral application contra-indicated in severe hypospadias · urethral application contra-indicated in urethral stricture · urethral application contra-indicated in urethritis

Specific Contra-indications
- With topical use Balanitis · severe curvature · severe hypospadias · urethral stricture · urethritis

Caution
- Anatomical deformations of penis (painful erection more likely) — follow up regularly to detect signs of penile fibrosis (consider discontinuation if angulation, cavernosal fibrosis or Peyronie’s disease develop) · priapism (patients should be instructed to report any erection lasting 4 hours or longer)

Interactions
- Appendix 1: alprostadil
Erectile and ejaculatory conditions

**SIDE-EFFECTS**

- **Common or very common**
  - With intracavernosal use: Haemorrhage, muscle spasms, penile disorders, sexual dysfunction, skin reactions
  - With topical use: Balanoposthitis, genital abnormalities, penile disorders, rash, sexual dysfunction, urinary tract pain
  - With urethral use: Dizziness, haemorrhage, headache, hypotension, muscle spasms, penile disorders, sexual dysfunction, urinary burning

- **Uncommon**
  - With intracavernosal use: Asthenia, balanoposthitis, dry mouth, extrasystole, hyperhidrosis, hypotension, increased risk of infection, inflammation, mydriasis, nausea, oedema, pelvic pain, peripheral vascular disease, presyncope, scrotal disorders, sensation abnormal, spermatocele, testicular disorders, urinary disorders, vascular disorders, vasodilation

- With topical use: Dizziness, hyperaesthesia, hypotension, pain in extremity, scrotal pain, syncope, urinary tract disorders

- With urethral use: Balanoposthitis, hyperhidrosis, increased risk of infection, leg pain, nausea, pelvic pain, perineal pain, peripheral vascular disease, scrotal disorders, sensation abnormal, skin reactions, spermatocele, syncope, testicular disorders, urinary disorders, vascular disorders, vasodilation

- **Frequency not known**
  - With intracavernosal use: Myocardial ischaemia, stroke
  - With intravenous use: Periurethral oedema

**CONCEPTION AND CONTRACEPTION**

- With urethral use: If partner is pregnant, barrier contraception should be used. No evidence of harm to latex condoms and diaphragms.
- With topical use: Condoms should be used to avoid exposure to women of child-bearing age, pregnant or lactating women. No evidence of harm to latex condoms.

**DIRECTIONS FOR ADMINISTRATION**

- With intracavernosal use: The first dose of the intracavernosal injection must be given by medically trained personnel; self-administration may only be undertaken after proper training.
- With urethral use: During initiation of treatment the urethral application should be used under medical supervision; self-administration may only be undertaken after proper training.

**PATIENT AND CARER ADVICE**

Patients should be instructed to report any erection lasting 4 hours or longer.

- With topical use: Counsel patients that condoms should be used to avoid local reactions and exposure of alprostadil to women of childbearing age, pregnant, or lactating women.

**NATIONAL FUNDING/ACCESS DECISIONS**

Caverject®, Viridal® Duo, Vitaros® and MUSE® are not prescribable in NHS primary care for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use BNF publications.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Stick**
  - Muse (Meda Pharmaceuticals Ltd)
  - Alprostadil 250 microgram: Muse 250microgram urethral sticks 1 applicator (PBD) £11.30 DT = £11.30 6 applicator (PBD) £67.79
  - Alprostadil 500 microgram: Muse 500microgram urethral sticks 1 applicator (PBD) £11.30 DT = £11.30 6 applicator (PBD) £67.79
  - Alprostadil 1 mg: Muse 1000microgram urethral sticks 1 applicator (PBD) £11.56 DT = £11.56 6 applicator (PBD) £65.67

- **Cream**
  - Vitaros® (Ferring Pharmaceuticals Ltd)
  - Alprostadil 3 mg per 1 gram: Vitaros 3mg/g cream 4 applicator (PBD) £40.00 DT = £40.00

**Powder and solvent for solution for injection**

- **Caverject® (Pfizer Ltd)**
  - Alprostadil 10 microgram: Caverject 10microgram powder and solvent for solution for injection vials 1 vial (PBD) £9.24 DT = £9.24
  - Caverject Dual Chamber 10microgram powder and solvent for solution for injection 2 pre-filled disposable injection (PBD) £14.70

- **Alprostadil 20 microgram**
  - Caverject Dual Chamber 20microgram powder and solvent for solution for injection 2 pre-filled disposable injection (PBD) £19.00
  - Caverject 20microgram powder and solvent for solution for injection vials 1 vial (PBD) £11.94 DT = £11.94

- **Alprostadil 40 microgram**
  - Caverject 40microgram powder and solvent for solution for injection vials 1 vial (PBD) £21.58 DT = £21.58

- **Viridal® (UCB Pharma Ltd)**
  - Alprostadil 10 microgram: Viridal Duo Starter Pack 10microgram powder and solvent for solution for injection cartridges with device 2 cartridge (PBD) £20.13 (Hospital only)
  - Viridal Duo Continuation Pack 10microgram powder and solvent for solution for injection cartridges 2 cartridge (PBD) £16.55

- **Alprostadil 20 microgram**
  - Viridal Duo Pack 20microgram powder and solvent for solution for injection cartridges with device 2 cartridge (PBD) £24.54 (Hospital only)
  - Viridal Duo Continuation Pack 20microgram powder and solvent for solution for injection cartridges 2 cartridge (PBD) £21.39

- **Alprostadil 40 microgram**
  - Viridal Duo Starter Pack 40microgram powder and solvent for solution for injection cartridges with device 2 cartridge (PBD) £29.83 (Hospital only)
  - Viridal Duo Continuation Pack 40microgram powder and solvent for solution for injection cartridges 2 cartridge (PBD) £27.22

**SYMPATHOMIMETICS > VASOCONSTRICTOR**

**Adrenaline/epinephrine**

- **DRUG ACTION**
  - Acts on both alpha and beta receptors and increases both heart rate and contractility (beta, effects); it can cause peripheral vasodilation (a beta1 effect) or vasoconstriction (an alpha effect).

- **INDICATIONS AND DOSE**
  - Priapism associated with alprostadil, if aspiration and lavage of corpora are unsuccessful (alternative to phenylephrine or metaraminol)

- **BY INTRACavernosal INJECTION**
  - Adult: 10–20 micrograms every 5–10 minutes, using a 20 microgram/mL solution. Important: If suitable strength of adrenaline not available may be specially prepared by diluting 0.1 mL of the adrenaline 1 in 1000 (1 mg/mL) injection to 5 mL with sodium chloride 0.9%, continuously monitor blood pressure and pulse; maximum 100 micrograms per course

**UNLICENSED USE**

The use of adrenaline for the treatment of priapism is an unlicensed indication.

- **CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

Cautions listed are only for non-life-threatening situations.

- **INTERACTIONS**
  - Appendix 1: sympathomimetics, vasoconstrictor

- **SIDE-EFFECTS**
  - Rare or very rare: Cardiomyopathy.
mouth - dyspnoea - headache - hepatic necrosis - hyperglycaemia - hyperhidrosis - hypertensation (increased risk of cerebral haemorrhage) - hypokalaemia - injection site necrosis - insomnia - intestinal necrosis - metabolic acidosis - mydriasis - myocardial infarction - nausea - pallor - palpitations - peripheral coldness - psychosis - pulmonary oedema (on excessive dosage or extreme sensitivity) - renal necrosis - soft tissue necrosis - tremor - urinary disorders - vomiting

**RENAL IMPAIRMENT** Manufacturers advise use with caution in severe impairment.

**MONITORING REQUIREMENTS** Monitor blood pressure and ECG.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

### Solution for injection

**EXCIPIENTS:** May contain Sulphites

- **Adrenaline/epinephrine (Non-proprietary)**
  - Adrenaline 100 microgram per 1 mL Adrenaline (base) 100 micrograms/mL (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (POM) £76.34
  - Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £6.87 | 1 pre-filled disposable injection (POM) £18.00 (Hospital only) | 10 pre-filled disposable injection (POM) £180.00 (Hospital only)
  - Adrenaline (as Adrenaline acid tartrate) 100 microgram per 1 mL Adrenaline (base) 100 micrograms/mL (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (POM) £88.48
  - Adrenaline (base) 500 micrograms/5 mL (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (POM) £81.33
  - Adrenaline 1 mg per 1 mL Adrenaline (base) 10 mg/10 mL (1 in 1,000) solution for injection ampoules | 10 ampoule (POM) £96.38
  - Adrenaline (base) for anaesthesia 1 mg/1 mL (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £11.88 DT + £11.71
  - Adrenaline (base) 1 mg/1 mL (1 in 1,000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £11.88 DT + £11.71
  - Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL Adrenaline (base) 5 mg/5 mL (1 in 1,000) solution for injection ampoules | 10 ampoule (POM) £33.58
  - Adrenaline (base) 500 micrograms/0.5 mL (1 in 1,000) solution for injection ampoules | 10 ampoule (POM) £6.95 DT + £6.01

- **Phenylephrine hydrochloride 100 microgram per 1 mL Phenylephrine hydrochloride 100 micrograms/10 mL solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £15.00 | 10 pre-filled disposable injection (POM) £150.00

### Phentolamine hydrochloride

- **BY INTRACAVERNOSAL INJECTION**
  - Phenylephrine hydrochloride (Non-proprietary) Phenylephrine (as Phenylephrine hydrochloride) 1 mg per 1 mL Phenylephrine hydrochloride 10 mg per 1 mL Phenylephrine hydrochloride 1 mg/1 mL solution for injection ampoules | 10 ampoule (POM) £40.00 Phenylephrine hydrochloride 10 mg per 1 mL Phenylephrine hydrochloride 10 mg/1 mL solution for injection ampoules | 10 ampoule (POM) £99.12

### Metaraminol

- **INDICATIONS AND DOSE**
  - Priapism (alternative to intracavernosal injections of phenylephrine and adrenaline)
    - Adult: 1 mg every 15 minutes

- **UNLICENSED USE** Use for priapism is an unlicensed indication.

- **CONTRA-INDICATIONS** Hypertension

- **CAUTIONS** Associated with fatal hypertensive crises - cirrhosis - coronary vascular thrombosis - diabetes mellitus - elderly - extravasation at injection site may cause necrosis - following myocardial infarction - hypercapnia - hyperthyroidism - hypoxia - mesenteric vascular thrombosis - peripheral vascular thrombosis - Prinzmetal’s variant angina - uncorrected hypovolaemia

- **INTERACTIONS** Appendix 1: sympathomimetics, vasoconstrictor

- **SIDE-EFFECTS**
  - Common or very common Headache - hypertension
  - Rare or very rare Skin exfoliation - soft tissue necrosis
  - Frequency not known Abscess - arrhythmias - nausea - palpitations - peripheral ischaemia

**MONITORING REQUIREMENTS** Monitor blood pressure and rate of flow frequently.

**DIRECTIONS FOR ADMINISTRATION** For intracavernosal injection, dilute 1 mg (0.1 mL of 10 mg/mL) metaraminol injection to 50 mL with Sodium chloride injection 0.9% and give carefully by slow injection into the corpora in 5 mL injections.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

### Solution for injection

- Metaraminol (Non-proprietary) Metaraminol (as Metaraminol tartrate) 10 mg per 1 mL Metaraminol 10 mg/1 mL solution for injection ampoules | 10 ampoule (POM) £43.90

**INDICATIONS AND DOSE**

- Priapism associated with alprostadil, if aspiration and lavage of the corpora are unsuccessful (alternative to adrenaline or metaraminol)
  - By intracavernosal injection
    - Adult: 100–200 micrograms every 5–10 minutes, dose to be administered using a 200 micrograms/mL solution; maximum 1 mg per course

**UNLICENSED USE** Use of phenylephrine hydrochloride injection in priapism is an unlicensed indication.

**CONTRA-INDICATIONS** Hypertension

**SIDE-EFFECTS** Angle closure glaucoma - anxiety - appetite decreased - arrhythmias - asthenia - confusion - dyspnoea - headache - hypertension - hypoxia - insomnia - nausea - palpitations - peripheral ischaemia - psychosis - tremor - urinary retention - vomiting

**DIRECTIONS FOR ADMINISTRATION** For intracavernosal injection, if suitable strength of phenylephrine injection is not available, it may be specially prepared by diluting 0.1 mL of the phenylephrine 1% (10 mg/mL) injection to 5 mL with sodium chloride 0.9%.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

### Solution for injection

- Phenylephrine hydrochloride (Non-proprietary) Phenylephrine (as Phenylephrine hydrochloride) 50 microgram per 1 mL Phenylephrine (as Phenylephrine hydrochloride) 50 microgram per 1 mL Phenylephrine 500 micrograms/10 mL solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £15.00 | 10 pre-filled disposable injection (POM) £150.00

- Phenylephrine hydrochloride 100 microgram per 1 mL Phenylephrine hydrochloride 100 microgram per 1 mL Phenylephrine 1 mg/10 mL solution for injection ampoules | 10 ampoule (POM) £40.00 Phenylephrine hydrochloride 10 mg per 1 mL Phenylephrine hydrochloride 10 mg/1 mL solution for injection ampoules | 10 ampoule (POM) £99.12
**4.2 Premature ejaculation**

**Description of condition**

Premature ejaculation is a common male sexual disorder characterised by brief ejaculatory latency, loss of control, and psychological distress.

**Treatment**

Non-drug treatment (including psychosexual counselling, education, and behavioural treatments) are recommended in patients for whom premature ejaculation causes few (if any) problems or in patients who prefer not to take drug treatment. These techniques can also be used in addition to a drug treatment.

For patients with life-long premature ejaculation, drug treatment is the recommended approach. Dapoxetine p. 821, a short-acting selective serotonin re-uptake inhibitor, is licensed to be used when required for this condition (not continuous daily use).

Other selective serotonin re-uptake inhibitors (citalopram p. 364, fluoxetine p. 369, fluvoxamine maleate p. 366, escitalopram p. 365, paroxetine p. 366, sertraline p. 367 [unlicensed indications]) and the tricyclic antidepressant clomipramine [unlicensed indication] have been widely used as regular, daily treatment. Caution is suggested in prescribing selective serotonin re-uptake inhibitors for young adolescents with premature ejaculation, and to men who also have a depressive disorder, particularly when associated with suicidal ideation. Ejaculation delay may start a few days after the start of treatment, but it is more evident after 1 to 2 weeks, since receptor desensitisation requires time to occur.

If premature ejaculation is secondary to erectile dysfunction p. 812, the erectile dysfunction should be treated first.

Topical anaesthetic preparations for the management of premature ejaculation are available without prescription.

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**Other drugs used for Premature ejaculation**

- Lidocaine with prilocaine, p. 1354

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**Scottish Medicines Consortium (SMC) decisions**

The **Scottish Medicines Consortium** has advised (December 2017) that aviptadil with phentolamine (Invicorp®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed aetiology in adult males who have failed on oral therapies (oral phosphodiesterase type-5 inhibitors) and other non-injectable formulations of erectile dysfunction medications.
selective serotonin re-uptake inhibitors

Dapoxetine

- **drug action** Dapoxetine is a short-acting selective serotonin re-uptake inhibitor.

- **indications and dose** Premature ejaculation in men who meet all the following criteria: poor control over ejaculation, a history of premature ejaculation over the past 6 months, marked distress or interpersonal difficulty as a consequence of premature ejaculation, and an intravaginal ejaculatory latency time of less than two minutes
  - **by mouth**
  - **adult:** Initially 30 mg, to be taken approximately 1–3 hours before sexual activity, subsequent doses adjusted according to response; review treatment after 4 weeks (or 6 doses) and at least every 6 months thereafter, not recommended for adults 65 years and over; maximum 1 dose per day; maximum 60 mg per day

- **dose adjustments due to interactions**
  - **manufacturer advises max. dose 30 mg with concurrent use of moderate inhibitors of CYP3A4 except in patients verified to be extensive CYP2D6 metabolisers where manufacturer recommends max. dose 60 mg.**
  - **manufacturer advises avoid with concurrent use of potent inhibitors of CYP3A4 except in patients verified to be extensive CYP2D6 metabolisers where manufacturer recommends max. dose 30 mg.**

- **contra-indications** History of bipolar disorder • history of mania • history of severe depression • history of syncope • significant cardiac disease • uncontrolled epilepsy

- **cautions** Bleeding disorders • epilepsy (discontinue if convulsions develop) • susceptibility to angle-closure glaucoma

- **interactions** → Appendix 1: SSRIs

- **side-effects**
  - **common or very common** Anxiety • asthenia • concentration impaired • constipation • diarrhoea • dizziness • drowsiness • dry mouth • gastrointestinal discomfort • gastrointestinal disorders • headache • hypotension • mood altered • nausea • paraesthesia • sexual dysfunction • sinus congestion • sleep disorders • sweat changes • syncope • tinnitus • tremor • vasodilation • vision blurred • vomiting • yawning
  - **uncommon** Akathisia • arrhythmias • behaviour abnormal • confusion • depression • eye pain • feeling abnormal • feeling hot • hypertension • level of consciousness decreased • mydriasis • pruritus • taste altered • thinking abnormal • vertigo

- **side-effects, further information** Discontinue if psychiatric disorder develops.

- **hepatic impairment** Manufacturer advises avoid in moderate to severe impairment.

- **renal impairment** Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

- **pre-treatment screening** Test for postural hypotension before starting treatment.

- **treatment cessation** The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

- **patient and carer advice** Postural hypotension and syncope Patients should be advised to maintain hydration and to sit or lie down until prodromal symptoms such as nausea, dizziness, and sweating abate.

- **medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**tablet**

**cautionary and advisory labels** 2, 25

- **priligy (A. Menarini Farmaceutica Internazionale SRL)**
  - **dapoxetine 30 mg** Priligy 30mg tablets | 3 tablet DT = £14.71 | 6 tablet DT = £26.48
  - **dapoxetine 60 mg** Priligy 60mg tablets | 3 tablet DT = £19.12 | 6 tablet DT = £34.42

5 Obstetrics

Prostaglandins and oxytocics

Prostaglandins and oxytocics are used to induce abortion or induce or augment labour and to minimise blood loss from the placental site. They include oxytocin p. 823, carbetocin p. 824, ergometrine maleate p. 824, and the prostaglandins. All induce uterine contractions with varying degrees of pain according to the strength of contractions induced.

**induction of abortion**

Gemeprost p. 826, a prostaglandin administered vaginally as pessaries, is suitable for the medical induction of late therapeutic abortion; gemeprost is also used to ripen the cervix before surgical abortion, particularly in primigravids. The prostaglandin misoprostol p. 827 is given by mouth, buccally, sublingually, or vaginally, to induce medical abortion [unlicensed indication]; intravaginal use ripens the cervix before surgical abortion [unlicensed indication]. Extra-amniotic dinoprostone is rarely used nowadays.

Pre-treatment with mifepristone p. 825 can facilitate the process of medical abortion. It sensitises the uterus to subsequent administration of a prostaglandin and, therefore, abortion occurs in a shorter time and with a lower dose of prostaglandin.

**induction and augmentation of labour**

Dinoprostone is available as vaginal tablets, pessaries and vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.

Oxytocin (Syntocinon®) is administered by slow intravenous infusion, using an infusion pump, to induce or augment labour, usually in conjunction with amniotomy. Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.

Misoprostol is given orally [unlicensed route] or vaginally for the induction of labour.


**prevention and treatment of haemorrhage**

Bleeding due to incomplete miscarriage or abortion can be controlled with ergometrine maleate and oxytocin (Syntometrine®) given intramuscularly; the dose is adjusted according to the patient’s condition and blood loss. This is commonly used before surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine maleate combined are more effective in early pregnancy than either drug alone.

Active management of the third stage of labour reduces the risk of postpartum haemorrhage; oxytocin is given by intramuscular injection [unlicensed] on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered. Alternatively, ergometrine maleate with oxytocin (Syntometrine®) can be given by intramuscular injection.
injection in the absence of hypertension; oxytocin alone causes less nausea, vomiting, and hypertension than when given with ergometrine maleate.

In excessive uterine bleeding, any placental products remaining in the uterus should be removed. Oxytocic drugs are used to treat postpartum haemorrhage caused by uterine atony; treatment options are as follows:

- oxytocin by slow intravenous injection, followed in severe cases by intravenous infusion of oxytocin at a rate that controls uterine atony or
gestures to prevent atony — risk of hypertension) or
- ergometrine with oxytocin (Syntometrine®) by intra muscular injection

Carboprost p. 824 has an important role in severe postpartum haemorrhage unresponsive to ergometrine maleate and oxytocin.

Misoprostol [unlicensed] can be used in postpartum haemorrhage when oxytocin, ergometrine maleate, and carboprost are not available or are inappropriate.

**Mifepristone**

For termination of pregnancy, a single dose of mifepristone is followed by administration of a prostaglandin (gemeprost or misoprostol [unlicensed]).

Guidelines of the Royal College of Obstetricians and Gynaecologists (November 2011) include [unlicensed] regimens for inducing medical abortion.

**Indications and Dose**

**Premature labour**

Oxytocin 0.5–1 ml 12-hourly or as directed. Ergometrine 0.5 ml 8-hourly or as directed. If tolerated, repeat at 4-hourly intervals. If the oxytocin dose is increased at 4-hourly intervals, the ergometrine dose should also be increased.

**Oxytocin**

**Premature labour**

By intravenous infusion grade 1 or 2, 0.1–0.5 ml/hour or as directed. By slow intravenous injection 0.5 ml 6-hourly or as directed. If tolerated, repeat at intervals of 1–2 hours and titrate dose to effect.

**Ergometrine**

**Premature labour**

By intravenous infusion 0.1–0.25 ml/hour or as directed. By slow intravenous injection 0.5 ml 6-hourly or as directed. If tolerated, repeat at intervals of 1–2 hours and titrate dose to effect.

**Dose equivalence and conversion**

**Oxytocin**

To convert from U to IU, multiply by 1.45.

**Ergometrine**

To convert from mg to ml, multiply by 4.

**5.1 Induction of labour**

Other drugs used for Induction of labour Misoprostol, p. 827
Oxytocin

**INDICATIONS AND DOSE**

**Induction of labour for medical reasons** | **Stimulation of labour in hypotonic uterine inertia**
---|---
| **By intravenous infusion** | • Adult: Initially 0.001–0.004 unit/minute, not to be started for at least 6 hours after administration of vaginal prostaglandin, dose increased at intervals of at least 30 minutes until a maximum of 3–4 contractions occur every 10 minutes (0.01 units/minute is often adequate) up to max. 0.02 units/minute, if regular contractions not established after a total 5 units, stop induction attempt (may be repeated next day starting again at 0.001–0.004 units/minute)

**Caesarean section**
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| **By slow intravenous infusion** | Adult: 5 units immediately after delivery

**Prevention of postpartum haemorrhage after delivery of placenta**
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| **By slow intravenous infusion** | Adult: 5 units, if infusion previously used for induction or enhancement of labour, increase rate during third stage and for next few hours

**By intramuscular injection**
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| Adult: 10 units, can be used instead of oxytocin with ergometrine (Syntometrine	extsuperscript{®}).

**Treatment of postpartum haemorrhage**
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| **By intravenous infusion** | Adult: 5 units, repeated if necessary

**Treatment of severe cases of postpartum haemorrhage (following intravenous injection)**
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| **By intravenous infusion** | Adult: 40 units, given in 500 mL infusion fluid given at a rate sufficient to control uterine atony

**Incomplete, inevitable, or missed miscarriage**
---
| **Initially by slow intravenous injection** | Adult: 5 units, followed by (by intravenous infusion) 0.02–0.04 unit/minute if required, the rate of infusion can be faster if necessary

**UNLICENSED USE** Oxytocin doses in the BNF may differ from those in the product literature. Administration by intramuscular injection is an unlicensed use.

**IMPORTANT SAFETY INFORMATION**

Prolonged intravenous administration at high doses with large volume of fluid (which is possible in inevitable or missed miscarriage or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (i.e. not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth, monitor fluid and electrolytes.

**CONTRA-INDICATIONS** Any condition where spontaneous labour is advisable - any condition where vaginal delivery is advisable - avoid intravenous injection during labour - avoid prolonged administration in oxytocin-resistant uterine inertia - avoid rapid intravenous injection (may transiently reduce blood pressure) - fetal distress (discontinue immediately if this occurs) - hypertonic uterine contractions (discontinue immediately if this occurs) - severe cardiovascular disease - severe pre-eclamptic toxemia.

**CAUTIONS** Avoid large infusion volumes and restrict fluid intake by mouth (risk of hyponatraemia and water-intoxication) - enhancement of labour - presence of borderline cephalopelvic disproportion (avoid if significant) - history of lower-uterine segment caesarean section - induction of labour - presence of borderline cephalopelvic disproportion (avoid if significant) - mild pregnancy-induced cardiac disease - mild pregnancy-induced hypertension - moderate pregnancy-induced cardiac disease - moderate pregnancy-induced hypertension - risk factors for disseminated intravascular coagulation - secondary uterine inertia - women over 35 years.

**SIDE-EFFECTS**
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| Common or very common | Arrhythmias - headache - nausea - vomiting

| Rare or very rare | Dyspnoea - hypotension - rash

| Frequency not known | Angioedema - disseminated intravascular coagulation - electrolyte imbalance - flushing - haemorrhage - myocardial ischaemia - pulmonary oedema - QT interval prolongation - uterine rupture - water intoxication

**SIDE-EFFECTS, FURTHER INFORMATION** Avoid rapid intravenous injection (may transiently reduce blood pressure).

**UTERINE HYPERSTIMULATION -** usually with excessive doses—may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture.

**Overdose** Placental abruption and amniotic fluid embolism reported on overdose.

**MONITORING REQUIREMENTS**
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| Careful monitoring of fetal heart rate and uterine motility essential for dose titration.

**Monitor for disseminated intravascular coagulation after parturition.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Syntocinon	extsuperscript{®}), give continuously in Glucose 5% or Sodium Chloride 0.9%. Preferably given via a variable-speed infusion pump in a concentration appropriate to the pump; if given by drip infusion for induction or enhancement of labour, dilute 5 units in 500 mL infusion fluid or for higher doses, 10 units in 500 mL; for treatment of postpartum uterine haemorrhage dilute 40 units in 500 mL; if high doses given for prolonged period (e.g. for inevitable or missed abortion or for postpartum haemorrhage), use low volume of an electrolyte-containing infusion fluid (not Glucose 5%) given at higher

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concentration than for induction or enhancement of labour; close attention to patient’s fluid and electrolyte status essential.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Solution for injection**
- **Oxytocin (non-proprietary)**
  - Oxytocin 5 unit per 1 ml Oxytocin 5 units/1ml solution for injection ampoules | 5 ampoule £0.55 | 10 ampoule £2.00
  - Oxytocin 10 unit per 1 ml Oxytocin 10 units/1ml solution for infusion ampoules | 5 ampoule £0.45 | 10 ampoule £0.90
  - Oxytocin 10 units/1ml solution for infusion ampoules | 5 ampoule £0.45 | 10 ampoule £0.90
- **Syntocinon (Mylan)**
  - Syntocinon 5 unit per 1 ml Syntocinon 5 units/1ml solution for injection ampoules | 5 ampoule £4.01 (Hospital only)
  - Syntocinon 10 unit per 1 ml Syntocinon 10 units/1ml solution for injection ampoules | 5 ampoule £4.53 (Hospital only)

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5.2 Postpartum haemorrhage

Other drugs used for Postpartum haemorrhage Oxytocin, p. 823

### Carboprost

**INDICATIONS AND DOSE**

Postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 250 micrograms, repeated if necessary, to be given at intervals of not less than 15 minutes. Total dose should not exceed 2 mg (8 doses)

**CONTRA-INDICATIONS** Cardiac disease - pulmonary disease - untreated pelvic infection

**CAUTIONS** Excessive dosage may cause uterine rupture - history of anaemia - history of asthma - history of diabetes - history of epilepsy - history of glaucoma - history of hypertension - history of hypotension - history of jaundice - history of raised intra-ocular pressure - uterine scars

**SIDE-EFFECTS**
- Common or very common Chills - cough - diarrhoea - headache - nausea - uterine disorders - vasodilatation - vomiting
- Frequency not known Anxiety - asthenia - blepharospasm - choking sensation - palpitations - rash - thirst - throat complaints - thyrotoxic crisis

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in active hepatic disease.

**RENAI IMPAIRMENT** Manufacturer advises avoid.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Hemabate (Pfizer Ltd)**
  - Carboprost (as Carboprost trometamol) 250 microgram per 1 ml Hemabate 250 micrograms/1ml solution for injection ampoules | 10 ampoule £182.01 (Hospital only)

### Ergometrine maleate

**INDICATIONS AND DOSE**

Postpartum haemorrhage caused by uterine atony
- **BY INTRAMUSCULAR INJECTION, OR BY SLOW INTRAVENOUS INJECTION**
  - Adult: 250–500 micrograms

**CONTRA-INDICATIONS** Eclampsia - first stage of labour - induction of labour - second stage of labour - sepsis - severe cardiac disease - severe hypertension - vascular disease

**CAUTIONS** Acute porphyrias p. 1058. cardiac disease - hypertension - multiple pregnancy - risk of hypertension associated with intravenous administration

**INTERACTIONS**
- Appendix 1: ergometrine

**SIDE-EFFECTS** Abdominal pain - arrhythmias - chest pain - coronary vasospasm - dizziness - dyspnoea - headache - hypertension - myocardial infarction - nausea - palpitations - pulmonary oedema - rash - tinnitus - vasoconstriction - vomiting

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAI IMPAIRMENT** Manufacturer advises caution in mild or moderate impairment. Manufacturer advises avoid in severe impairment.
Ergometrine with oxytocin

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergometrine maleate p. 824, oxytocin p. 823.

- **INDICATIONS AND DOSE**
  - **Active management of the third stage of labour** | **Postpartum haemorrhage caused by uterine atony**
  - **BY INTRAMUSCULAR INJECTION**
  - **Adult:** 1 mL for one dose
  - **BY INTRAVENOUS INJECTION**
  - **Adult:** No longer recommended

- **Bleeding due to incomplete miscarriage or abortion**
  - **BY INTRAMUSCULAR INJECTION**
  - **Adult:** Adjusted according to response to, the patient’s condition and blood loss

- **INTERACTIONS** → Appendix 1: ergometrine

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Ergometrine maleate (Non-proprietary)**
      - Ergometrine maleate 500 microgram per 1 mL
      - 10 ampoule (£/unit) £15.00

- **Contraception**
  - **Premature labour**
  - **5.3 Premature labour**

### Other drugs used for Premature labour
- Indomethacin, p. 1143
- Nifedipine, p. 162
- Salbutamol, p. 252
- Terbutaline, p. 255

### OXYTOCIN RECEPTOR ANTAGONISTS

#### Atosiban

- **INDICATIONS AND DOSE**
  - **Uncomplicated premature labour between 24 and 33 weeks of gestation**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - **Adult:** Initially 6.75 mg over 1 minute, then (by intravenous infusion) 18 mg/hour for 3 hours, then (by intravenous infusion) reduced to 6 mg/hour for up to 45 hours. Maximum duration of treatment is 48 hours

- **CONTRA-INDICATIONS**
  - Abruptio placenta • antepartum haemorrhage (requiring immediate delivery) • eclampsia • intra-uterine fetal death • intra-uterine infection • intra-uterine growth restriction with abnormal fetal heart rate • placenta praevia • premature rupture of membranes after 30 weeks’ gestation • severe pre-eclampsia

- **CAUTIONS**
  - Abnormal placental site • intra-uterine growth restriction

- **SIDE-EFFECTS**
  - **Common or very common**
    - Dizziness • headache • hot flush • hyperglycaemia • hypotension • nausea • tachycardia • vomiting
  - **Uncommon**
    - Fever • insomnia • skin reactions
  - **Rare or very rare**
    - Uterine atony • uterine haemorrhage
  - **Frequency not known**
    - Dyspnoea • pulmonary oedema

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Atosiban 6.75 mg/0.9 mL solution for injection vials**
      - 1 vial (£) £18.41 (Hospital only)
    - **Atosiban 6.75 mg/0.9 mL solution for injection vials**
      - 1 vial (£) £18.41 (Hospital only)
  - **Solution for infusion**
    - **Atosiban 6.75 mg/0.9 mL solution for infusion vials**
      - 1 vial (£) £50.18–£52.82 (Hospital only)

#### Mifepristone

- **DRUG ACTION**
  - Mifepristone, an antiprogestogenic steroid, sensitises the myometrium to prostaglandin-induced contractions and ripens the cervix.

- **INDICATIONS AND DOSE**
  - **Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 84 days gestation**
    - **BY MOUTH**
    - **Adult:** 200 mg for 1 dose, to be taken 36–48 hours before procedure
  - **Labour induction in fetal death in utero where prostaglandin or oxytocin inappropriate**
    - **BY MOUTH**
    - **Adult:** 600 mg once daily for 2 days, if labour not started within 72 hours of first dose, another method should be used

### 5.4 Termination of pregnancy

#### PROGESTERONE RECEPTOR MODULATORS

- **Mifepristone**

  - **Drug action**
    - Mifepristone, an antiprogestogenic steroid, sensitises the myometrium to prostaglandin-induced contractions and ripens the cervix.

  - **Indications and dose**
    - **Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 84 days gestation**
      - **By mouth**
      - **Adult:** 200 mg for 1 dose, to be taken 36–48 hours before procedure
    - **Labour induction in fetal death in utero where prostaglandin or oxytocin inappropriate**
      - **By mouth**
      - **Adult:** 600 mg once daily for 2 days, if labour not started within 72 hours of first dose, another method should be used

### Medical termination of intra-uterine pregnancy of up to 49 days gestation

- **By mouth**
- **Adult:** 600 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina or misoprostol 400 micrograms by mouth, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding continued →
Medical termination of intra-uterine pregnancy of 50–63 days gestation (under close medical supervision)

- **BY MOUTH**
  - Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow–up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding

Termination of pregnancy of 13–24 weeks gestation (in combination with a prostaglandin) (under close medical supervision)

- **BY MOUTH**
  - Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later by gemeprost 1 mg by vagina every 3 hours up to max. 5 mg or misoprostol; if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg by vagina up to max. 5 mg; follow-up visit after appropriate interval to assess vaginal bleeding recommended

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 - chronic adrenal failure - suspected ectopic pregnancy (use other specific means of termination) - uncontrolled severe asthma

- **CAUTIONS** Adrenal suppression (may require corticosteroid) - anti-coagulant therapy - asthma (avoid if severe and uncontrolled) - existing cardiovascular disease - haemorrhagic disorders - history of endocarditis - prosthetic heart valve - risk factors for cardiovascular disease

- **INTERACTIONS** & Appendix 1: mifepristone

- **SIDE-EFFECTS**
  - Common or very common Abdominal cramps - diarrhoea - infection - nausea - pelvic inflammatory disease - uterine disorders - vaginal haemorrhage (sometimes severe) - vomiting
  - Uncommon Hypotension
  - Rare or very rare Angioedema - chills - dizziness - erythema nodosum - fever - headache - hot flush - malaise - skin reactions - toxic epidermal necrolysis - toxic shock syndrome - uterine rupture

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in hepatic failure (no information available).

- **RENAL IMPAIRMENT** Manufacturer advises avoid.

- **MONITORING REQUIREMENTS** Careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension).

- **PRESCRIBING AND DISPENSING INFORMATION** Supplied to NHS hospitals and premises approved under Abortion Act 1967.

- **PATIENT AND CARER ADVICE** Patient information leaflet to be provided.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 10
  - Mifepristone (Non-proprietary)
  - Mifepristone 200 mg Mifepristone 200mg tablets | 1 tablet [POM] £9.48
  - Mifepristone 200 mg Mifepristone 200mg tablets | 3 tablet [POM] £52.66 (Hospital only)

**Pessary**

- Gemeprost 1 mg Cervagam 1mg pessaries | 5 pessary [POM] S (Hospital only)

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**PROSTAGLANDINS AND OXYTOCICS**

### Gemeprost

- **INDICATIONS AND DOSE**
  - Cervical ripening prior to first trimester surgical abortion
    - **BY VAGINA**
    - Adult: 1 mg, dose to be inserted into posterior fornix 3 hours before surgery
  - Second trimester abortion
    - **BY VAGINA**
    - Adult: 1 mg every 3 hours for maximum 5 administrations, to be inserted into posterior fornix, second course may begin 24 hours after start of treatment (if treatment fails, pregnancy should be terminated by another method)
  - Second trimester intra-uterine death
    - **BY VAGINA**
    - Adult: 1 mg
  - **T**ermination of pregnancy of 13–24 weeks gestation (in combination with a prostaglandin) following mifepristone
    - **BY VAGINA**
    - Adult: 1 mg
  - Medical termination of intra-uterine pregnancy of up to 49 days gestation following mifepristone
    - **BY VAGINA**
    - Adult: 1 mg every 3 hours, if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg by vagina up to max. 5 mg; follow-up visit after appropriate interval to assess vaginal bleeding recommended, careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension); maximum 5 mg per course

- **CONTRA-INDICATIONS** Placenta praevia - unexplained vaginal bleeding - uterine scarring

- **CAUTIONS** Cardiovascular insufficiency - cervicitis - obstructive airways disease - raised intra-ocular pressure - vaginitis


- **RENAL IMPAIRMENT** Manufacturer advises avoid.

- **MONITORING REQUIREMENTS**
  - If used in combination with mifepristone, carefully monitor blood pressure and pulse for 3 hours.
  - When used for second trimester intra-uterine death, monitor for coagulopathy during treatment.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

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Misoprostol

**DRUG ACTION** Misoprostol is a synthetic prostaglandin analogue that acts as a potent uterine stimulant.

**INDICATIONS AND DOSE**

- **Termination of pregnancy following mifepristone**
  - (gestation up to 49 days)
  - **By mouth**
  - Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone

- **Termination of pregnancy following mifepristone**
  - (gestation 50 to 63 days)
  - **INITIALLY BY VAGINA**
  - Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, if abortion has not occurred 4 hours after first misoprostol dose a further dose may be given, (by mouth or by vagina) 400 micrograms for 1 dose

- **Termination of pregnancy following mifepristone**
  - (gestation of 9 to 13 weeks)
  - **INITIALLY BY VAGINA**
  - Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses

- **Termination of pregnancy following mifepristone**
  - (gestation of 13 to 24 weeks)
  - **INITIALLY BY VAGINA**
  - Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, followed by (by vagina or by mouth) 200 micrograms every 3 hours if required for a maximum of 4 doses, if abortion has not occurred 3 hours after the last dose of misoprostol, a further dose of mifepristone may be given, and misoprostol may be recommenced 12 hours later

**MYSODELLE® VAGINAL DELIVERY SYSTEM**

- **Induction of labour (specialist supervision in hospital)**
  - **By Vagina**
  - Adult: 200 micrograms for 1 dose, to be inserted (in vaginal delivery system) high into posterior fornix; if oxytocin required, remove at least 30 minutes before oxytocin administration, for information on when to remove the delivery system—consult product literature

**UNLICENSED USE** Misoprostol doses for termination of pregnancy may differ from those in product literature.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVISE: MISOPOROSTOL VAGINAL DELIVERY SYSTEM (MYSODELLE®). REPORTS OF EXCESSIVE UTERINE CONTRACTIONS (TACHYSYSTOLE) UNRESPONSIVE TO TOCOLYTIC TREATMENT (FEBRUARY 2018)

*Mysodelle (MYSODELLE®) can cause excessive uterine tachysystole that may not respond to tocolytic treatment. Monitor patients closely and remove the vaginal delivery system at the onset of labour, or if there is clinical concern for mother or baby.

Be prepared to administer tocolytic therapy—if needed, it can be administered immediately after removal of *Mysodelle®*.

**CONTRA-INDICATIONS**

- **MYSODELLE® VAGINAL DELIVERY SYSTEM** Before 36 weeks’ gestation - chorioamnionitis (unless adequate prior treatment initiated) - fetal malpresentation - placenta previa - suspicion or evidence of fetal compromise - unexplained vaginal bleeding after 24 weeks gestation - uterine abnormality - uterine scar

**CAUTIONS**

- When used for termination of pregnancy Cardiovascular disease - risk factors for cardiovascular disease

**MYSODELLE® VAGINAL DELIVERY SYSTEM** Modified Bishop score greater than 4

**SIDE-EFFECTS**

- **Common or very common**
  - Nausea - neonatal respiratory depression - rash - transient tachypnoea of the newborn - vomiting

- **Uncommon**
  - Genital pruritus - hypoxic–ischaemic encephalopathy - uterine rupture

**BREAST FEEDING**

- Manufacturer advises avoid—present in milk, and may cause diarrhoea in nursing infants.

**Tertiary sources state present in milk but amount probably too small to be harmful; to further reduce risk following termination of pregnancy, consider interrupting breastfeeding for 5 hours after a dose.

**HANDLING AND STORAGE**

- MYSODELLE® VAGINAL DELIVERY SYSTEM Manufacturer advises store in a freezer (-10 to -25°C); no thawing required prior to use.

**PATIENT AND CARER ADVICE**

- **Driving and skilled tasks** Manufacturer advises patients should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness.

**NATIONAL FUNDING/ACCESS DECISIONS**

**MYSODELLE® VAGINAL DELIVERY SYSTEM**

All Wales Medicines Strategy Group (AWMSG) decisions

AWMSG No. 3627

The All Wales Medicines Strategy Group has advised (March 2018) that misoprostol (*Mysodelle®*) is recommended as an option for use within NHS Wales for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
  - Misoprostol (Non-proprietary)

  - Misoprostol 200 microgram Misoprostol 200microgram vaginal tablets | 4 tablet (£245.00 (Hospital only))

  - Topogyn (Nordic Pharma Ltd)

  - Misoprostol 400 microgram Topogyn 400microgram tablets | 16 tablet (£128.00 (Hospital only))

**Vaginal delivery system**

- *Mysodelle* (Ferring Pharmaceuticals Ltd)

- Misoprostol 7 microgram per 1 hour Mysodelle 200micrograms vaginal delivery system | 5 unit (£465.00)

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**6 Vaginal and vulval conditions**

**Vaginal and vulval conditions**

**Management**

Symptoms are often restricted to the vulva, but infections almost invariably involve the vagina which should also be treated. Applications to the vulva alone are likely to give only symptomatic relief without cure.

*Aqueous medicated douches* may disturb normal vaginal acidity and bacterial flora.

*Topical anaesthetic agents* give only symptomatic relief and may cause sensitivity reactions. They are indicated only in cases of pruritus where specific local causes have been excluded.
Systemic drugs are required in the treatment of infections such as gonorrhoea and syphilis.

Vaginal and vulval changes

Topical HRT for vaginal atrophy
A cream containing an oestrogen may be applied on a short-term basis to improve the vaginal epithelium in menopausal atrophic vaginitis. It is important to bear in mind that topical oestrogens should be used in the smallest effective amount to minimise systemic effects. Modified-release vaginal tablets and an impregnated vaginal ring are also available.

The risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods. The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Topical oestrogens are also used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy.

Non-hormonal preparations for vaginal atrophy
Several non-hormonal vaginal moisturisers are available and some are prescribable on the NHS (consult Drug Tariff).

Vaginal and vulval infections
Effective specific treatments are available for the common vaginal infections.

Fungal infections
*Candidal vulvitis* can be treated locally with cream, but is almost invariably associated with vaginal infection which should also be treated. *Vaginal candidiasis* is treated primarily with antifungal pessaries or cream inserted high into the vagina (including during menstruation). Single-dose preparations offer an advantage when compliance is a problem. Local irritation may occur on application of vaginal antifungal products.

*Imidazole* drugs ( clotrimazole p. 829, econazole nitrate p. 830, miconazole nitrate p. 830, and miconazole p. 830) are effective against candida in short courses of 1 to 14 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur. Vaginal applications may be supplemented with antifungal cream for vulvitis and to treat other superficial sites of infection.

Oral treatment of vaginal infection with fluconazole p. 595 or itraconazole p. 597 is also effective.

*Vulvovaginal candidiasis in pregnancy*
Vulvovaginal candidiasis is common during pregnancy and can be treated with vaginal application of an imidazole (such as clotrimazole), and a topical imidazole cream for vulvitis. Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

*Recurrent vulvovaginal candidiasis*
Recurrence of vulvovaginal candidiasis is particularly likely if there are predisposing factors, such as antibacterial therapy, pregnancy, diabetes mellitus, or possibly oral contraceptive use. Reservoirs of infection may also lead to recontamination and should be treated; these include other skin sites such as the digits, nail beds, and umbilicus as well as the gastro-intestinal tract and the bladder. The partner may also be the source of reinfection and, if symptomatic, should be treated with a topical imidazole cream at the same time.

Treatment against candida may need to be extended for 6 months in recurrent vulvovaginal candidiasis.

Other infections
*Trichomonal infections* commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole p. 542 or tinidazole p. 544. *Bacterial infections* with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effective against certain Gram-negative organisms, especially *Bacteroides* spp. and can be used prophylactically in gynaecological surgery.

Clindamycin below cream and metronidazole gel are indicated for bacterial vaginosis.

Vaginal preparations intended to restore normal acidity may prevent recurrence of vaginal infections and permit the re-establishment of the normal vaginal flora.

The antiviral drugs aciclovir p. 633, famciclovir p. 635, and valaciclovir p. 636 can be used in the treatment of genital infection due to *herpes simplex virus*, the HSV type 2 being a major cause of genital ulceration; they have a beneficial effect on virus shedding and healing, generally giving relief from pain and other symptoms.

6.1 Vaginal and vulval infections

6.1a Vaginal and vulval bacterial infections

Other drugs used for Vaginal and vulval bacterial infections Metronidazole, p. 542

**ANTIBACTERIALS** > LINCOSAMIDES

Clindamycin

- **INDICATIONS AND DOSE**
  - **DALACIN® 2% CREAM**
    - **Bacterial vaginosis**
      - **BY VAGINA**
        - **Adult:** 1 applicatorful daily for 3–7 nights, dose to be administered at night
    - **DOSE EQUIVALENCE AND CONVERSION**
      - 1 applicatorful delivers a 5 g dose of clindamycin 2%.

  - **INTERACTIONS** > Appendix 1: clindamycin
  - **SIDE-EFFECTS**
    - **Common or very common** Skin reactions
    - **Frequency not known** Constipation; diarrhoea (discontinue); dizziness; gastrointestinal discomfort; headache; increased risk of infection; nausea; vertigo; vomiting; vulvovaginal irritation
  - **SIDE-EFFECTS, FURTHER INFORMATION** Clindamycin 2% cream is poorly absorbed into the blood—low risk of systemic effects.

- **CONCEPTION AND CONTRACEPTION**
  - **DALACIN® 2% CREAM** Damages latex condoms and diaphragms.

  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Cream EXCipients:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol
  - **Dalacin® (Pfizer Ltd)**
    - Clindamycin (as Clindamycin phosphate) 20 mg per 1 gram Dalacin 2% cream | 40 gram pack £10.86 DT + £10.86

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Vaginal and vulval fungal infections

Dequalinium chloride

**Dequalinium chloride**

- **Drug action** Dequalinium chloride is a bactericidal anti-infective which causes bacterial cell death by increasing cell permeability and reducing enzyme activity.

**Indications and dose**

**Bacterial vaginosis**
- **BY VAGINA**
  - Adult 18–55 years: 10 mg once daily for 6 days, inserted at night

**Contra-indications** Vaginal ulceration

**Side-effects**
- Common or very common Increased risk of infection - vulvovaginal disorders
- Uncommon Haemorrhage, headache, nausea
- Frequency not known Cystitis, fever

**Conception and contraception** Does not affect efficacy of latex condoms; however, manufacturer advises avoid use of non-latex condoms and intravaginal devices — no information available.

**Pregnancy** Manufacturer advises avoid unless essential — limited information available.

**National funding/access decisions**

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (November 2016) that dequalinium chloride (Fluomizin®) is accepted for restricted use within NHS Scotland for treatment of bacterial vaginosis in patients for whom the initial treatment is not effective or well tolerated.

All Wales Medicines Strategy Group (AWMSG) decisions
The All Wales Medicines Strategy Group has advised (November 2016) that dequalinium chloride (Fluomizin®) is recommended as an option for restricted use within NHS Wales for the treatment of bacterial vaginosis only after initial treatment is ineffective or not tolerated, as an alternative option to clindamycin vaginal cream.

**Medicinal forms**

- **TABLET**
  - Fluomizin (KoRa Healthcare)
  - Dequalinium chloride 10 mg Fluomizin 10mg vaginal tablets | 6 tablet | £6.95 DT + £6.95

Lactic acid

**Indications and dose**

**Balance Activ RX® Gel**

- **Prevention of bacterial vaginosis**
  - **BY VAGINA**
  - Adult: 5 mL 1–2 times a week, insert the content of 1 tube (5 mL)

**Relactagel® Gel**

- **Prevention of bacterial vaginosis**
  - **BY VAGINA**
  - Adult: 5 mL daily for 2–3 nights after menstruation, insert the contents of one tube

- **Treatment of bacterial vaginosis**
  - **BY VAGINA**
  - Adult: 5 mL daily for 7 nights, insert the contents of one tube

**Allergy and cross-sensitivity** Contra-indicated in shellfish allergy.

**Conception and contraception**

Relactagel® Gel Not recommended if trying to conceive.

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Products without form**

- **Excipients:** May contain Propylene glycol
  - Balance Activ (BBI Healthcare Ltd)
    - Balance Activ BV vaginal pH correction gel | 7 device £5.25
  - Relactagel (KoRa Healthcare)
    - Relactagel vaginal pH correction gel | 7 device £5.25

6.1b Vaginal and vulval fungal infections

Other drugs used for Vaginal and vulval fungal infections
Flucnazole, p. 595. Itraconazole, p. 597

Clotrimazole

**Indications and dose**

**Superficial sites of infection in vaginal and vulval candidiasis (dose for 1% or 2% cream)**
- **BY VAGINA USING CREAM**
  - Adult: Apply 2–3 times a day, to be applied to anogenital area

**Vaginal candidiasis (dose for 10% intravaginal cream)**
- **BY VAGINA USING VAGINAL CREAM**
  - Adult: 5 g for 1 dose, one applicatorful to be inserted into the vagina at night, dose can be repeated once if necessary

**Vaginal candidiasis**
- **BY VAGINA USING PESSIONS**
  - Adult: 200 mg for 3 nights, course can be repeated once if necessary, alternatively 100 mg for 6 nights, course can be repeated once if necessary, alternatively 500 mg for 1 night, dose can be repeated once if necessary

**Recurrent vulvovaginal candidiasis**
- **BY VAGINA USING PESSIONS**
  - Adult: 500 mg every week for 6 months, dose to be administered following topical imidazole for 10–14 days

**Interactions** 
- Appendix 1: antifungals, azoles

**Side-effects** Abdominal pain, discomfort, genital peeling, oedema, paraesthesia, pelvic pain, skin reactions, syncope, vaginal haemorrhage

**Conception and contraception** Cream and pessaries may damage latex condoms and diaphragms.

**Pregnancy**

- **Dose adjustments** Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

**Exceptions to legal category** Brands for sale to the public include Canesten® Internal Cream.

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

**Pessary**

- **Excipients:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - Canesten (clotrimazole) (Bayer Plc)
    - Clotrimazole 100 mg Canesten 100mg pessaries | 6 pessary £3.85 DT + £3.85
    - Clotrimazole 200 mg Canesten 200mg pessaries | 3 pessary £3.41 DT + £3.41

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**830 Vaginal and vulval conditions**

Clotrimazole 500 mg Canesten Vaginal 500mg pessaries
1 pessary £2.00 DT = £4.71

**Cream**

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates

- Clotrimazole (Non-proprietary)
  - Clotrimazole 10 mg per 1 gram Clotrimazole 1% cream
    - 20 gram £1.80 DT = £10.95 | 50 gram £5.45 DT = £3.38
  - Canesten (clotrimazole) (Bayer Plc)
    - Clotrimazole 10 mg per 1 gram Canesten 1% cream
      - 20 gram £2.20 DT = £0.95 | 50 gram £3.64 DT = £3.38

**SIDE-EFFECTS**

- Vaginal and vulval candidiasis
- Vaginal and vulva candidiasis
- Vaginal and vulval candidiasis
- Vaginal and vulval candidiasis

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058
- Skin reactions
- Angioedema
- Common or very common
- Rare or very rare
- Taste altered

**DOSE EQUIVALENCE AND CONVERSION**

- With topical use
- 1 applicatorful delivers a 5 g dose of fenticonazole 2 %.

**SIDE-EFFECTS**

- Paraesthesia

**CONCEPTION AND CONTRACEPTION**

- Intravaginal cream and vaginal capsules damage latex condoms and diaphragms.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Cream**

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol, woolfat and related substances (including lanolin)

- Gyno-Pevaryl (Recordati Pharmaceuticals Ltd)
  - Fenticonazole nitrate 20 mg per 1 gram Gyno-Pevaryl 2% vaginal cream
    - 30 gram £3.74

**Capssule**

EXCIPIENTS: May contain Hydroxybenzoates (parabens)

- Gyno-Pevaryl (Recordati Pharmaceuticals Ltd)
  - Fenticonazole nitrate 200 mg Gyno-Pevaryl 200mg vaginal capsules
    - 3 capsule £2.42
  - Fenticonazole nitrate 600 mg Gyno-Pevaryl 600mg vaginal capsules
    - 1 capsule £2.62

**Econazole nitratoe**

**INDICATIONS AND DOSE**

**GYN-PEVARYL® ONCE**

Vaginal and vulval candidiasis

- BY VAGINA
  - Adult: 1 pessary for 1 dose, pessary to be inserted at night, dose to be repeated once if necessary

**GYN-PEVARYL® CREAM**

Vaginal and vulval candidiasis

- INITIALLY BY VAGINA USING VAGINAL CREAM
  - Adult: 1 applicatorful daily for at least 14 days, dose to be inserted vaginally at night (and to the skin) apply daily for at least 14 days, to be applied to vulva at night, course can be repeated once if necessary

**GYN-PEVARYL® PESSARY**

Vaginal and vulval candidiasis

- BY VAGINA
  - Adult: 1 pessary daily for 3 days, pessary to be inserted at night, course can be repeated once if necessary

**SIDE-EFFECTS**

- Common or very common
- Skin reactions
- Vaginal burning
- Frequency not known
- Angioedema

**CONCEPTION AND CONTRACEPTION**

- Cream and pessaries damage latex condoms and diaphragms.

**PREGNANCY**

- Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Pessary**

- Gyno-Pevaryl (Janssen-Cilag Ltd)
  - Econazol nitratoe 150 mg Gyno-Pevaryl 150mg vaginal pessary
    - 1 pessary £1.89 | 3 pessary £4.17
  - Gyno-Pevaryl 150mg vaginal pessaries
    - 3 pessary £4.17

**Cream**

EXCIPIENTS: May contain Butylated hydroxyanisole, fragrances

- Gyno-Pevaryl (Janssen-Cilag Ltd)
  - Econazol nitratoe 10 mg per 1 gram Gyno-Pevaryl 1% cream
    - 15 gram £2.11 | 30 gram £3.78

**Fenticonazole nitrate**

**INDICATIONS AND DOSE**

Vaginal and vulva candidiasis

- BY VAGINA USING CAPSULES
  - Adult: 200 mg daily for 3 days, alternatively 600 mg daily for 1 dose, to be inserted at night
  - BY VAGINA USING CREAM
  - Adult: 1 applicatorful twice daily for 3 days

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058

**INTERACTIONS**

- Appendix 1: antifungals, azoles

**SIDE-EFFECTS**

- Common or very common
- Dysmenorrhoea - skin reactions - vulvovaginal disorders

**DOSE EQUIVALENCE AND CONVERSION**

- With topical use
- 1 applicatorful delivers a 5 g dose of fenticonazole 2 %.

**SIDE-EFFECTS**

- Paraesthesia

**CONCEPTION AND CONTRACEPTION**

- Intravaginal cream and vaginal capsules damage latex condoms and diaphragms.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Cream**

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol

- Gyno-Pevaryl (Recordati Pharmaceuticals Ltd)
  - Fenticonazole nitrate 20 mg per 1 gram Gyno-Pevaryl Once 2% vaginal cream
    - 30 gram £3.74

**Ketoconazole**

**INDICATIONS AND DOSE**

Vaginal and vulva candidiasis

- BY VAGINA USING CREAM
  - Adult: Apply 1–2 times a day, to be applied to the anogenital area

**CONTRA-INDICATIONS**

- Acute porphyrias p. 1058

**INTERACTIONS**

- Appendix 1: antifungals, azoles

**SIDE-EFFECTS**

- Common or very common
- Skin reactions
- Alopecia - angioedema
- Rare or very rare
- Taste altered

**CONCEPTION AND CONTRACEPTION**

- Effect on latex condoms and diaphragms not yet known.

**MEDI CANAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Cream**

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol

- Nizoral (Janssen-Cilag Ltd)
  - Ketoconazole 20 mg per 1 gram Nizoral 2% cream
    - 30 gram £4.24 DT = £4.24

**Miconazole**

**INDICATIONS AND DOSE**

Vaginal and vulva candidiasis

- BY VAGINA USING CREAM
  - Adult: 1 applicatorful once daily for 7 days, to be inserted into the vagina before bedtime, course can be repeated once if necessary

**Superficial sites of infection in vaginal and vulval candidiasis | Vulvitis**

- BY VAGINA USING VAGINAL CREAM
  - Adult: Apply twice daily, apply to the anogenital area

**CAUTIONS**

- Avoid in Acute porphyrias p. 1058

**INTERACTIONS**

- Appendix 1: antifungals, azoles

**SIDE-EFFECTS**

- Common or very common
- Dysmenorrhoea - skin reactions - vulvovaginal disorders

www.getintopharma.com
6.2 Vaginal atrophy

**OESTROGENS**

*Estradiol*

- **INDICATIONS AND DOSE**
  - **ESTRING®**
  - Postmenopausal urogenital conditions (not suitable for vasoconstrictor symptoms or osteoporosis prophylaxis)
    - **BY VAGINA**
    - Adult: To be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years
  - **VAGIFEM®**
  - Improve the vaginal epithelium in menopausal atrophic vaginitis
    - **BY VAGINA**
    - Adult: 1 tablet daily for 2 weeks, then reduced to 1 tablet twice weekly

- **CONTRA-INDICATIONS**
  - Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis - Dubin-Johnson syndrome (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - Rotor syndrome (or monitor closely) - thrombophlebitic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

- **CAUTIONS**
  - Acute porphyrias p. 1058 - diabetes (increased risk of heart disease) - history of breast nodules - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - factors predisposing to thromboembolism - history of fibrocystic disease - closely monitor breast status (risk of breast cancer) - hypophysial tumours - increased risk of gall-bladder disease - interrupt treatment periodically to assess need for continued treatment - migraine (or migraine-like headaches) - presence of antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size

- **INTERACTIONS**
  - Appendix 1: hormone replacement therapy

- **SIDE-EFFECTS**
  - **Common or very common**
    - Abdominal pain - headaches - nausea - skin reactions - vaginal haemorrhage - vulvovaginal disorders
  - **Uncommon**
    - Hypertension - vulvovaginal fungal infection - weight increased
  - **Rare or very rare**
    - Diarrhoea - embolism and thrombosis - endometrial hyperplasia - fluid retention - genital pruritus - increased risk of ischaemic stroke - insomnia - neoplasm malignant - neoplasms - vaginismus

**SIDE-EFFECTS, FURTHER INFORMATION**

Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. Continuous combined HRT commonly produces irregular breakthrough bleeding in the first 4–6 months of treatment. Bleeding beyond 6 months or the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

- Risk of endometrial cancer
  - The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.
  - In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously.
  - However, this should be weighed against the increased risk of breast cancer.

- Risk of ovarian cancer
  - Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

- Risk of venous thromboembolism
  - Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.
  - In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.

- Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

- Risk of stroke
  - Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke.
  - Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

- Risk of coronary heart disease
  - HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

- **Other conditions**
  - The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.
after a spell of amenorrhoea requires further investigation to exclude serious gynaecological pathology.

- **CONCEPTION AND CONTRACEPTION** HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant. VAGIFEM® No evidence of damage to latex condoms and diaphragms.

- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Avoid; adverse effects on lactation.
- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

- **MONITORING REQUIREMENTS**
  - History of breast nodules or fibrocystic disease—closely monitor breast status (risk of breast cancer).
  - The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Pessary**
  - **Vagifem** (Novo Nordisk Ltd)
    - Estradiol 10 microgram Vagifem 10microgram vaginal tablets
    - 24 pessary
  - **Vagifem** (Novo Nordisk Ltd)
  - **Estring** (Pfizer Ltd)
    - Estradiol (as Estradiol hemihydrate) 7.5 microgram/24 hour
    - Vaginal delivery system
  - **Estring** (Pfizer Ltd)

- **Estring** (Pfizer Ltd)
  - Estradiol (as Estradiol hemihydrate) 7.5 microgram per 24 hour
  - Estring 7.5micrograms/24hours vaginal delivery system
  - 1 device

  **Benefits**
  - **INDICATIONS AND DOSE**
    - **OVESTIN**®
    - Improve the vaginal epithelium in menopausal atrophic vaginitis (short-term use)
    - BY VAGINA
      - Adult: Apply 1 applicatorful daily for 2–3 weeks, then reduced to 1 applicatorful twice weekly, discontinue every 2–3 months for 4 weeks to assess need for further treatment
    - Vaginal surgery for prolapse when there is epithelial atrophy in postmenopausal women (before surgery)
      - BY VAGINA
        - Adult: Apply 1 applicatorful daily for 2 weeks before surgery, resume 2 weeks after surgery

- **CONTRA-INDICATIONS** Active arterial thromboembolic disease (e.g. angina or myocardial infarction) · Rotor syndrome (or monitor closely) · thrombophilic disorder · undiagnosed vaginal bleeding · untreated endometrial hyperplasia · venous thromboembolism

- **CAUTIONS** Acute porphyrias p. 1058 · diabetes (increased risk of heart disease) · factors predisposing to thromboembolism · history of breast nodules—closely monitor breast status (risk of breast cancer) · history of endometrial hyperplasia · history of fibrocystic disease—closely monitor breast status (risk of breast cancer) · hypophyseal tumours · increased risk of gall-bladder disease · interrupt treatment periodically to assess need for continued treatment · migraine (or migraine-like headaches) · presence of antiphospholipid antibodies (increased risk of thrombotic events) · prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer · risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) · symptoms of endometriosis may be exacerbated · uterine fibroids may increase in size

  **CAUTIONS, FURTHER INFORMATION**
  - Risk of breast cancer It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.
  - Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.
  - Risk of endometrial cancer The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.
    - In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously.
    - However, this should be weighed against the increased risk of breast cancer.
  - Risk of ovarian cancer Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.
  - Risk of venous thromboembolism Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.
  - In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.
  - Travel Involving prolonged immobility further increases the risk of deep vein thrombosis.
  - Risk of stroke Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.
  - Risk of coronary heart disease HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.
  - Other conditions The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, rectal or colorectal disease.
otitis media, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **INTERACTIONS** → Appendix 1: hormone replacement therapy
- **SIDE EFFECTS**
  - Breast abnormalities - cervical mucus increase, headache, increased risk of coronary artery disease, increased risk of ischaemic stroke, increased risk of venous thromboembolism, nausea, neoplasms, skin reactions, vaginal haemorrhage, vaginal spotting, vomiting
- **CONCEPTION AND CONTRACEPTION**
  - Effect on latex condoms and diaphragms not yet known.
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Avoid; adverse effects on lactation.
- **HEPATIC IMPAIRMENT**
  - Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.
- **RENA L IMPAIRMENT** Manufacturer advises caution in renal disease. Evidence for caution is unsatisfactory and many women with these conditions may stand to benefit from HRT.
- **MONITORING REQUIREMENTS**
  - Closely monitor breast status if history of breast nodules or fibrocystic disease (risk of breast cancer).
  - The endometrial safety of long-term or repeated use of oestrogen products for vaginal application, where systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestogen.
  - Risk of ovarian cancer Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.
  - Risk of venous thromboembolism Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use.
  - In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, major surgery or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits.
  - Travel involving prolonged immobility further increases the risk of deep vein thrombosis.
  - Risk of stroke Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke.
  - Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.
- **OTHER CONDITIONS**
  - The product literature advises caution in other conditions including hypertension, asthma, epilepsy, otosclerosis, and systemic lupus erythematosus.
  - Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - EXCIPIENTS: May contain Arachis (peanut) oil, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
    - Ovestin (Aspen Pharma Trading Ltd)
    - Estradiol 1 mg per 1 gram Ovestin 1mg cream 15 gram £4.45 DT = £4.45

### Prasterone

**Drug action** Prasterone is biochemically and biologically identical to endogenous dehydroepiandrosterone (DHEA), and is converted to oestrogens and androgens.

- **INDICATIONS AND DOSE**
  - Vulvar and vaginal atrophy [in postmenopausal women with moderate to severe symptoms]
    - Adults: 6.5 mg once daily, at bedtime. Treatment should be reassessed at least every 6 months

- **CONTRA-INDICATIONS**
  - Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction). acute liver disease, acute porphyrias, history of breast cancer, history of liver disease (where liver function tests have failed to return to normal), oestrogen-dependent cancer, thrombophilic disorder, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, venous thromboembolism

- **CAUTIONS**
  - Assess need for continued treatment at least every 6 months: cholestasis, diabetes mellitus, factors predisposing to thromboembolism, history of endometrial hyperplasia, hypertriglyceridaemia, liver disorders (discontinue if jaundice or deterioration in liver function occurs during treatment)
  - migraine (or migraine-like headaches) prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size

- **CAUTIONS, FURTHER INFORMATION**
  - Risk of breast cancer It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.
  - Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.
  - Risk of endometrial cancer The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT.
  - Bleeding or spotting occurring during treatment should be investigated.
  - For oestrogen products for vaginal application, where systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestogen.

### Ovestin

**Expiry Date**

- May 2019

**Interactions**

- **Anticoagulants** Risk of bleeding increases (use lower dose and monitor closely). Risk of venous thromboembolism (e.g. angina or myocardial infarction) increases. Risk of peptic ulcer increases (may require increase in dose of omeprazole). Risk of deep vein thrombosis increases (may require reduction in dose of dabigatran, rivaroxaban or apixaban).

**Effects of other drugs**

- **Selective oestrogen receptor modulators** Risk of endometrial cancer increases (increase monitoring frequency). Risk of thromboembolism increases (some need for dose adjustment)

**Pharmacokinetics**

- **Absorption** Almost complete. Absorption is increased by food and antacids.
- **Distribution** Varies with dose and duration of HRT use. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

**Indications and Dose**

- **Vulvar and vaginal atrophy** [in postmenopausal women with moderate to severe symptoms]
  - Adults: 6.5 mg once daily, at bedtime. Treatment should be reassessed at least every 6 months.
SELECTIVE OESTROGEN RECEPTOR MODULATORS

Ospemifene

18-Oct-2018

DRUG ACTION Ospemifene is a selective oestrogen receptor modulator that has an oestrogen-like effect in the vagina, increasing the cellular maturation and mucusification of the vaginal epithelium.

INDICATIONS AND DOSE

Moderate to severe symptomatic vulvar and vaginal atrophy [in post-menopausal women who are not candidates for local vaginal oestrogen therapy]

BY MOUTH

Adult: 60 mg once daily

CONTRA-INDICATIONS

Breast cancer (suspected or actively treated) • endometrial hyperplasia • history of venous thromboembolism • sex-hormone dependent malignancy (suspected or active) • unexplained vaginal bleeding

CAUTIONS

Risk factors for stroke • risk factors for venous thromboembolism (discontinue if prolonged immobilisation)

INTERACTIONS

→ Appendix 1: ospemifene

SIDE-EFFECTS

Common or very common Genital discharge • hot flush • increased risk of infection • muscle spasms • skin reactions • vaginal discharge

Uncommon Endometrial thickening • hypersensitivity • tongue swelling

PREGNANCY

Manufacturer advises avoid—toxicity in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises avoid in severe impairment—no information available.

PATIENT AND CARER ADVICE

Manufacturer advises patients and their carers should be advised to seek immediate medical attention if they experience symptoms of thromboembolism (such as sudden chest pain, dyspnoea or swelling of a leg).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

Senshio (Shionogi Ltd)▼

Ospemifene 60 mg Senshio 60mg tablets | 28 tablet £39.50
Chapter 8
Immune system and malignant disease

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Immune system

1 Immune system disorders and transplantation

Immune response

Inflammatory bowel disease
Azathioprine p. 836, ciclosporin p. 838, mercaptopurine p. 912, and methotrexate p. 913 have a role in the treatment of inflammatory bowel disease.
Folic acid p. 1025 should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid is usually given weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

Immunosuppressant therapy
Immunosuppressants are used to suppress rejection in organ transplant recipients and to treat a variety of chronic inflammatory and autoimmune diseases. Solid organ transplant patients are maintained on drug regimens, which may include antiproliferative drugs (azathioprine or mycophenolate mofetil p. 846), calcineurin inhibitors (ciclosporin or tacrolimus p. 841), corticosteroids, or sirolimus p. 840. Choice is dependent on the type of organ, time after transplantation, and clinical condition of the patient. Specialist management is required and other immunomodulators may be used to initiate treatment or to treat rejection.

Impaired immune responsiveness
Modification of tissue reactions caused by corticosteroids and other immunosuppressants may result in the rapid spread of infection. Corticosteroids may suppress clinical signs of infection and allow diseases such as septicaemia or tuberculosis to reach an advanced stage before being recognised—important: normal immunoglobulin administration should be considered as soon as possible after measles exposure, and varicella–zoster immunoglobulin (VZIG) is recommended for individuals who have significant chickenpox (varicella) exposure. Specialist advice should be sought on the use of live vaccines for those being treated with immunosuppressive drugs.

Antiproliferative immunosuppressants
Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced when allopurinol p. 1121 is given concurrently.
Mycophenolate mofetil is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine.
There is evidence that compared with similar regimens incorporating azathioprine, mycophenolate mofetil reduces the risk of acute rejection episodes; the risk of opportunistic infections (particularly due to tissue-invasive cytomegalovirus) and the occurrence of blood disorders such as leucopenia may be higher.
Cyclophosphamide p. 894 is less commonly prescribed as an immunosuppressant.

Corticosteroids and other immunosuppressants
Prednisolone p. 678 is widely used in oncology. It has a marked antitumour effect in acute lymphoblastic leukaemia, Hodgkin’s disease, and the non-Hodgkin lymphomas. It has a role in the palliation of symptomatic end-stage malignant disease when it may enhance appetite and produce a sense of well-being.
The corticosteroids are also powerful immunosuppressants. They are used to prevent organ transplant rejection, and in high dose to treat rejection episodes.
Ciclosporin a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-myelotoxic but markedly nephrotoxic. It has an important role in organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, and for prophylaxis and treatment of graft-versus-host disease.
Tacrolimus is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity appears to be greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant.
Sirolimus is a non–calcineurin inhibiting immunosuppressant licensed for renal transplantation. Basiliximab p. 844 is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is given with ciclosporin and corticosteroid immunosuppression regimens; its use should be confined to specialist centres.
Belatacept p. 847 is a fusion protein and co-stimulation blocker that prevents T-cell activation; it is licensed for prophylaxis of graft rejection in adults undergoing renal transplantation who are seropositive for the Epstein–Barr virus. It is used with interleukin-2 receptor antagonist induction, in combination with corticosteroids and a mycophenolic acid.

Antithymocyte immunoglobulin (rabbit) below is licensed for the prophylaxis of organ rejection in renal and heart allograft recipients and for the treatment of corticosteroid-resistant allograft rejection in renal transplantation. Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

Other drugs used for immune system disorders and transplantation

**Antithymocyte immunoglobulin (rabbit)**

28-Nov-2017

- **INDICATIONS AND DOSE**
  - **Prophylaxis of organ rejection in heart allograft recipients**
    - Adult: 1–2.5 mg/kg daily for 3–5 days, to be given over at least 6 hours
  - **Prophylaxis of organ rejection in renal allograft recipients**
    - Adult: 1–1.5 mg/kg daily for 3–9 days, to be given over at least 6 hours
  - **Treatment of corticosteroid-resistant allograft rejection in renal transplantation**
    - Adult: 1.5 mg/kg daily for 7–14 days, to be given over at least 6 hours

- **DOSES AT EXTREMES OF BODY-WEIGHT**
  - To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight.

- **CONTRA-INDICATIONS**
- Infection

- **INTERACTIONS** → Appendix 1: immunoglobulins

- **SIDE-EFFECTS**
  - **Common or very common**
    - Chills · diarrhea · dysphagia · dyspnæa · fever · hypotension · infection · lymphopenia · myalgia · nausea · neoplasms · neutropenia · reactivation of infection · secondary malignancy · sepsis · skin reactions · thrombocytopenia · vomiting
  - **Uncommon**
    - Cytokine release syndrome · hepatic disorders · hypersensitivity · infusion related reaction

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

- **PREGNANCY**
  - Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor blood count.

- **DIRECTIONS FOR ADMINISTRATION**
  - For continuous intravenous infusion (Thymoglobulin®) in Glucose 5% or Sodium chloride 0.9%; reconstitute each vial with 5 mL water for injections to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with infusion fluid to a total volume of 50–500 mL (usually 50 mL/vial); begin infusion immediately after dilution; give through an in-line filter (pore size 0.22 micron); not to be given with unfractonated heparin and hydrocortisone in glucose infusion—precipitation reported.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **MEPYRAMINES**
  - Available.

- **IMMUNOCORES**
  - Antithymocyte immunoglobulin (rabbit) is not recommended as an initial treatment to prevent organ rejection in adults having a kidney transplant. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/TA481

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder and solvent for solution for infusion**
    - Thymoglobulin (Sanofi)
      - Antithymocyte immunoglobulin (rabbit) 25 mg
      - Thymoglobuline 25 mg powder and solvent for solution for infusion vials | 1 vial | £158.77 (Hospital only)

**IMMUNOSUPPRESSANTS › ANTIMETABOLITES**

**Azathioprine**

13-Jun-2018

- **DRUG ACTION**
  - Azathioprine is metabolised to mercaptopurine.

- **INDICATIONS AND DOSE**
  - Severe acute Crohn’s disease | Maintenance of remission of Crohn’s disease | Maintenance of remission of acute ulcerative colitis
    - **BY MOUTH**
      - Adult: 2–2.5 mg/kg daily, some patients may respond to lower doses

  - Rheumatoid arthritis that has not responded to other disease-modifying drugs | Severe systemic lupus erythematosus and other connective tissue disorders | Polymyositis in cases of corticosteroid resistance
    - **BY MOUTH**
      - Adult: Initially up to 2.5 mg/kg daily in divided doses, adjusted according to response, rarely more than 3 mg/kg daily; maintenance 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months

  - Autoimmune conditions
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 1–3 mg/kg daily, adjusted according to response, consider withdrawal if no improvement within 3 months, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

  - Suppression of transplant rejection
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: 1–2.5 mg/kg daily, adjusted according to response, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

  - Severe refractory eczema, normal or high TPMT activity
    - **BY MOUTH**
      - Adult: 1–3 mg/kg daily
## Immune system disorders and transplantation

### Severe refractory eczema, intermediate TPMT activity
- **BY MOUTH**
  - Adult: 0.5–1.5 mg/kg daily

### Generalised myasthenia gravis
- **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Initially 0.5–1 mg/kg daily, then increased to 2–2.5 mg/kg daily, dose is increased over 3–4 weeks, azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of the corticosteroid to be used, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

#### Dose adjustments due to interactions
- Monitor dose and reduce dose to one-quarter of the usual dose with concurrent use of allopurinol.

### Contra-indications
- Hypersensitivity to mercaptopurine.

### Interactions
- Reduce dose in elderly.

### Side-effects
- **General side-effects**
  - Common or very common: Bone marrow depression (dose-related), increased risk of infection, leucopenia, thrombocytopenia.
  - Uncommon: Anaemia, hepatic disorders, hypersensitivity, pancreatitis.
  - Rare or very rare: Agranulocytosis, alopecia, bone marrow suppression, gastrointestinal disorders, neoplasms, photosensitivity reaction, pneumonia.
  - Severe cutaneous adverse reactions (SCARs).
  - Frequency not known: Nodular regenerative hyperplasia, sinusoidal obstruction syndrome.

### Specific side-effects
- With oral use: Nausea.

### Further information
- Side-effects may require drug withdrawal.

### Hypersensitivity reactions
- Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and renal dysfunction) call for immediate withdrawal.

### Neutropenia and thrombocytopenia
- Neutropenia is dose-dependent. Management of neutropenia and thrombocytopenia requires careful monitoring and dose adjustment.

### Nausea
- Nausea is common early in the course of treatment and usually resolves after a few weeks without an alteration in dose. Moderate nausea can be managed by using divided daily doses, taking doses after food, prescribing concurrent antiemetics or temporarily reducing the dose.

### Allergy and cross-sensitivity
- Contra-indicated in hypersensitivity to mercaptopurine.

### Pregnancy
- Transplant patients immunosuppressed with azathioprine should not discontinue it on becoming pregnant. However, there have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure. Azathioprine is teratogenic in animal studies. The use of azathioprine during pregnancy needs to be supervised in specialist units. Treatment should not generally be initiated during pregnancy.

### Breast feeding
- Present in milk in low concentration. No evidence of harm in small studies—use if potential benefit outweighs risk.

### Hepatic impairment
- Manufacturer advises caution (impaired metabolism)—monitor liver function and complete blood count more frequently in those with severe impairment.

### Dose adjustments
- Manufacturer advises use doses at lower end of the dose range in hepatic failure; reduce dose if hepatic or haematological toxicity occur.

### Renal impairment
- Dose adjustments: Reduce dose.

### Pre-treatment screening
- Thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Consider measuring TPMT activity before starting azathioprine, mercaptopurine, or tioguanine therapy. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

### Monitoring requirements
- Monitor for toxicity throughout treatment.
- Monitor full blood count weekly (more frequently with higher doses or if severe renal impairment) for first 4 weeks (manufacturer advises weekly monitoring for 8 weeks but evidence of practical value unsatisfactory), thereafter reduce frequency of monitoring to at least every 3 months.

### Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment.

### Directions for administration
- With intravenous use: For intravenous injection, give over at least 1 minute (followed by 50 mL sodium chloride intravenous infusion). For intravenous infusion (Imuran®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 50 mg with 5–15 mL Water for Injections; dilute requisite dose to a volume of 20–200 mL with infusion fluid. Intravenous injection is alkaline and very irritant, intravenous route should therefore be used only if oral route not feasible.

### Patient and carer advice
- Bone marrow suppression. Patients and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.

### Medicinal forms
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.

## Table

### Azathioprine (Non-proprietary)
- **Azathioprine 25 mg** (Azathioprine 25mg tablets) | 28 tablet pack
- **Azathioprine 50 mg** (Azathioprine 50mg tablets) | 56 tablet pack
- **Azathioprine 100 mg** (Azathioprine 100mg tablets) | 56 tablet pack
- **Azathioprine 250 mg** (Azathioprine 250mg tablets) | 56 tablet pack
- **Azathioprine 500 mg** (Azathioprine 500mg tablets) | 56 tablet pack

### Azapress (Emmgen Pharma Ltd)
- **Azathioprine 25 mg** (Azapress 25mg tablets) | 100 tablet pack
- **Azathioprine 50 mg** (Azapress 50mg tablets) | 100 tablet pack
- **Azathioprine 100 mg** (Azapress 100mg tablets) | 100 tablet pack

### Imuran (Aspen Pharma Trading Ltd)
- **Azathioprine 25 mg** (Imuran 25mg tablets) | 100 tablet pack
- **Azathioprine 50 mg** (Imuran 50mg tablets) | 100 tablet pack
- **Azathioprine 100 mg** (Imuran 100mg tablets) | 100 tablet pack

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**www.getintopharma.com**
Ciclosporin

(Cyclosporin)

**IMMUNOSUPPRESSANTS > CALCINEURIN INHIBITORS AND RELATED DRUGS**

**Drug Action**
Ciclosporin inhibits production and release of lymphokines, thereby suppressing cell-mediated immune response.

**Indications and Dose**

- **Severe acute ulcerative colitis refractory to corticosteroid treatment**
  - **By mouth**
  - Adult: Initially 1.5 mg/kg twice daily, increased if necessary up to 2.5 mg/kg twice daily after 6 weeks, dose increases should be made gradually, for maintenance treatment, titrate dose individually to the lowest effective dose according to tolerability, treatment may be required for up to 12 weeks.

- **Severe active rheumatoid arthritis (administered on expert advice)**
  - **By mouth**
  - Adult: Initially 2 mg/kg, to be given over 24 hours, dose adjusted according to blood-ciclosporin concentration and response.

- **Severe active rheumatoid arthritis (in combination with low-dose methotrexate, when methotrexate monotherapy has been ineffective) (administered on expert advice)**
  - **By mouth**
  - Adult: Initially 1.25 mg/kg twice daily, increased if necessary up to 2.5 mg/kg twice daily after 6 weeks, dose increases should be made gradually, for maintenance treatment, titrate dose individually to the lowest effective dose according to tolerability, treatment may be required for up to 12 weeks.

- **Short-term treatment of severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice)**
  - **By mouth**
  - Adult: 25 mg/kg twice daily usual maximum duration of 8 weeks but may be used for longer under specialist supervision, if good initial response not achieved within 2 weeks, increase dose rapidly up to maximum.

- **Short-term treatment of very severe atopic dermatitis where conventional therapy ineffective or inappropriate (administered on expert advice)**
  - **By mouth**
  - Adult: 2.5 mg/kg twice daily usual maximum duration of 8 weeks but may be used for longer under specialist supervision.

- **Severe psoriasis where conventional therapy ineffective or inappropriate (administered on expert advice)**
  - **By mouth**
  - Adult: Initially 1.25 mg/kg twice daily (max. per dose 2.5 mg/kg twice daily) usual maximum duration of 8 weeks but may be used for longer under specialist supervision.

**Indications and Dose**

- **Bone-marrow transplantation**
  - **Initially by intravenous infusion**
    - Adult: 3–5 mg/kg daily, to be administered over 2–6 hours from day before transplantation to 2 weeks postoperatively, alternatively (by mouth) initially 12.5–15 mg/kg daily, then (by mouth) 12.5 mg/kg daily for 3–6 months and then tailed off (may take up to a year after transplantation).

- **Nephrotic syndrome**
  - **By mouth**
  - Adult: 5 mg/kg daily in 2 divided doses, for maintenance reduce to lowest effective dose according to proteinuria and serum creatinine measurements; discontinue after 3 months if no improvement in glomerulonephritis or glomerulosclerosis (after 6 months in membranous glomerulonephritis).

**Interactions due to interactions**

- With oral use. Manufacturer advises increase dose by 50% or switch to intravenous administration with concurrent use of octreotide.

**Unlicensed Use**
Not licensed for use in severe acute ulcerative colitis refractory to corticosteroid treatment.

**Contra-indications**


**Caution**

- Elderly - monitor renal function.
- Hyperuricaemia - in atopic dermatitis, active herpes simplex infections — allow infection to clear before starting (if they occur during treatment withdraw if severe) - in atopic dermatitis, *Staphylococcus aureus* skin infections — not absolute contra-indication providing controlled (but avoid erythromycin unless no other alternative) - in psoriasis treat, patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option) - in uveitis, Behçet’s syndrome (monitor neurological status) - lymphoproliferative disorders (discontinue treatment) - malignancy.

**Important Safety Information**

MHRA/CHM Advice: Ciclosporin must be prescribed and dispensed by brand name (December 2009)

Patients should be stabilised on a particular brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration.

**Interactions**

- Appendix 1: ciclosporin
**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Common or very common: Eye inflammation

**SPECIFIC SIDE-EFFECTS**
- Common or very common: Appetite decreased, diarrhoea, electrolyte imbalance, fatigue, fever, flushing, gastrointestinal discomfort, gingival hyperplasia, hair changes, headaches, hepatic disorders, hyperglycaemia, hyperlipidaemia, hypertension, hyperuricaemia, leucopenia, muscle complaints, nausea, paraesthesia, peptic ulcer, renal impairment (renal structural changes on long-term administration), seizure, skin reactions, tremor, vomiting
- Uncommon: Anaemia, encephalopathy, oedema, thrombocytopenia, weight increased
- Rare or very rare: Gynaecomastia, haemolytic anaemia, idiopathic intracranial hypertension, menstrual disorder, multifocal motor neuropathy, muscle weakness, myopathy, pancreatitis
- Frequency not known: Pain in extremity, thrombotic microangiopathy

**PREGNANCY**
- Crosses placenta; manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies

**BREAST FEEDING**
- Manufacturer advises avoid—present in milk.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in severe impairment (risk of increased exposure).

**Dose adjustments**
- Manufacturer advises consider dose reduction in severe impairment to maintain blood-cyclosporin concentration in target range—monitor until concentration stable.

**RENAL IMPAIRMENT**
- Dose adjustments
  - In non-transplant indications, manufacturer advises establishing baseline renal function before initiation of treatment; if baseline function is impaired in non-transplant indications, except nephrotic syndrome—avoid. In nephrotic syndrome, manufacturer advises initial dose should not exceed 2.5 mg/kg daily in patients with baseline renal impairment. *During treatment* for non-transplant indications, manufacturer recommends if eGFR decreases by more than 25% below baseline on more than one measurement, reduce dose by 25–50%. If the eGFR decrease from baseline exceeds 35%, further dose reduction should be considered (even if within normal range); discontinue if reduction not successful within 1 month.

**MONITORING REQUIREMENTS**
- Monitor whole blood ciclosporin concentration (trough level dependent on indication—consult local treatment protocol for details).
- Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting treatment for psoriasis or atopic dermatitis.
- Monitor liver function.
- Monitor serum potassium, especially in renal dysfunction (risk of hyperkalaemia).
- Monitor serum magnesium.
- Measure blood lipids before treatment and after the first month of treatment.
- In psoriasis and atopic dermatitis monitor serum creatinine every 2 weeks for first 3 months then every month.
- Investigate lymphadenopathy that persists despite improvement in atopic dermatitis.
- Monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction in transplant patients (exclude rejection if kidney transplant) or discontinuation in non-transplant patients.
- Monitor blood pressure—discontinue if hypertension develops that cannot be controlled by antihypertensives.
- In long-term management of nephrotic syndrome, perform renal biopsies at yearly intervals.
- In rheumatoid arthritis measure serum creatinine at least twice before treatment. During treatment, monitor serum creatinine every 2 weeks for first 3 months, then every month for a further 3 months, then every 4–8 weeks depending on the stability of the disease, concomitant medication, and concomitant diseases (or more frequently if dose increased or concomitant NSAIDs introduced or increased).
- Monitor hepatic function if concomitant NSAIDs given.

**DIRECTIONS FOR ADMINISTRATION**
- With oral use: Mix solution with orange or apple juice, or other soft drink (to improve taste) immediately before taking (and rinse with more to ensure total dose). Do not mix with grapefruit juice. Total daily dose should be taken in 2 divided doses.
- With intravenous use: For *intravenous infusion* (*Sandimmun*®), give intermittently or continuously in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 50 mg in 20–100 ml; give intermittent infusion over 2–6 hours; not to be used with PVC equipment. Observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

**PRESCRIBING AND DISPENSING INFORMATION**
- Brand name prescribing: Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand of ciclosporin, the patient should be monitored closely for changes in blood-cyclosporin concentration, serum creatinine, blood pressure, and transplant function (for transplant indications). *Sandimmun*® capsules and oral solution are available direct from Novartis for patients who cannot be transferred to a different oral preparation.

**PATIENT AND CARER ADVICE**
- Patients and carers should be counselled on the administration of different formulations of ciclosporin. Manufacturer advises avoid excessive exposure to UV light, including sunlight. In psoriasis and atopic dermatitis, avoid use of UVB or PUVA.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

**CAUTIONARY AND ADVISORY LABELS**

**EXCIPIENTS:** May contain Alcohol, poloxyl castor oils
- *Sandimmun* (Novartis Pharmaceuticals UK Ltd)
  - Ciclosporin 50 mg per 1 ml
  - Ciclosporin 100 mg per 1 ml

**Neoral** (Novartis Pharmaceuticals UK Ltd)
- Ciclosporin 100 mg per 1 ml

**Ciclosporin 100 mg per 1 ml**
- Concentrate for infusion ampoules

**Sandimmun 50 mg/ml oral solution**
- Concentrate for infusion ampoules

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS**

**EXCIPIENTS:** May contain Alcohol, propylene glycol
- *Capsorin* (Morningside Healthcare Ltd)
  - Ciclosporin 100 mg/ml oral solution sugar-free
  - Ciclosporin 1000 mg/ml oral solution sugar-free

**Neoral** (Novartis Pharmaceuticals UK Ltd)
- Ciclosporin 100 mg/ml oral solution sugar-free
- Ciclosporin 1000 mg/ml oral solution sugar-free

**Sandimmun** (Novartis Pharmaceuticals UK Ltd)
- Ciclosporin 100 mg/ml oral solution sugar-free

### Capsule

**CAUTIONARY AND ADVISORY LABELS**

**EXCIPIENTS:** May contain Ethanol, ethyl lactate, propylene glycol
- *Ciclosporin* (Non-proprietary)
  - Capsules

**Ciclosporin 25 mg**
- Capsules

**Ciclosporin 50 mg**
- Capsules
Immune system disorders and transplantation

Sirolimus

**DRUG ACTION** Sirolimus is a non-calcineurin inhibiting immunosuppressant.

**INDICATIONS AND DOSE**

Prophylaxis of organ rejection in kidney allograft recipients

**BY MOUTH**

- Adult: Initially 6 mg for 1 dose, to be given after surgery once wound has healed, then 2 mg once daily; to be given in combination with ciclosporin and corticosteroid for 2–3 months (sirolimus doses should be given 4 hours after ciclosporin), ciclosporin should then be withdrawn over 4–8 weeks (if not possible, sirolimus should be discontinued and an alternate immunosuppressive regimen used), dose to be adjusted according to whole blood-sirolimus trough concentration

**DOSE EQUIVALENCE AND CONVERSION**

- The 500 mg microgram tablet is not bioequivalent to the 1 mg and 2 mg tablets. Multiples of 500 microgram tablets should not be used as a substitute for other tablet strengths.

**CAUTIONS** Hyperlipidaemia - increased susceptibility to infection (especially urinary-tract infection) - increased susceptibility to lymphoma and other malignancies, particularly of the skin (limit exposure to UV light)

**INTERACTIONS** → Appendix 1: sirolimus

**SIDE-EFFECTS**

- **Hyperlipidaemia**

- **Uncommon** Antibiotic associated colitis - focal segmental glomerulosclerosis - headache - nephrotic syndrome - pancytopenia - post-transplant lymphoproliferative disorder

**Frequency not known** Posterior reversible encephalopathy syndrome (PRES)

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment and for 12 weeks after stopping.

**PREGNANCY** Avoid unless essential—toxicity in animal studies.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure).

**Dose adjustments** Manufacturer advises maintenance dose reduction of approx. 50% in severe impairment—monitor whole blood-sirolimus trough concentration every 5–7 days until 3 consecutive measurements have shown stable blood-sirolimus concentration.

**MONITORING REQUIREMENTS**

- Monitor whole blood-sirolimus trough concentration (Afro-Caribbean patients may require higher doses).

- Manufacturer advises pre-dose (‘trough’) whole blood-sirolimus concentration (using chromatographic assay) when used with ciclosporin should be 4–12 micrograms/litre (local treatment protocols may differ); after withdrawal of ciclosporin pre-dose whole blood-sirolimus concentration should be 12–20 micrograms/litre (local treatment protocols may differ).

- Close monitoring of whole blood-sirolimus concentration required if concomitant treatment with potent inducers or inhibitors of metabolism and after discontinuing them, or if ciclosporin dose reduced significantly or stopped.

- When changing between oral solution and tablets, measurement of whole blood ‘trough’ sirolimus concentration after 1–2 weeks is recommended.

- Therapeutic drug monitoring assays Sirolimus whole-blood concentration is measured using either high performance liquid chromatography (HPLC) or immunoassay. Switching between different immunoassays or between an immunoassay and HPLC can lead to clinically significant differences in results and therefore incorrect dose adjustments. Adjustment to the target therapeutic dose range should be made with knowledge of the assay used and corresponding reference range.

- Monitor kidney function when given with ciclosporin; monitor lipids; monitor urine proteins.

**DIRECTIONS FOR ADMINISTRATION** Food may affect absorption (take at the same time with respect to food). Sirolimus oral solution should be mixed with at least 60 mL water or orange juice in a glass or plastic container immediately before taking; refill container with at least 120 mL of water or orange juice and drink immediately (to ensure total dose). Do not mix with any other liquids.

Ciclosporin 100 mg

Ciclosporin 100 mg capsules

- Adult: 840 micrograms/day + 30 capsule

- **Capimmune** (Mylan)
  - Ciclosporin 25 mg: 2 capsules/day 840 micrograms/day + 30 capsule
  - Ciclosporin 50 mg: 4 capsules/day 840 micrograms/day + 30 capsule

- **Ciclosporin** (Novartis Pharmaceuticals UK Ltd)
  - Ciclosporin 100 mg: 3 capsules/day 840 micrograms/day + 30 capsule

- **Neoral** (Teva UK Ltd)
  - Ciclosporin 25 mg: 1 capsule/day 840 micrograms/day + 30 capsule

- **Sandimmune** (Morningside Healthcare Ltd)
  - Ciclosporin 50 mg: 1 capsule/day 840 micrograms/day + 30 capsule

- **Sandimmune** (Mylan)
  - Ciclosporin 100 mg: 1 capsule/day 840 micrograms/day + 30 capsule

- **Vanquoral** (Afro-Caribbean patients may require higher doses)
  - Ciclosporin 100 mg: 1 capsule/day 840 micrograms/day + 30 capsule
  - Ciclosporin 25 mg: 1 capsule/day 840 micrograms/day + 30 capsule

- **Mycophenolate** 1000 mg

- **Mycophenolate** 1000 capsules

- **Mycophenolate** 1000 micrograms/litre

- **Mycophenolate** 2500 micrograms/litre

- **Mycophenolate** 5000 micrograms/litre

- **Mycophenolate** 7500 micrograms/litre

- **Mycophenolate** 10000 micrograms/litre

- **Mycophenolate** 12500 micrograms/litre

- **Mycophenolate** 15000 micrograms/litre

- **Mycophenolate** 17500 micrograms/litre

- **Mycophenolate** 20000 micrograms/litre

- **Mycophenolate** 22500 micrograms/litre

- **Mycophenolate** 25000 micrograms/litre

- **Mycophenolate** 27500 micrograms/litre

- **Mycophenolate** 30000 micrograms/litre

- **Mycophenolate** 32500 micrograms/litre

- **Mycophenolate** 35000 micrograms/litre

- **Mycophenolate** 37500 micrograms/litre

- **Mycophenolate** 40000 micrograms/litre

- **Mycophenolate** 42500 micrograms/litre

- **Mycophenolate** 45000 micrograms/litre

- **Mycophenolate** 47500 micrograms/litre

- **Mycophenolate** 50000 micrograms/litre

- **Mycophenolate** 52500 micrograms/litre

- **Mycophenolate** 55000 micrograms/litre

- **Mycophenolate** 57500 micrograms/litre

- **Mycophenolate** 60000 micrograms/litre

- **Mycophenolate** 62500 micrograms/litre

- **Mycophenolate** 65000 micrograms/litre

- **Mycophenolate** 67500 micrograms/litre

- **Mycophenolate** 70000 micrograms/litre

- **Mycophenolate** 72500 micrograms/litre

- **Mycophenolate** 75000 micrograms/litre

- **Mycophenolate** 77500 micrograms/litre

- **Mycophenolate** 80000 micrograms/litre

- **Mycophenolate** 82500 micrograms/litre

- **Mycophenolate** 85000 micrograms/litre

- **Mycophenolate** 87500 micrograms/litre

- **Mycophenolate** 90000 micrograms/litre

- **Mycophenolate** 92500 micrograms/litre

- **Mycophenolate** 95000 micrograms/litre

- **Mycophenolate** 97500 micrograms/litre

- **Mycophenolate** 100000 micrograms/litre

- **Mycophenolate** 102500 micrograms/litre

- **Mycophenolate** 105000 micrograms/litre

- **Mycophenolate** 107500 micrograms/litre

- **Mycophenolate** 110000 micrograms/litre

- **Mycophenolate** 112500 micrograms/litre

- **Mycophenolate** 115000 micrograms/litre

- **Mycophenolate** 117500 micrograms/litre
Immune system disorders and transplantation

Tacrolimus

**DRUG ACTION** Tacrolimus is a calcineurin inhibitor.

**INDICATIONS AND DOSE**

**ADOPORT®**

**Prophylaxis of graft rejection following liver transplantation, starting 12–18 hours after transplantation**

- **BY MOUTH**
  - Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation**

- **BY MOUTH**
  - Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation**

- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation**

- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

**Allograft rejection resistant to conventional immunosuppressive therapy**

- **BY MOUTH**
  - Adult: Seek specialist advice

**MODIGRAF®**

**Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation**

- **BY MOUTH**
  - Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation**

- **BY MOUTH**
  - Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation**

- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

**Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation**

- **BY MOUTH**
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

**Rejection therapy**

- **BY MOUTH**
  - Adult: Seek specialist advice

**PROGRAF® CAPSULES**

**Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation**

- **BY MOUTH**
  - Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

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Immune system and malignant disease

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

- BY MOUTH
  - Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

- BY MOUTH
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

- BY MOUTH
  - Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

- BY INTRAVENOUS INFUSION
  - Adult: Seek specialist advice

PROgraf® INFUSION

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation when oral route not appropriate

- BY INTRAVENOUS INFUSION
  - Adult: Initially 10–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate

- BY INTRAVENOUS INFUSION
  - Adult: Initially 50–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

- BY INTRAVENOUS INFUSION
  - Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

- BY INTRAVENOUS INFUSION
  - Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Allograft rejection resistant to conventional immunosuppressive therapy

- BY CONTINUOUS INTRAVENOUS INFUSION
  - Adult: Seek specialist advice (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: ORAL TACROLIMUS PRODUCTS: PRESCRIBE and DISPENSE BY BRAND NAME ONLY, TO MINIMISE THE RISK OF INADVERTENT SWITCHING BETWEEN PRODUCTS, WHICH HAS BEEN ASSOCIATED WITH REPORTS OF TOXICITY AND GRAFT REJECTION (JUNE 2012)

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

- Adoport®, Prograf® and Capexion® are immediate-release capsules that are taken twice daily, once in the morning and once in the evening;
- Modigraf® granules are used to prepare an immediate-release oral suspension which is taken twice daily, once in the morning and once in the evening;
- Advagraf® is a prolonged-release capsule that is taken once daily in the morning.

Switching between tacrolimus brands requires careful supervision and therapeutic monitoring by an appropriate specialist.

Important: Envarsus® is not interchangeable with other oral tacrolimus containing products; the MHRA has advised (June 2012) that oral tacrolimus products should be prescribed and dispensed by brand only.

**CAUTIONS**
- Increased risk of infections – lymphoproliferative disorders – malignancies – neurotoxicity – QT-interval prolongation – UV light (avoid excessive exposure to sunlight and sunlamps)

**INTERACTIONS**

- Appendix 1: tacrolimus

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common

- Uncommon

- Rare or very rare

- Frequency not known

**SPECIFIC SIDE-EFFECTS**

- Frequency not known
- With intravenous use
- Anaphylactoid reaction (due to excipient) – hypersensitivity
SIDE-EFFECTS, FURTHER INFORMATION  Cardiomyopathy has been reported to occur primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Patients should be monitored by echocardiography for hypertrophic changes—consider dose reduction or discontinuation if these occur.

- ALLERGY AND CROSS-SENSITIVITY  Contra-indicated if history of hypersensitivity to macrolides.
- CONCEPTION AND CONTRACEPTION  Exclude pregnancy before treatment.
- PREGNANCY  Avoid unless potential benefit outweighs risk—crosses the placenta and risk of premature delivery, intra-uterine growth restriction, and hyperkalaemia.
- BREAST FEEDING  Avoid—present in breast milk (following systemic administration).
- HEPATIC IMPAIRMENT  Manufacturer advises caution in severe impairment.

Dose adjustments  Manufacturer advises consider dose reduction in severe impairment.

- MONITORING REQUIREMENTS
  - After initial dosing, and for maintenance treatment, tacrolimus doses should be adjusted according to whole-blood concentration. Monitor whole blood-tacrolimus trough concentration (especially during episodes of diarrhoea)—consult local treatment protocol for details.
  - Monitor blood pressure, ECG (for hypertrophic changes—risk of cardiomyopathy), fasting blood-glucose concentration, haematological and neurological (including visual) and coagulation parameters, electrolytes, hepatic and renal function.

- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use  For intravenous infusion (Prograf®); give continuously in Glucose 5% or Sodium Chloride 0.9%.
  - Dilute concentrate in infusion fluid to a final concentration of 4–100 micrograms/mL; give over 24 hours. Tacrolimus is incompatible with PVC.
- PATIENT AND CARER ADVICE  Avoid excessive exposure to UV light including sunlight.

Driving and skilled tasks  May affect performance of skilled tasks (e.g. driving).

- NATIONAL FUNDING/ACCESS DECISIONS
  - NICEdgments
    - Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE T4A81
    - Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. Treatment should be started with the least expensive product, but if this is not suitable, an alternative dosage form may be given. Tacrolimus granules for oral suspension (Modigraft®) should be used only if the manufacturer provides it at the same price or lower than that agreed with the Commercial Medicines Unit. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/T4A81

- Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE T4A81
  - Prolonged-release tacrolimus is not recommended as an initial treatment to prevent organ rejection in adults having a kidney transplant. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/T4A81

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2010) that tacrolimus granules for suspension (Modigraft®) are accepted for restricted use within NHS Scotland in patients for whom tacrolimus is an appropriate choice of immunosuppressive therapy and where small changes (less than 500 micrograms) in dosing increments are required (such as, in paediatric patients) or in seriously ill patients who are unable to swallow tacrolimus capsules.

The Scottish Medicines Consortium has advised (April 2015) that tacrolimus (Envarsus®) is accepted for use in NHS Scotland for prophylaxis of graft rejection and treatment of rejection resistant to treatment with other immunosuppressive medicinal products in adults.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

- Envarsus® (Chiesi Ltd) Tacrolimus (as Tacrolimus monohydrate) 750 microgram Envarsus 750 microgram modified-release tablets | 30 tablet (Pst) £44.33 DT = £44.33
- Tacrolimus (as Tacrolimus monohydrate) 1 mg Tacrolimus 1 mg modified-release tablets | 30 tablet (Pst) £59.10 DT = £59.10
- Tacrolimus (as Tacrolimus monohydrate) 4 mg Tacrolimus 4 mg modified-release tablets | 30 tablet (Pst) £236.40 DT = £236.40

Granules

CAUTIONARY AND ADVISORY LABELS 13, 23

- Modigraf® (Astellas Pharma Ltd) Tacrolimus (as Tacrolimus monohydrate) 200 microgram Tacrolimus 0.2mg granules sachets sugar-free | 50 sachet (Pst) £17.30 DT = £17.30
- Tacrolimus (as Tacrolimus monohydrate) 1 mg Tacrolimus 1 mg granules sachets sugar-free | 50 sachet (Pst) £356.65 DT = £356.65

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 23, 25

- Advagraf® (Astellas Pharma Ltd) Tacrolimus (as Tacrolimus monohydrate) 500 microgram Tacrolimus 0.5mg modified-release capsules | 50 capsule (Pst) £35.79 DT = £35.79
- Tacrolimus (as Tacrolimus monohydrate) 1 mg Advagraf 1mg modified-release capsules | 50 capsule (Pst) £71.59 DT = £71.59
- Tacrolimus (as Tacrolimus monohydrate) 3 mg Advagraf 3mg modified-release capsules | 50 capsule (Pst) £214.76 DT = £214.76
- Tacrolimus (as Tacrolimus monohydrate) 5 mg Advagraf 5mg modified-release capsules | 50 capsule (Pst) £266.92 DT = £266.92

Solution for infusion

EXCIPIENTS: May contain Polyoxyl castor oils

- Prograf® (Astellas Pharma Ltd) Tacrolimus 5 mg per 1 ml Prograf 5mg/1ml solution for infusion ampoules | 10 ampoule (Pst) £384.51

Capsule

CAUTIONARY AND ADVISORY LABELS 23

- Adoport® (Sandzol Ltd) Tacrolimus 500 microgram Adoport 0.5mg capsules | 50 capsule (Pst) £42.92 DT = £43.88
- Tacrolimus 1 mg Adoport 1mg capsules | 50 capsule (Pst) £55.69 DT = £80.28
- Tacrolimus 5 mg Adoport 5mg capsules | 50 capsule (Pst) £205.74 DT = £239.58
- Prograf® (Astellas Pharma Ltd) Tacrolimus 500 microgram Prograf 500microgram capsules | 50 capsule (Pst) £61.88 DT = £61.88
- Tacrolimus 1 mg Prograf 1mg capsules | 50 capsule (Pst) £80.28 DT = £80.28
- Tacrolimus 5 mg Prograf 5mg capsules | 50 capsule (Pst) £296.58 DT = £296.58
IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES

Canakinumab

- **DRUG ACTION** Canakinumab is a recombinant human monoclonal antibody that selectively inhibits interleukin-1 beta receptor binding.

- **INDICATIONS AND DOSE**
  - **Gouty arthritis [in patients whose condition has not responded adequately to treatment with NSAIDs or colchicine, or in those with concomitant drug intolerances or to them, and in whom repeated courses of corticosteroids are inappropriate]**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 150 mg for 1 dose, in patients who respond, dose may be repeated after at least 12 weeks if symptoms recur, to be administered to the upper thigh, abdomen, upper arm or buttocks
  - **Gouty arthritis associated periodic syndromes [specialist use only]**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult (body-weight 41 kg and above): 150 mg every 8 weeks, to be administered to the upper thigh, abdomen, upper arm or buttocks, additional doses may be considered if clinical response not achieved within 7 days—consult product literature
  - **Tumour necrosis factor receptor associated periodic syndrome [specialist use only]**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 150 mg per 1 ml Ilaris 150mg/1ml solution for injection vials | 1 vial (POT £9,927.80)
  - **Still's disease [specialist use only]**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 4 mg/kg every 4 weeks (max. per dose 300 mg), to be administered to the upper thigh, abdomen, upper arm or buttocks

- **CONTRA-INDICATIONS** Active infection · leucopenia · neutropenia
- **CAUTIONS** History of recurrent infection · latent and active tuberculosis · predisposition to infection

- **VACCINATIONS** Patients should receive all recommended vaccinations (including pneumococcal and inactivated influenza vaccine) before starting treatment; avoid live vaccines unless potential benefit outweighs risk—consult product literature for further information.

- **INTERACTIONS** → Appendix 1: monoclonal antibodies
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain upper · arthralgia · asthenia · dizziness · increased risk of infection · leucopenia · neutropenia · pain · proteinuria · vertigo
  - **Uncommon** Gastrooesophageal reflux disease
  - **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment and for up to 3 months after last dose.
  - **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.
  - **BREAST FEEDING** Consider if benefit outweighs risk—not known if present in human milk.
  - **RENAL IMPAIRMENT** Limited information available but manufacturer advises no dose adjustment required.

- **PRE-TREATMENT SCREENING** Patients should be evaluated for latent and active tuberculosis before starting treatment.
- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor full blood count including neutrophil count before starting treatment, 1–2 months after starting treatment, and periodically thereafter.
  - Manufacturer advises monitor for signs and symptoms of infection (including tuberculosis) during and after treatment.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8 °C).

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Manufacturer advises patients and carers should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (including persistent cough, weight loss and subfebrile temperature) occur.
  - **Consult product literature**—there can be variation in the licensing of different medicines containing the same drug.

IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES > ANTI-LYMPHOCYTE

Basiliximab

- **DRUG ACTION** Basiliximab is a monoclonal antibody that acts as an interleukin-2 receptor antagonist and prevents T-lymphocyte proliferation.

- **INDICATIONS AND DOSE**
  - **Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens [specialist use only]**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - Adult: Initially 20 mg, administered within 2 hours before transplant surgery, followed by 20 mg after 4 days, dose to be administered after surgery, withhold second dose if severe hypersensitivity or graft loss occurs.

- **CAUTIONS** Off-label use in cardiac transplantation—increased risk of serious cardiac side-effects
- **INTERACTIONS** → Appendix 1: monoclonal antibodies
- **SIDE-EFFECTS** Anaemia · capillary leak syndrome · constipation · cytokine release syndrome · diarrhoea · dyspnoea · electrolyte imbalance · headache · heart failure · hypercholesterolaemia · hypersensitivity · hypertension · hypotension · increased risk of infection · myocardial infarction · nausea · pain · peripheral oedema · post procedural wound complication · pulmonary oedema · respiratory disorders · skin reactions · sneezing · tachycardia · weight increased
- **CONCEPTION AND CONTRACEPTION** Adequate contraception must be used during treatment and for 16 weeks after last dose.
- **PREGNANCY** Manufacturer advises avoid—no information available.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Simulect ®) give intermittently in Glucose 5% or Sodium...
chloride 0.9%; reconstitute 10 mg with 2.5 mL water for injections then dilute to at least 25 mL with infusion fluid; reconstitute 20 mg with 5 mL water for injections then dilute to at least 50 mL with infusion fluid; give over 20-30 minutes.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE TA481
    - Basiliximab, when used as part of an immunosuppressive regimen that includes a calcineurin inhibitor, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. The use of basiliximab with tacrolimus is outside the terms of the marketing authorisation. If this combination is prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
    - **www.nice.org.uk/guidance/TA481**

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - Powder and solvent for solution for injection
    - Simulect® (Novartis Pharmaceuticals UK Ltd)
    - Basiliximab 10 mg Simulect 10mg powder and solvent for solution for injection vials | 1 vial (£358.69 Hospital only)
    - Basiliximab 20 mg Simulect 20mg powder and solvent for solution for injection vials | 1 vial (£842.38 Hospital only)

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**Belimumab**

- **INDICATIONS AND DOSE**
  - Adjuvant therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy
    - **BY INTRAVENOUS INFUSION**
    - Adult: 10 mg/kg every 2 weeks for 3 doses, then 10 mg/kg every 4 weeks, review treatment if no response within 6 months

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**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: BELIMUMAB (BELNLYSTA®): INCREASED RISK OF SERIOUS PSYCHIATRIC EVENTS SEEN IN CLINICAL TRIALS (APRIL 2019)

Clinical trials show an increased risk of depression, suicidal ideation or behaviour, or self-injury in patients with systemic lupus erythematosus on belimumab. Healthcare professionals should assess patients for these risks before starting treatment, monitor for new or worsening signs of these risks during treatment, and advise patients to seek immediate medical attention if new or worsening symptoms occur.

- **CAUTIONS** Do not initiate until active infections controlled • history or development of malignancy • predisposition to infection
- **INTERACTIONS** • Appendix 1: monoclonal antibodies
- **SIDE-EFFECTS**
  - Common or very common Cystitis • depression • diarrhoea • fever • hypersensitivity • increased risk of infection • infusion related reaction • insomnia • leucopenia • migraine • nausea • pain in extremity
  - Uncommon Angioedema • skin reactions
  - Frequency not known Progressive multifocal leukoencephalopathy (PML) • self-injurious behaviour • suicidal tendencies • vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Infusion-related side-effects are reported commonly, including severe or life-threatening hypersensitivity and infusion reactions. Premedication with an antihistamine, with or without an antipyretic may be considered.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises adequate contraception during treatment and for at least 4 months after last dose.
- **PREGNANCY** Avoid unless essential.
- **BREAST FEEDING** Avoid—present in milk in animal studies.
- **RENAL IMPAIRMENT** Caution in severe impairment—no information available.
- **MONITORING REQUIREMENTS** Delay in the onset of acute hypersensitivity reactions has been observed; patients should remain under clinical supervision for several hours following at least the first 2 infusions.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Belnlysta®), give intermittently in Sodium chloride 0.9%; reconstitute with water for injections (120 mg in 1.5 mL, 400 mg in 4.8 mL) to produce a solution containing 80 mg/mL; gently swirl vial for 60 seconds, then allow to stand; swirl vial (without shaking) for 60 seconds every 5 minutes until dissolved; dilute requisite dose with infusion fluid to a final volume of 250 mL and give over 1 hour.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Belimumab for treating active autoantibody-positive systemic lupus erythematosus (June 2016) NICE TA397
    - Belimumab (Benlysta®) is recommended as an add-on treatment option in adults with active autoantibody-positive systemic lupus erythematosus, only if all of the following criteria apply:
      - there is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of greater than or equal to 10 despite standard therapy;
      - treatment with belimumab is continued after 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more;
      - the manufacturer provides belimumab with the discount agreed in the patient access scheme; and
      - under the conditions specified in the NICE managed access agreement documentation.

Patients whose treatment was started before this guidance was published should continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

- **www.nice.org.uk/guidance/ta397**

Scottish Medicines Consortium (SMC) decisions

SMC No. 775/12

The Scottish Medicines Consortium has advised (May 2017) that belimumab (Benlysta®) is accepted for restricted use within NHS Scotland as adjuvant therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy, and who have evidence of serological disease activity and a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of 10 or greater. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

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**www.getintopharma.com**
**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- Benlysta (GliazoSmithKline UK Ltd) ▼
  - Belimumab 120 mg Benlysta 120mg powder for concentrate for solution for infusion vials | 1 vial (PZN) 1213.50 (Hospital only)
  - Belimumab 400 mg Benlysta 400mg powder for concentrate for solution for infusion vials | 1 vial (PZN) 1405.00 (Hospital only)

**IMMUNOSUPPRESSANTS** > PURINE SYNTHESIS INHIBITORS

**Mycophenolate mofetil**

**INDICATIONS AND DOSE**

Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and ciclosporin) (under expert supervision)
- **BY MOUTH**
  - Adult: 1 g twice daily, to be started within 72 hours of transplantation
  - **BY INTRAVENOUS INFUSION**
    - Adult: 1 g twice daily for maximum 14 days, then transfer to oral therapy, to be started within 24 hours of transplantation

Prophylaxis of acute rejection in cardic transplantation (in combination with ciclosporin and corticosteroids) (under expert supervision)
- **BY MOUTH**
  - Adult: 1.5 g twice daily, to be started within 5 days of transplantation

Prophylaxis of acute rejection in hepatic transplantation (in combination with ciclosporin and corticosteroids) (under expert supervision)
- **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: 1 g twice daily for 4 days, up to a maximum of 14 days, to be started within 24 hours of transplantation, then (by mouth) 1.5 g twice daily, the dose route should be changed as soon as is tolerated.

**CEPTAVA®**

Renal transplantation (specialist use only)
- **BY MOUTH**
  - Adult: 720 mg twice daily, to be started within 72 hours of transplantation

**DOSE EQUIVALENCE AND CONVERSION**
- For Ceptava®: Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences.

**MYFORTIC®**

Renal transplantation (specialist use only)
- **BY MOUTH**
  - Adult: 720 mg twice daily, to be started within 72 hours of transplantation

**DOSE EQUIVALENCE AND CONVERSION**
- For Myfortic®: Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: MYCOPHENOLATE MOFETIL, MYCOPHENOLIC ACID: UPDATED CONTRACEPTION ADVICE FOR MALE PATIENTS (FEBRUARY 2018)**

Available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded; for further information, see Conception and contraception and Patient and carer advice.

**CAUTIONS** Active serious gastro-intestinal disease (risk of haemorrhage, ulceration and perforation) - children (higher incidence of side-effects may call for temporary reduction of dose or interruption) - delayed graft function - elderly (increased risk of infection, gastro-intestinal haemorrhage and pulmonary oedema) - increased susceptibility to skin cancer (avoid exposure to strong sunlight) - risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants.

**INTERACTIONS** → Appendix 1: mycophenolate

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Common or very common
  - Acne
  - Alopecia
  - Anaemia
  - Appetite decreased
  - Arthralgia
  - Asthenia
  - Bone marrow disorders
  - Chills
  - Constipation
  - Cough
  - Depression
  - Diarrhoea
  - Drowsiness
  - Dyslipidaemia
  - Dysphonia
  - Electrolyte imbalance
  - Fever
  - Gastrointestinal discomfort
  - Gastrointestinal disorders
  - Gastrointestinal haemorrhage
  - Headache
  - Hyperglycaemia
  - Hypertension
  - Hypotension
  - Increased risk of infection
  - Insomnia
  - Leucocytosis
  - Leucopenia
  - Malaise
  - Nausea
  - Neoplasms
  - Oedema
  - Oral disorders
  - Pain
  - Pancreatitis
  - Paraesthesia
  - Renal impairment
  - Respiratory disorders
  - Seizure
  - Sepsis
  - Skin reactions
  - Tachycardia
  - Thinking abnormal
  - Thrombocytopenia
  - Tremor
  - Vomiting
  - Weight decreased

- Uncommon
  - Agranulocytosis

- Frequency not known
  - Endocarditis
  - Hypogammaglobulinaemia
  - Malignancy
  - Meningitis
  - Neuropathy
  - Neutropenia
  - Pancreatitis
  - Paraesthesia
  - Progressive multifocal leukoencephalopathy
  - Renal impairment
  - Respiratory disorders
  - Seizure
  - Sepsis
  - Skin reactions
  - Tachycardia
  - Thinking abnormal

**SPECIFIC SIDE-EFFECTS**
- Common or very common
  - With intravenous use
    - Hepatitis
    - Muscle tone increased
  - With oral use
    - Anxiety
    - Burping
    - Confusion
    - Dizziness
    - Gout
    - Hepatic disorders
    - Hyperbilirubinaemia
    - Hyperuricaemia
    - Neuromuscular dysfunction
    - Taste altered
    - Vasodilation

**SIDE-EFFECTS, FURTHER INFORMATION**
Cases of pure red cell aplasia have been reported with mycophenolate mofetil; dose reduction or discontinuation should be considered under specialist supervision.

**CONCEPTION AND CONTRACEPTION**

Pregnancy prevention. The MHRA advises to exclude pregnancy in females of child-bearing potential before treatment. After 2 months of treatment— 2 pregnancy tests 8–10 days apart are recommended. Women should use at least 1 method of effective contraception before and during treatment, and for 6 weeks after discontinuation—2 methods of effective contraception are preferred. Male patients or their female partner should use effective contraception during treatment and for 90 days after discontinuation.

**PREGNANCY** Avoid unless no suitable alternative—will be required for infusion.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**RENAL IMPAIRMENT** No data available in cardiac or hepatic transplantation patients with renal impairment.

**MONITORING REQUIREMENTS** Monitor full blood count every week for 4 weeks then twice a month for 2 months.
then every month in the first year (consider interrupting treatment if neutropenia develops).

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use: For intravenous infusion (CellCept®), give intermittently in Glucose 5%; reconstitute each 500–mg vial with 14 mL glucose 5% and dilute the contents of 2 vials in 140 mL infusion fluid; give over 2 hours.

**PATIENT AND CARER ADVICE**
- Pregnancy prevention advice: The MHRA advises that prescribers should ensure that female patients understand the implications of both immunosuppression and the effect of the prescribed medications on the pregnancy. Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexpressible bruising or bleeding.

**NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE decisions**
  - Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE TA481
  - Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. Treatment should be started with the least expensive product, but if this is not suitable, an alternative dosage form may be given. The use of mycophenolate mofetil with tacrolimus is outside the terms of the marketing authorisation. If this combination is prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.
  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop. 

  www.nice.org.uk/guidance/TA481

- Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE TA481

  Mycophenolate sodium (Ceptava®, Myfortic®) is not recommended as an initial treatment to prevent organ rejection in adults having a kidney transplant. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/TA481

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Gastro-resistant tablet**

  CAUTIONARY AND ADVISORY LABELS 25

  - Mycophenolate mofetil (Non-proprietary)
    - Mycophenolic acid (as Mycophenolate sodium) 180 mg Mycophenolic acid 180 mg gastro-resistant tablets | 120 tablet (PB) £101.07 DT = £96.72
    - Mycophenolic acid (as Mycophenolate sodium) 360 mg Mycophenolic acid 360 mg gastro-resistant tablets | 120 tablet (PB) £202.13 DT = £193.43
    - Ceptava (Sandiz Ltd)
      - Mycophenolic acid (as Mycophenolate sodium) 180 mg Ceptava 180mg gastro-resistant tablets | 120 tablet (PB) £77.38 DT = £76.72
      - Mycophenolic acid (as Mycophenolate sodium) 360 mg Ceptava 360mg gastro-resistant tablets | 120 tablet (PB) £154.75 DT = £149.43

  - Myfortic (Novartis Pharmaceuticals UK Ltd)
    - Mycophenolic acid (as Mycophenolate sodium) 180 mg Myfortic 180mg gastro-resistant tablets | 120 tablet (PB) £96.72 DT = £96.72
    - Mycophenolic acid (as Mycophenolate sodium) 360 mg Myfortic 360mg gastro-resistant tablets | 120 tablet (PB) £193.43 DT = £193.43

**Tablet**

- Mycophenolate mofetil (Non-proprietary)
  - Mycophenolate mofetil 500 mg Mycophenolate mofetil 500mg tablets | 50 tablet (PB) £42.50 DT = £5.83
  - CellCept (Roche Products Ltd)
    - Mycophenolate mofetil 500 mg CellCept 500mg tablets | 50 tablet (PB) £82.26 DT = £16.53
  - Myfenox (Teva UK Ltd)
    - Mycophenolate mofetil 500 mg Myfenax 500mg tablets | 50 tablet (PB) £78.15 DT = £5.83

**Oral suspension**

  EXCIPIENTS: May contain Aspartame

  - CellCept (Roche Products Ltd)
    - Mycophenolate mofetil 200 mg per 1 ml CellCept 1g/5ml oral suspension sugar-free | 175 ml (PB) £115.16 DT = £65.16

**Powder for solution for infusion**

- Mycophenolate mofetil (as Mycophenolate mofetil hydrochloride) 500 mg Mycophenolate mofetil 500mg powder for concentrate for solution for infusion vials | 4 vial (PB) £34.67 (hospital only)

- CellCept (Roche Products Ltd)
  - Mycophenolate mofetil (as Mycophenolate mofetil hydrochloride) 500 mg CellCept 500mg powder for solution for infusion vials | 4 vial (PB) £36.49

- Capsule

  - Mycophenolate mofetil (Non-proprietary)
    - Mycophenolate mofetil 250 mg Mycophenolate mofetil 250mg capsules | 100 capsule (PB) £82.26 DT = £82.26
    - CellCept (Roche Products Ltd)
      - Mycophenolate mofetil 250 mg CellCept 250mg capsules | 100 capsule (PB) £82.26 DT = £82.26
    - Myfenox (Teva UK Ltd)
      - Mycophenolate mofetil 250 mg Myfenax 250mg capsules | 100 capsule (PB) £78.15 DT = £82.26

**IMMUNOSUPPRESSANTS > T-CELL ACTIVATION INHIBITORS**

**Belatacept**

- **INDICATIONS AND DOSE**
  - Prophylaxis of graft rejection in adults undergoing renal transplantation who are seropositive for the Epstein-Barr virus
  - By intravenous infusion
  - Adult: (consult product literature)

- **CAUTIONS**
  - Increased risk of acute graft rejection—with tapering of corticosteroid, particularly in patients with high immunologic risk
  - Increased risk of infection—latent and active tuberculosis
  - Risk factors for post-transplant lymphoproliferative disorder

- **INTERACTIONS**
  - Appendix 1: belatacept

- **SIDE-EFFECTS**
  - Common or very common
  - Acne, alopecia, anaemia, angina pectoris, arthralgia, arthritides, arterial fibrosis, atrial fibrillation, chest pain, constipation, cough, Cushing’s syndrome, decreased leucocytes, diabetes mellitus, diarrhoea, dizziness, dyslipidaemia, dysphoria, ear pain, electrolyte imbalance, embolism and thrombosis, eye erythema, fatigue, fever, fluid imbalance, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, headaches, healing impaired, heart failure, hepatic disorders, hypercapnia, hyperglycaemia, hypertension, hypoproteinaemia, hypotension, increased risk of infection, intervertebral disc disorder, joint disorders, laryngitis, leucocytosis, lymphocele, malaise, muscle complaints, muscle weakness, nausea, neoplasms, nerve
Multiple sclerosis

Description of condition

Multiple sclerosis is a chronic, immune-mediated, demyelinating inflammatory condition of the central nervous system, which affects the brain, optic nerves and spinal cord, and leads to progressive severe disability.

Relapsing-remitting multiple sclerosis is the most common pattern of the disease. It is characterised by periods of exacerbation of symptoms (relapses) followed by unpredictable periods of stability (remission). The severity and frequency of relapses varies greatly between patients, but on average occur once or twice per year. This clinical pattern often develops into secondary-progressive multiple sclerosis, with progressive disability unrelated to relapses. Most patients develop secondary progressive disease 6–10 years after onset.

Primary-progressive multiple sclerosis follows a gradual course, with the development of symptoms that worsen over time, without relapses and remissions.

Progressive-relapsing multiple sclerosis follows a course of steadily worsening neurological function from onset, in addition to acute relapses.

Disease activity in relapsing-remitting multiple sclerosis

Active disease is defined as at least two clinically significant relapses occurring within the last 2 years. Highly active disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year, despite treatment with interferon beta p. 850. Rapidly-evolving severe relapsing-remitting multiple sclerosis is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

Aims of treatment

There is no cure for multiple sclerosis. The overall aims of treatment are to modify the course of the disease and manage symptoms, in order to improve quality of life. Treatment is aimed at reducing the frequency and duration of relapses and at preventing or slowing disability.

Drug treatment

Shared decision-making between the patient and their clinicians is particularly important in the treatment of multiple sclerosis, due to the unpredictability of the condition and the lack of evidence of long-term benefit of treatments. A discussion about treatment options, disease activity, risk, and benefit should take place to ensure that treatment choices are right for the patient and their circumstances. The choice of drug also depends on the patient’s disability status, individual tolerance, disease severity and disease activity (see Disease activity in relapsing-remitting multiple sclerosis above). Treatment should be initiated as early as possible, under the supervision of a specialist.

Note: NHS England (May 2014) has provided guidance on the use of interferon beta, glatiramer acetate p. 852, fingolimod p. 854 and natalizumab p. 857 for the treatment of multiple sclerosis in England, see Useful resources below. This Clinical Commissioning Policy outlines the funding arrangements and the criteria for initiating and discontinuing these treatment options. See also National funding/access decisions, under individual monographs for teriflunomide p. 859, dimethyl fumarate p. 853 and alemtuzumab p. 857.

848 Immune system disorders and transplantation

1.1 Multiple sclerosis

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www.getintopharma.com
Low levels of vitamin D are believed to be a risk factor for developing multiple sclerosis. Patients with diagnosed multiple sclerosis are usually given regular vitamin D after assessment of their serum levels of vitamin D, but there is insufficient evidence to support its use as a treatment for multiple sclerosis. Patients should not be offered vitamin D solely for the purpose of treating multiple sclerosis.

Relapsing-remitting multiple sclerosis

Disease-modifying drugs are the recommended treatment for patients presenting with active relapsing-remitting multiple sclerosis. Interferon beta and glatiramer acetate may be the preferred choice for some patients, due to their established safety profile, and the long term clinical experience associated with their use. Peginterferon beta-1a p. 852 requires less frequent administration and is available as an alternative to the non-pegylated interferon beta therapies.

Teriflunomide and dimethyl fumarate are treatment options for patients with active disease. They may be preferred due to their oral route of administration. There is insufficient evidence for the use of either drug to treat highly active or rapidly-evolving severe relapsing-remitting multiple sclerosis.

More active disease may be treated with natalizumab or alemtuzumab. Natalizumab may be preferred due to the complex safety profile associated with alemtuzumab. Natalizumab is only recommended for the treatment of rapidly-evolving severe relapsing-remitting multiple sclerosis. Although licensed as a treatment option in all patients with active disease, alemtuzumab may be used more frequently in patients for whom other disease-modifying treatments have not been effective, due to the risk of serious side effects associated with its use.

Fingolimod is also taken by the oral route and is the recommended treatment for patients with highly active disease. The NHS England Clinical Commissioning Policy (see Useful resources below) advises that fingolimod is a suitable alternative for patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (defined as patients previously exposed to the JC virus or who are receiving immunosuppressants or who have been receiving treatment with natalizumab for more than 2 years).

Secondary progressive multiple sclerosis

Currently, only interferon beta 1b is licensed for use in secondary progressive multiple sclerosis. Interferon beta 1b reduces the risk of relapse and of short-term relapse-related disability, but does not prevent the development of permanent physical disability or retard progression once it is established. Therefore its role in secondary progressive disease is limited.

Primary progressive multiple sclerosis

Currently there are no effective disease-modifying treatments licensed for primary progressive multiple sclerosis. Interferon beta [unlicensed indication] has been used, but there is limited evidence to support its use due to the lack of a significant reduction in disability progression.

Progressive-relapsing multiple sclerosis

There are no specific treatment options for this type of multiple sclerosis. None of the currently licensed disease-modifying drugs are recommended in non-relapsing progressive disease.

Management of symptoms

Other than episodes of neurological dysfunction, chronic symptoms (such as fatigue, spasticity, visual problems, and emotional lability) produce much of the disability in multiple sclerosis. Smoking may increase the progression of disability in multiple sclerosis, and Smoking cessation p. 497 should be encouraged.

Relapses

Suspected relapses should be referred to a specialist for diagnosis and treatment. Corticosteroids are recommended for reducing inflammation and accelerating recovery in acute relapses of relapsing-remitting multiple sclerosis. Oral methylprednisolone p. 678 is recommended as the first-line option. Intravenous methylprednisolone should be considered as an alternative if oral methylprednisolone has failed or is not tolerated or if hospitalisation is required.

Fatigue and impaired mobility

Regular exercise may have beneficial effects on mobility and fatigue in patients with multiple sclerosis, and should be encouraged. Cognitive behavioural techniques for fatigue should also be considered in combination with exercise. Amantadine hydrochloride p. 418 [unlicensed indication] may be used to treat fatigue related to multiple sclerosis. Vitamin B12 injections are not recommended as a treatment for fatigue in patients with multiple sclerosis. NICE do not consider it to be a cost-effective treatment and do not recommend its use.

Spasticity

Many factors may aggravate spasticity in multiple sclerosis, including constipation, infection, poor mobility aids, pressure ulcers, posture and pain. These should be managed appropriately. The first-line options for managing spasticity in multiple sclerosis are baclofen p. 1128 or gabapentin p. 315 [unlicensed indication]. They may be used cautiously in combination if the individual drugs are ineffective or if side effects prevent an increase in the dose of either drug. Tizanidine p. 1129 or dantrolene sodium p. 1346 are second-line options; benzodiazepines may be used as third-line therapy and may also be effective in treating nocturnal spasms. A cannabis extract p. 1127 containing dronabinol and cannabidiol is licensed as an adjunct treatment for moderate-to-severe spasticity associated with multiple sclerosis in patients who have not responded adequately to other skeletal muscle relaxants. NICE do not consider it to be a cost-effective treatment and do not recommend its use.

Oscillopsia

Gabapentin [unlicensed indication] is the first-line treatment for oscillopsia; memantine hydrochloride p. 304 [unlicensed indication] is the second-line option.

Emotional lability

Amitriptyline hydrochloride p. 372 [unlicensed indication] may be used to treat emotional lability in patients with multiple sclerosis.

Useful Resources

group-d/d04/

Other drugs used for Multiple sclerosis Cladribine, p. 906
CHOLINERGIC RECEPTOR STIMULATING DRUGS

Fampridine

**INDICATIONS AND DOSE**

*Improvement of walking disability in multiple sclerosis (specialist use only)*

- **BY MOUTH**
  - Adult: 10 mg every 12 hours, discontinue treatment if no improvement within 2 weeks

**CONTRA-INDICATIONS**

- History of seizures (discontinue treatment if seizures occur)

**CAUTIONS**

- Atrioventricular conduction disorders - predisposition to seizures - sinoatrial conduction disorders - symptomatic cardiac rhythm disorders

**INTERACTIONS**

> Appendix 1: fampridine

**SIDE-EFFECTS**

- Common or very common
  - Anxiety - asthenia - balance impaired - constipation - dizziness - dyspepsia - dysphonia - headache - insomnia - laryngeal pain - nausea - pain - palpitations - paraesthesia - tremor - uriitary tract infection - vomiting

- Uncommon
  - Seizure - skin reactions - tachycardia

**PREGNANCY**

- Avoid—toxicity in animal studies.

**BREAST FEEDING**

- Avoid—no information available.

**RENAL IMPAIRMENT**

- Avoid if eGFR less than 80 mL/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

- Dispense in original container (pack contains a desiccant) and discard any tablets remaining 7 days after opening.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. SMC2107

The Scottish Medicines Consortium has advised (November 2018) that fampridine (Fampyra®) is not recommended for use within NHS Scotland for the improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS [expanded disability status scale] 4 to 7) as the economic case was not demonstrated.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule Modified-release tablet

  **CAUTIONARY AND ADVISORY LABELS**

  23, 25

  - **Fampyra** (Biogen Idec Ltd)
    - Fampridine 10 mg
      - 28 tablet £21.00 | 56 tablet £36.00

IMMUNOSTIMULANTS

**INTERFERONS**

AVONEX® VIAL

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided. For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

- **BY INTRAMUSCULAR INJECTION**
  - Adult: (consult product literature)

BETAFERON® INJECTION

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided. For secondary progressive multiple sclerosis with active disease. For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

REBIF® CARTRIDGE

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided. For secondary progressive multiple sclerosis with active disease. For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

REBIF® PRE-FILLED PEN AND SYRINGE

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided. For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS**

- Decompensated liver disease - severe depressive illness

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Consult product literature for further information on contra-indications.

**CAUTIONS**

- History of cardiac disorders - history of depressive disorders (avoid in severe depression or in those with suicidal ideation) - history of seizures - history of severe myelosuppression

**CAUTIONS, FURTHER INFORMATION**

Consult product literature for further information on cautions.
Monitor for signs of hepatic injury

MONITORING REQUIREMENTS

- With subcutaneous use
- With intramuscular use
- With subcutaneous use

Uncommon

With subcutaneous use

Rare or very rare

- Cardiomyopathy-dyspnoea-haemolytic uraemic syndrome-hyperthyroidism-thrombotic microangiopathy

Frequency not known

- Anxiety-chest pain-dizziness
- Injection site necrosis-muscle weakness-palpitations-pulmonary arterial hypertension

SPECIFIC SIDE-EFFECTS

- Common or very common
- Uncommon
- Rare or very rare

SPECIFIC SIDE-EFFECTS

- With intramuscular use
- With subcutaneous use

Frequency not known

- With intramuscular use
- With subcutaneous use

Frequency not known

- With intramuscular use

SPECIFIC SIDE-EFFECTS

- Common or very common
- Uncommon
- Rare or very rare

SPECIFIC SIDE-EFFECTS

- With intramuscular use
- With subcutaneous use

Frequency not known

- With intramuscular use

SPECIFIC SIDE-EFFECTS

- Common or very common
- Uncommon
- Rare or very rare

SPECIFIC SIDE-EFFECTS

- With intramuscular use

SPECIFIC SIDE-EFFECTS

- Common or very common
- Uncommon
- Rare or very rare

CONCEPTION AND CONTRACEPTION

Effective contraception required during treatment—consult product literature.

PREGNANCY

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

BETAFERON® INJECTION

An auto-injector device (Betaject® Light) is available from Bayer Schering.

EXTAVIA®

An auto-injector device (ExtaviPro® 30G) is supplied as part of the ExtaviPro® 30G kit.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Beta interferons and glatiramer acetate for treating multiple sclerosis (June 2018) NICE TA527

INTERFERON BETA-1A (AVONEX®)

- Beta interferon-beta-1a (Avonex®) is recommended as an option for treating multiple sclerosis, only if:
  - the person has relapsing–remitting multiple sclerosis, and
  - the manufacturer provides it according to the commercial arrangement.

INTERFERON BETA-1B (EXTAVIA®)

- Extavia® (Avonex® 12 million units) solution for injection pre-filled disposable injection £654.00 | 12 pre-filled disposable injection £1,962.00
- Extavia® (Avonex® 30 million units) solution for injection £664.00 | 12 pre-filled disposable injection £1,962.00

- Rebif® (Merck Serono Ltd) 850 micrograms/millilitre solution for injection pre-filled disposable injection £613.52
- Rebif® (Gilenya®) 16 micrograms/millilitre solution for injection pre-filled disposable injection £613.52
- Rebif® (Gilenya®) 8 micrograms/millilitre solution for injection pre-filled disposable injection £613.52
- Rebif® (Gilenya®) 4 micrograms/millilitre solution for injection pre-filled disposable injection £613.52

NHS restrictions

NHS England Clinical Commissioning Policy


MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

SOLUTION FOR INJECTION

EXCIPIENTS: May contain Benzyl alcohol

- Avonex® (Biogen Idec Ltd)

INTERFERON BETA-1A 12 MEGA U PER 1 ML

Avenex 30 micrograms/millilitre solution for injection £654.00 | 12 pre-filled disposable injection £1,962.00
Avenex 30 micrograms/millilitre solution for injection £664.00 | 12 pre-filled disposable injection £1,962.00

- Rebif® (Merck Serono Ltd)

INTERFERON BETA-1A 12 MEGA U PER 1 ML

Rebif® 22 micrograms/millilitre solution for injection £613.52
Rebif® 22 micrograms/millilitre solution for injection £613.52
Rebif® 8 micrograms/millilitre solution for injection £613.52
Rebif® 4 micrograms/millilitre solution for injection £613.52

- Extavia® (Avonex®)

INTERFERON BETA-1A 24 MEGA U PER 1 ML

Extavia® 6 micrograms/millilitre solution for injection £613.52
Extavia® 3 micrograms/millilitre solution for injection £613.52
Extavia® 1 micrograms/millilitre solution for injection £613.52

- Rebif® (Gilenya®)

INTERFERON BETA-1A 12 MEGA U PER 1 ML

Rebif® 12 micrograms/millilitre solution for injection £613.52
Rebif® 6 micrograms/millilitre solution for injection £613.52
Rebif® 3 micrograms/millilitre solution for injection £613.52
Rebif® 1 micrograms/millilitre solution for injection £613.52
Peginterferon beta-1a

**DRUG ACTION** Peginterferon beta-1a is a polyethylene glycol-conjugated (‘pegylated’) derivative of interferon beta; pegylation increases the persistence of interferon in blood.

**INDICATIONS AND DOSE**

- **Treatment of relapsing, remitting multiple sclerosis**
  - By subcutaneous injection
  - Adult: consult product literature

**CONTRA-INDICATIONS** Severe depression - suicidal ideation

**CAUTIONS** History of cardiac disorders - history of depressive disorders (avoid in severe depression or those with suicidal ideation) - history of seizures - history of severe myelosuppression

**CAUTIONS, FURTHER INFORMATION** Consult product literature for further information about cautions.

**INTERACTIONS** → Appendix 1: peginterferon beta-1a

**SIDE-EFFECTS**

- **Common or very common** Arthralgia - asthenia - chills - depression - fever - headache - hyperthermia - influenza like illness - myalgia - nausea - pain - skin reactions - vomiting
- **Uncommon** Seizure - thrombocytopenia
- **Rare or very rare** Glomerulonephritis - haemolytic uraemic syndrome - injection site necrosis - nephrotic syndrome - thrombotic microangiopathy
- **Frequency not known** Pulmonary arterial hypertension

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment—consult product literature.

**PREGNANCY** Do not initiate during pregnancy. Avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe hepatic impairment.

**RENAL IMPAIRMENT** Caution in severe renal impairment.

**MONITORING REQUIREMENTS**

- Monitor for signs of hepatic injury—hepatic failure has been reported rarely.
- Thrombotic microangiopathy. Patients should be monitored for clinical features of thrombotic microangiopathy (TMA), including thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis), and impaired renal function. Any signs of TMA should be investigated fully and, if diagnosed, interferon beta should be stopped immediately and treatment for TMA promptly initiated (consult product literature for details).
- Nephrotic syndrome. Patients should also be monitored for signs and symptoms of nephrotic syndrome, including oedema, proteinuria, and impaired renal function—monitor renal function periodically. If nephrotic syndrome develops, treat promptly and consider stopping interferon beta treatment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Plergyrid (Biogen Idec Ltd)
  - Peginterferon beta-1a 126 microgram per 1 ml Plergyrid 63 micrograms/0.5 ml solution for injection pre-filled pen | 1 pre-filled disposable injection (PFS) £596.63
  - Peginterferon beta-1a 188 microgram per 1 ml Plergyrid 94 micrograms/0.5 ml solution for injection pre-filled pen | 1 pre-filled disposable injection (PFS) £654.00
  - Peginterferon beta-1a 250 microgram per 1 ml Plergyrid 125 micrograms/0.5 ml solution for injection pre-filled pen | 2 pre-filled disposable injection (PFS) £1,962.00

**IMMUNOSTIMULANTS > OTHER**

Glatiramer acetate

**DRUG ACTION** Glatiramer is an immunomodulating drug comprising synthetic polypeptides.

**INDICATIONS AND DOSE**

- **Multiple sclerosis [relapsing-remitting] (initiated under specialist supervision)**
  - By subcutaneous injection
  - Adult: 20 mg once daily, alternatively 40 mg 3 times a week, doses to be separated by an interval of at least 48 hours

**CAUTIONS** Cardiac disorders

**SIDE-EFFECTS**

- **Common or very common** Anxiety - appetite decreased - arrhythmia - asthenia - chest pain - chills - constipation - cough - depression - dyspepsia - dysphagia - dyspnoea (may occur within minutes of injection) - ear disorder - eye disorders - fever - gastrointestinal disorders - headache - hyperhidrosis - hypersensitivity - increased risk of infection - joint disorders - local reaction - lymphadenopathy - nausea - neoplasms - neuromuscular dysfunction - oedema - oral disorders - pain - palpitations - rhinitis - skin reactions - speech disorder - syncope - taste altered - tremor - urinary disorders - vasodilation - vision disorders - vomiting - weight increased
- **PREGNANCY** Manufacturer advises avoid—no information available.
- **BREAST FEEDING** Manufacturer advises caution—no information available.
- **RENAL IMPAIRMENT** No information available—manufacturer advises caution.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NICE decisions
  - Beta interferons and glatiramer acetate for treating multiple sclerosis (June 2018) NICE TAS57
  - Glatiramer acetate (Copaxone®) is recommended as an option for treating multiple sclerosis, only if:
the patient has relapsing-remitting multiple sclerosis, and
the manufacturer provides it according to the
commercial arrangement. Patients whose treatment was
started within the NHS before this guidance was published
should have the option to continue treatment, without
change to their funding arrangements, until they and their
NHS clinician consider it appropriate to stop.
www.nice.org.uk/guidance/ta527

Scottish Medicines Consortium (SMC) decisions
SMC No. 1108/15
The Scottish Medicines Consortium has advised (December 2015) that glatiramer acetate (Copaxone®) is accepted for
use within NHS Scotland for the treatment of relapsing
forms of multiple sclerosis.

NHS restrictions
NHS England Clinical Commissioning Policy
An NHS England Clinical Commissioning Policy outlines
the funding arrangements and the criteria for initiating
and discontinuing this treatment option, see www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04.

Medicinal forms
There can be variation in the licensing of
different medicines containing the same drug.

Solution for injection
• Brablo (Mylan)
Glatiramer acetate 20 mg per 1 ml Brablo 20mg/1ml solution for injection pre-filled syringes £462.56
Glatiramer acetate 40 mg per 1 ml Brablo 40mg/1ml solution for injection pre-filled syringes £462.56
• Copaxone (Teva UK Ltd)
Glatiramer acetate 20 mg per 1 ml Copaxone 20mg/1ml solution for injection pre-filled syringes £513.95
Glatiramer acetate 40 mg per 1 ml Copaxone 40mg/1ml solution for injection pre-filled syringes £513.95

IMMUNOSUPPRESSANTS
IMMUNOMODULATING DRUGS

Dimethyl fumarate

Drug action
Dimethyl fumarate has immunomodulatory and anti-inflammatory properties.

Indications and dose

**SKILARENCE®**

**Plaque psoriasis [moderate-to-severe] (under expert supervision)**

• **BY MOUTH**
• Adult: Initially 30 mg once daily for 1 week, dose to be
taken in the evening, then increased in steps of 30 mg
every week for 3 weeks, then increased in steps of 120 mg every week for 5 weeks, for further information
on the dose titration and administration schedule, advice on establishing a maintenance dose, and for
dose adjustments due to side-effects, consult product literature; maximum 720 mg per day

**TECFIDERA®**

**Multiple sclerosis [relapsing-remitting] (initiated by a specialist)**

• **BY MOUTH**
• Adult: Initially 120 mg twice daily for 7 days, then
increased to 240 mg twice daily, for dose adjustments
due to side-effects—consult product literature

**Contra-indications**

SKILARENCE®
Do not initiate if leucocyte count below
3 x 10⁹/litre - do not initiate if lymphocyte count below
1 x 10⁹/litre - do not initiate if pathological haematological
abnormalities identified - severe gastro-intestinal disorders

Cautions
Reduced lymphocyte count

TECFIDERA®
Serious infection (do not initiate until
infection resolved; consider suspending treatment if
infection develops) - severe active gastro-intestinal disease

SKILARENCE®
Significant infection (consider avoiding
initiation until infection resolved and suspending
treatment if infection develops)

**Interactions** → Appendix 1: dimethyl fumarate

**Side-effects**

• Common or very common
  • Appetite decreased - asthenia
  • Constipation - decreased leucocytes - diarrhoea
  • Eosinophilia - feeling hot - flattulence - gastrointestinal discomfort - headache - leucocytosis - nausea - paraesthesia
  • Skin reactions - vasodilation - vomiting
• Uncommon
  • Dizziness - proteinuria
• Rare or very rare
  • Acute lymphocytic leukaemia - pancytopenia
• Frequency not known
  • Progressive multifocal leukoencephalopathy (PML) - renal failure

**Side-effects, further information**
Severe prolonged lymphopenia reported, and patients are exposed to a potential risk of PML. Treatment should be stopped immediately if PML is suspected.

**Pregnancy**

TECFIDERA®
Manufacturer advises avoid unless essential and potential benefit outweighs risk—toxicity in animal studies.

SKILARENCE®
Manufacturer advises avoid—toxicity in animal studies.

**Breast feeding**
Manufacturer advises avoid.

**Hepatic impairment**

TECFIDERA®
Manufacturer advises caution in severe
impairment (no information available).

SKILARENCE®
Manufacturer advises avoid in severe
impairment (no information available).

**Renal impairment**

TECFIDERA®
Manufacturer advises caution in severe
impairment—no information available.

SKILARENCE®
Manufacturer advises avoid in severe
impairment—no information available.

**Monitoring requirements**

• Manufacturer advises monitor full blood count before
treatment initiation then every 3 months thereafter—
consult product information for further information.

• Manufacturer advises monitor patient closely for features of
progressive multifocal leukoencephalopathy (PML) (e.g.
signs and symptoms of neurological dysfunction) and
other opportunistic infections.

• Manufacturer advises monitor renal and hepatic function
before treatment initiation and during treatment—consult
product literature for further information.

• Manufacturer of Tecfidera® advises perform a baseline MRI as a reference and repeat as required during treatment.

**Prescribing and dispensing information**

SKILARENCE®
The manufacturer of Skilarence® has
provided a Healthcare Professional Guideline, which
includes important safety information on the risk of serious infections.

**Patient and carer advice**
Manufacturer advises patients and their carers should be informed of the possibility of experiencing symptoms of flushing; they
should also be advised to report symptoms of infection to
their doctor. The MHRA recommends that patients and their carers should be counselled on the risk of progressive multifocal leuкоencephalopathy and advised to seek immediate medical attention if symptoms develop.

- NATIONAL FUNDING/ACCESS DECISIONS

TECFIDERA®

NICE decisions

- Dimethyl fumarate (Tecfidera®) for treating relapsing-remitting multiple sclerosis (August 2014) NICE TA320

Dimethyl fumarate (Tecfidera®) is recommended for the treatment of active relapsing-remitting multiple sclerosis, only if:

- the patient does not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
- the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (April 2014) that dimethyl fumarate (Tecfidera®) is accepted for use within NHS Scotland for the treatment of patients with relapsing remitting multiple sclerosis. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

SKILARENCE®

NICE decisions

- Dimethyl fumarate for treating moderate-to-severe plaque psoriasis (September 2017) NICE TA475

Dimethyl fumarate is recommended as an option for treating plaque psoriasis in adults, only if the disease:

- is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10, and
- has not responded to other systemic therapies, including, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contra-indicated or not tolerated. Stop dimethyl fumarate treatment at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started, or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

Scottish Medicines Consortium (SMC) decisions

SMC No. 1313/18

The Scottish Medicines Consortium has advised (April 2018) that dimethyl fumarate (Skilarence®) is accepted for restricted use within NHS Scotland for the treatment of moderate-to-severe plaque psoriasis in adults in need of systemic medicinal therapy, whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gastro-resistant capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

- Tecfidera (Biogen Idec Ltd)
  - Dimethyl fumarate 120 mg Tecfidera 120mg gastro-resistant capsules | 14 capsule | £343.00
  - Dimethyl fumarate 240 mg Tecfidera 240mg gastro-resistant capsules | 56 capsule | £1,373.00

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

- Skilarence (Almirall Ltd)
  - Dimethyl fumarate 30 mg Skilarence 30mg gastro-resistant tablets | 42 tablet | £89.04 DT + £89.04
  - Dimethyl fumarate 120 mg Skilarence 120mg gastro-resistant tablets | 90 tablet | £190.80 DT + £190.80 | 180 tablet | £381.60 DT + £381.60

Fingolimod

- DRUG ACTION

Fingolimod is an immunomodulating drug.

- INDICATIONS AND DOSE

Treatment of highly active relapsing-remitting multiple sclerosis in patients who have high disease activity despite treatment with at least one disease modifying therapy or in those with rapidly evolving severe relapsing-remitting multiple sclerosis (initiated under specialist supervision)

- BY MOUTH
  - Adult: 500 micrograms once daily

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: MULTIPLE SCLEROSIS THERAPIES: SIGNAL OF REBOUND EFFECT AFTER STOPPING OR SWITCHING THERAPY (APRIL 2017)

A signal of rebound syndrome in multiple sclerosis patients whose treatment with fingolimod was stopped or switched to other treatments has been reported in two recently published articles. The MHRA advise to be vigilant for such events and report any suspected adverse effects relating to fingolimod, or other treatments for multiple sclerosis, via the Yellow Card Scheme, while this report is under investigation.

MHRA/CHM ADVICE: FINGOLIMOD—NOT RECOMMENDED FOR PATIENTS AT KNOWN RISK OF CARDIOVASCULAR EVENTS. ADVICE FOR EXTENDED MONITORING FOR THOSE WITH SIGNIFICANT BRADYCARDIA OR HEART BLOCK AFTER THE FIRST DOSE AND FOLLOWING TREATMENT INTERRUPTION (JANUARY 2013)

Fingolimod is known to cause transient bradycardias and heart block after the first dose—see Cautions, Contra-indications and Monitoring for further information.

MHRA/CHM ADVICE: FINGOLIMOD: NEW CONTRA-INDICATIONS IN RELATION TO CARDIAC RISK (DECEMBER 2017)

Fingolimod can cause persistent bradycardia, which can increase the risk of serious cardiac arrhythmias. New contra-indications have been introduced for patients with pre-existing cardiac disorders—see Contra-indications for further information.

MHRA/CHM ADVICE: FINGOLIMOD: UPDATED ADVICE ABOUT RISK OF CANCERS AND SERIOUS INFECTIONS (DECEMBER 2017)

Fingolimod has an immunosuppressive effect and can increase the risk of skin cancers and lymphoma. Following a recent EU review, the MHRA has recommended the following strengthened warnings:

- re-assess the benefit-risk balance of fingolimod therapy in individual patients, particularly those with additional risk factors for malignancy—either closely monitor for skin cancers or consider discontinuation on a case-by-case basis
- examine all patients for skin lesions before they start fingolimod and then re-examine at least every 6 to 12 months

www.getintopharma.com
Multiple sclerosis

Progressive multifocal leukoencephalopathy (PML) and other opportunistic infections Patients should be advised to seek medical attention if they have any signs of PML or any other infections. Suspension of treatment should be considered if a patient develops a severe infection, taking into consideration the risk-benefit.

CONCEPTION AND CONTRACEPTION Exclude pregnancy before treatment. Ensure effective contraception during and for at least 2 months after treatment.

PREGNANCY Avoid (toxicity in animal studies).

BREAST FEEDING Avoid.

HEPATIC IMPAIRMENT Manufacturer advises caution when initiating treatment in mild to moderate impairment; avoid in severe impairment.

MONITORING REQUIREMENTS
- All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring—before, during and after dose), and after treatment interruption (see note below); monitoring should include:
  - Pre-treatment
    - an ECG and blood pressure measurement before starting
  - During the first 6 hours of treatment
    - continuous ECG monitoring for 6 hours
    - blood pressure and heart rate measurement every hour
  - After 6 hours of treatment
    - a further ECG and blood pressure measurement
  - If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases
  - If post-dose bradycardia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. If pharmacological intervention is required during the first-dose monitoring, overnight monitoring should follow, and the first-dose monitoring should then be repeated after the second dose.
  - If after 6 hours, the heart rate is less than 45 beats per minute, or the ECG shows new onset second degree, higher grade AV block, or a QTc interval of 500 milliseconds or greater, or if third degree AV block occurs, monitoring should be extended (at least overnight, until side-effect resolution).
  - The occurrence at any time of third degree AV block requires extended monitoring (at least overnight, until side-effect resolution).
  - In case of T-wave inversion, ensure there are no associated signs or symptoms of myocardial ischaemia—if suspected seek advice from a cardiologist.

Note First dose monitoring as above should be repeated in all patients whose treatment is interrupted for:
- 1 day or more during the first 2 weeks of treatment
- more than 7 days during weeks 3 and 4 of treatment
- more than 2 weeks after one month of treatment
- If the treatment interruption is of shorter duration than the above, treatment should be continued with the next dose as planned
- Manufacturer advises eye examination recommended 3–4 months after initiation of treatment (and before initiation of treatment in patients with diabetes or history of uveitis).
- Manufacturer advises skin examination for skin lesions before starting treatment and then every 6 to 12 months thereafter or as clinically indicated
- Monitor hepatic transaminases before treatment, then every 3 months for 1 year, then periodically thereafter.
- Monitor full blood count before treatment, at 3 months, then at least yearly thereafter and if signs of infection (interrupt treatment if lymphocyte count reduced)—consult product literature.
Monitor for signs and symptoms of haemophagocytic syndrome (including pyrexia, asthenia, hepato-splenomegaly and adenopathy)—may be associated with hepatic failure and respiratory distress; also progressive cytopenia, elevated serum-ferritin concentrations, hypertriglyceridaemia, hypofibrinogenaeemia, coagulopathy, hepatic cytolysis, hyponatraemia)—initiate treatment immediately.

Manufacturer advises to monitor routine MRI for lesions suggestive of progressive multifocal leukoencephalopathy (PML), particularly in patients considered at increased risk; monitor for signs and symptoms of new neurological dysfunction.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (April 2012) NICE TA254

Fingolimod is recommended as an option for the treatment of highly active relapsing-remitting multiple sclerosis in adults, only if:

- they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with interferon beta, and
- the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme

Patients currently receiving fingolimod whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta254

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2012) that fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland as single disease modifying therapy in highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta, with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

The Scottish Medicines Consortium has advised (October 2014) that fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland as a single disease modifying therapy in highly active relapsing-remitting multiple sclerosis for adults with rapidly evolving severe relapsing remitting multiple sclerosis. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland, or a list price that is equivalent or lower.

The Scottish Medicines Consortium has advised (April 2015) that fingolimod (Gilenya®) is accepted for use within NHS Scotland as a single disease modifying therapy in highly active relapsing remitting multiple sclerosis for adults with high disease activity despite treatment with at least one disease modifying therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland, or a list price that is equivalent or lower.

All Wales Medicines Strategy Group (AWMSG) decisions

The All Wales Medicines Strategy Group has advised (January 2017) that fingolimod (Gilenya®) is recommended as an option for use within NHS Wales as a single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis only in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous recent MRI, only if the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme or where the list price is equivalent or lower.

NHS restrictions


MEDIUM FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

- Gilenya (Novartis Pharmaceuticals UK Ltd)
- Fingolimod (as Fingolimod hydrochloride)

500 microgram Gilenya 0.5mg capsules | 7 capsule £67.50
(Hospital only) | 28 capsule £230 1,470.00 (Hospital only)

IMMUNOSUPPRESSANTS > MONOCOVAL ANTIBODIES > ANTI-LYMPHOCYTE

Anti-lymphocyte monoclonal antibodies

DRUG ACTION

The anti-lymphocyte monoclonal antibodies cause lysis of B lymphocytes.

IMPORTANT SAFETY INFORMATION

All anti-lymphocyte monoclonal antibodies should be given under the supervision of an experienced specialist, in an environment where full resuscitation facilities are immediately available.

SIDE-EFFECTS

- Common or very common Alopecia - anaemia - arthralgia - asthenia - back pain - constipation - depression - diarrhoea - fever - headache - hypersensitivity (discontinue permanently) - hypertension - increased risk of infection - infusion related reaction - leucopenia - myocardial infarction - neutropenia - night sweats - thrombocytopenia - vomiting
- Uncommon Progressive multifocal leukoencephalopathy (PML)
- Frequency not known Anaphylactic reaction

SIDE-EFFECTS, FURTHER INFORMATION

Infusion-related side-effects In rare cases infusion reactions may be fatal. Infusion-related side-effects occur predominantly during the first infusion. Patients should receive premedication before administration of anti-lymphocyte monoclonal antibodies to reduce these effects—consult product literature for details of individual regimens. The infusion may have to be stopped temporarily and the infusion-related effects treated—consult product literature for appropriate management.

Cytokine release syndrome Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred after infusions of anti-lymphocyte monoclonal antibodies. Patients with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).

PRE-TREATMENT SCREENING

All patients should be screened for hepatitis B before treatment.

MONITORING REQUIREMENTS

Patients should also be monitored for cytopenias—consult product literature for specific recommendations.
Alemtuzumab

INDICATIONS AND DOSE
Treatment of adults with relapsing-remitting multiple sclerosis with active disease defined by clinical or imaging features

BY INTRAVENOUS INFUSION

Adults: (consult product literature)

- BY INTRAVENOUS INFUSION
- Adults: (consult product literature)

UNLICENSED USE

Although no longer licensed for oncological and transplant indications, alemtuzumab is also available through a patient access programme for these indications.

IMPRESSA

Alemtuzumab should be given under the care of a specialist with facilities for the management of hypersensitivity and anaphylactic reactions.

MHRA/CHM ADVICE: ALEMTUZUMAB (LEMTRADA®): RESTRICTION OF USE DUE TO SERIOUS SAFETY CONCERNS (APRIL 2019)

There have been reports of severe cardiovascular reactions, autoimmune hepatitis, and haemophagocytic lymphohistiocytosis with the use of Lemtrada®. Whilst a review by the European Medicines Agency is ongoing, healthcare professionals are advised to only initiate treatment in new patients with relapsing-remitting multiple sclerosis (RRMS) that is highly active despite a full and adequate course of treatment with at least two other disease-modifying treatments, or in patients with highly active RRMS where all other disease-modifying treatments are contra-indicated or unsuitable.

Healthcare professionals should monitor liver function and vital signs, including blood pressure before and during treatment. Stop infusions if clinically significant changes in vital functions are observed and consider additional monitoring, including ECG. Re-administration should be carefully considered if symptoms of hepatic injury or other serious immune-mediated reactions occur. Patients should be advised to seek immediate medical attention if they experience symptoms within a few days of the infusion or if symptoms of hepatic injury occur.

CONTRA-INDICATIONS

Human immunodeficiency virus

CAUTIONS

Hepatitis B carriers • hepatitis C carriers • in patients with active infection, a delay in initiation of alemtuzumab treatment should be considered until the infection is fully controlled • not recommended for inactive disease • not recommended for stable disease • patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course • patients with previous autoimmune conditions other than multiple sclerosis • pretreatment before administration is required (consult product literature)

CAUTIONS, FURTHER INFORMATION

For full details of cautions, consult product literature.

Autoimmune mediated conditions

The risk of autoimmune-mediated reactions occur. Patients should be advised to seek immediate medical attention if they experience symptoms within a few days of the infusion or if symptoms of hepatic injury occur.

INTERACTIONS

Appendix 1: monoclonal antibodies

SIDE-EFFECTS

Common or very common

Abdominal pain • anxiety • autoimmune thyroiditis • cough • cytokine release syndrome • goitre • haemorrhage • hyperhidrosis • hyperthyroidism • hypothyroidism • influenza-like illness • lymphadenopathy • lymphopenia • malaise • menstrual cycle irregularities • multiple sclerosis exacerbated • muscle complaints • muscle weakness • oropharyngeal pain • pain • palpitations • peripheral oedema • proteinuria • sensation abnormal • skin reactions • stomatitis • tremor • vertigo • vision blurred

Uncommon

Cervical dysplasia • conjunctivitis • dysphagia • gastroesophageal reflux disease • hiccups • throat complaints • weight decreased

Rare or very rare

Haemophagocytic lymphohistiocytosis

Frequency not known

Artery dissection • cerebrovascular insufficiency • Goodpasture’s syndrome • hepatitis autoimmune (including fatal cases) • liver injury • meningitis listeria • nephropathy

CONCEPTION AND CONTRACEPTION

Women of childbearing potential should use effective contraception during and for 4 months after treatment.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies.

Autoimmune thyroid disease during treatment may affect fetus (consult product literature).

BREAST FEEDING

Manufacturer advises avoid during and for 4 months after each treatment course unless potential benefit outweighs risk.

PRE-TREATMENT SCREENING

Screening patients at high risk of hepatitis B or C is recommended before treatment. All patients should be evaluated for active or latent tuberculosis before starting treatment.

MONITORING REQUIREMENTS

For further information on monitoring, see Important safety information.

HPV screening should be carried out annually in female patients.

PRESCRIBING AND DISPENSING INFORMATION

All patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course.

PATIENT AND CARER ADVICE

Patients should be provided with a patient alert card and patient guide.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Alemterol for treating relapsing-remitting multiple sclerosis (May 2014) NICE TA312
- Alemterol (Lemtrada®) is recommended as an option, within its marketing authorisation, for treating adults with active relapsing-remitting multiple sclerosis.

www.nice.org.uk/guidance/ta312

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

- Lemtrada (Genzyme Therapeutics Ltd)
  - Alemterol 10 mg per 1 ml (Hospital only)
  - Alemterol 30 mg per 1 ml (Hospital only)
  - Alemterol 30 mg per 1 ml

- MabCampath (Genzyme Therapeutics Ltd)
  - Alemterol 30 mg per 1 ml

- MabCampath 30 mg per 1 ml

- MabCampath 30 mg per 1 ml

Natalizumab

INDICATIONS AND DOSE

Highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta or glatiramer acetate, or those patients with rapidly evolving severe relapsing-remitting multiple sclerosis (initiated under specialist supervision)

- BY INTRAVENOUS INFUSION
- Adult 18–65 years: 300 mg every 4 weeks, treatment should be discontinued if no response after 6 months

CONTRA-INDICATIONS

Active infection • active malignancies (except cutaneous basal cell carcinoma) •
Progressive Multifocal Leucoencephalopathy  Patients should be informed about the risks of PML before starting treatment with natalizumab and again after 2 years; they should be given an alert card which includes information about the symptoms of PML.  
Lever toxicity  Advise patients to seek immediate medical attention if symptoms such as jaundice or dark urine develop.  
Alert card  A patient alert card should be provided.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions  
Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (August 2007)  
NICE TA127

Natalizumab is an option for the treatment only of rapidly evolving severe relapsing-remitting multiple sclerosis (RES). RES is defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

Scottish Medicines Consortium (SMC) decisions  
The Scottish Medicines Consortium has advised (August 2007) that natalizumab is accepted for restricted use as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis only in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

NHS restrictions

NHS England Clinical Commissioning Policy  

- MEDICINAL FORMS  
There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion  
ELECTROLYTES: May contain Sodium

- Tysabri (Biogen Idec Ltd)  
Natalizumab 20 mg per 1 ml  
Tysabri 300mg/15ml concentrate for solution for infusion via 1 vial (Product) £1,120.00 (Hospital only)

Ocrelizumab

- INDICATIONS AND DOSE

Multiple sclerosis (specialist use only)  

- BY INTRAVENOUS INFUSION

- Adult: Initially 300 mg, then 300 mg after 2 weeks; maintenance 600 mg every 6 months, the first maintenance dose should be given 6 months after the first initial dose; a minimum interval of 5 months should be maintained between each maintenance dose, for dose interruption, adjustment of infusion rate or discontinuation of treatment due to infusion-related reactions or side-effects—consult product literature

- CONTRA-INDICATIONS  
Active infection - active malignancies - severely immunocompromised patients

- CAUTIONS

Complete required vaccinations at least 6 weeks before treatment initiation - hepatitis B reactivation

- INTERACTIONS

Appendix 1: monoclonal antibodies

- CONCEPTION AND CONTRACEPTION

Manufacturer advises women of childbearing potential should use contraception during treatment and for 12 months after the last dose.

www.getintopharma.com
Teriflunomide

**Drug Action** Teriflunomide is a metabolite of leflunomide which has immunomodulating and anti-inflammatory properties.

### Indications and Dose

#### Treatment of relapsing-remitting multiple sclerosis (initiated under specialist supervision)

- **By mouth**
- **Adult:** 14 mg once daily

#### Contra-Indications

- Anaemia
- Leucopenia
- Neutropenia
- Serious infection
- Severe hypoproteinaemia
- Severe immunodefi ciency
- Significantly impaired bone-marrow function
- Thrombocytopenia

#### Caution

- Adult over 65 years
- Anaemia
- Dyspnée—assess for interstitial lung disease and consider suspending treatment;
- Hypoproteinaemia (avoid if severe)
- Impaired bone-marrow function (avoid if severe)
- Latent tuberculosis
- Leucopenia
- Persistent cough—assess for interstitial lung disease and consider suspending treatment;
- Severe infection—delay or suspend treatment until resolved
- Significant alcohol consumption—signs or symptoms of serious skin reactions (including ulcerative stomatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)—discontinue treatment—switching between other immunomodulating drugs
- Thrombocytopenia

#### Interactions

- Appendix 1: teriflunomide

#### Side-effects

- **Common or very common**
  - Abdominal pain upper
  - Alopecia
  - Anaemia
  - Anxiety
  - Arthralgia
  - Cystitis
  - Diarrhoea
  - Headache
  - Hypersensitivity
  - Hypertension
  - Increased risk of infection
  - Menorrhagia
  - Myalgia
  - Nausea
  - Nerve disorders
  - Neutropenia
  - Oral disorders
  - Pain
  - Palpitations
  - Sensation abnormal—skin reactions
  - Urinary frequency increased
  - Vomiting
  - Weight decreased

- **Uncommon**
  - Thrombocytopenia

- **Frequency not known**
  - Asthenia
  - Hepatitis acute
  - Interstitial lung disease
  - Nail disorder
  - Pancreatitis
  - Sepsis

**Side-effects, Further Information** Hepatic injury

Discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**Important**: accelerated elimination procedure recommended following discontinuation due to serious adverse effects (consult product literature).

#### Conception and Contraception

Effective contraception essential for women of child-bearing potential during treatment and for up to 2 years after treatment. In patients undergoing treatment with teriflunomide that are planning to conceive, the accelerated elimination procedure should be used prior to conception. Use of non-oral contraception is recommended during the accelerated elimination procedure—consult product literature.

#### Pregnancy

Avoid—toxicity in animal studies.

#### Breast Feeding

Present in milk in animal studies—manufacturer advises avoid.

#### Hepatic Impairment

Manufacturer advises avoid in severe impairment.

#### Monitoring Requirements

- Monitor full blood count (including differential white cell count and platelet count) before treatment and as clinically indicated during treatment.
- Monitor blood pressure before treatment and periodically thereafter.

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**Immunosuppressants** > Pyrimidine synthesis inhibitors

#### Teriflunomide

- **Drug action** Teriflunomide is a metabolite of leflunomide which has immunomodulating and anti-inflammatory properties.

#### Indications and Dose

**Treatment of relapsing-remitting multiple sclerosis (initiated under specialist supervision)**

- **By mouth**
- **Adult:** 14 mg once daily

#### Contra-Indications

- Anaemia
- Leucopenia
- Neutropenia
- Serious infection
- Severe hypoproteinaemia
- Severe immunodeficiency
- Significantly impaired bone-marrow function
- Thrombocytopenia

#### Caution

- Adult over 65 years
- Anaemia
- Dyspnée—assess for interstitial lung disease and consider suspending treatment;
- Hypoproteinaemia (avoid if severe)
- Impaired bone-marrow function (avoid if severe)
- Latent tuberculosis
- Leucopenia
- Persistent cough—assess for interstitial lung disease and consider suspending treatment;
- Severe infection—delay or suspend treatment until resolved
- Significant alcohol consumption—signs or symptoms of serious skin reactions (including ulcerative stomatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)—discontinue treatment—switching between other immunomodulating drugs
- Thrombocytopenia

#### Interactions

- Appendix 1: teriflunomide

#### Side-effects

- **Common or very common**
  - Abdominal pain upper
  - Alopecia
  - Anaemia
  - Anxiety
  - Arthralgia
  - Cystitis
  - Diarrhoea
  - Headache
  - Hypersensitivity
  - Hypertension
  - Increased risk of infection
  - Menorrhagia
  - Myalgia
  - Nausea
  - Nerve disorders
  - Neutropenia
  - Oral disorders
  - Pain
  - Palpitations
  - Sensation abnormal—skin reactions
  - Urinary frequency increased
  - Vomiting
  - Weight decreased

- **Uncommon**
  - Thrombocytopenia

- **Frequency not known**
  - Asthenia
  - Hepatitis acute
  - Interstitial lung disease
  - Nail disorder
  - Pancreatitis
  - Sepsis

**Side-effects, Further Information** Hepatic injury

Discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**Important**: accelerated elimination procedure recommended following discontinuation due to serious adverse effects (consult product literature).

#### Conception and Contraception

Effective contraception essential for women of child-bearing potential during treatment and for up to 2 years after treatment. In patients undergoing treatment with teriflunomide that are planning to conceive, the accelerated elimination procedure should be used prior to conception. Use of non-oral contraception is recommended during the accelerated elimination procedure—consult product literature.

#### Pregnancy

Avoid—toxicity in animal studies.

#### Breast Feeding

Present in milk in animal studies—manufacturer advises avoid.

#### Hepatic Impairment

Manufacturer advises avoid in severe impairment.

#### Monitoring Requirements

- Monitor full blood count (including differential white cell count and platelet count) before treatment and as clinically indicated during treatment.
- Monitor blood pressure before treatment and periodically thereafter.
Malignant disease

1 Antibody responsive malignancy

ANTINEOPLASTIC DRUGS > MONOCLONAL ANTIBODIES

Atezolizumab

- **Drug action** Atezolizumab is a monoclonal antibody, which binds to the programmed death-ligand 1 (PD-L1), thereby reactivating the immune response to tumour cells.

- **Indications and dose**
  - **Urothelial carcinoma [as monotherapy] (specialist use only)**
  - **By intravenous infusion**
  - **Adult:** 1200 mg every 3 weeks, for dose interruption, adjustment of infusion rate or discontinuation of treatment due to side-effects or infusion-related reactions—consult product literature

- **Treatment cessation**
  - Accelerated elimination procedures To aid drug elimination in case of serious adverse effect or before conception, stop treatment and give either colestyramine p. 197 or charcoal, activated p. 1366. After the accelerated elimination procedure a plasma concentration of less than 20 micrograms/litre (measured on 2 occasions at least 14 days apart) and a waiting period of one and a half months are necessary before conception.

- **National funding/access decisions**
  - **Nice decisions**
    - Teriflunomide for treating relapsing-remitting multiple sclerosis (January 2014) NICE TA303
      - Teriflunomide is recommended for the treatment of adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), in adults who:
        - do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
        - the manufacturer provides teriflunomide with the discount agreed in the patient access scheme www.nice.org.uk/TA303
  - Scottish Medicines Consortium (SMC) decisions
    - The Scottish Medicines Consortium has advised (February 2014) that the use of teriflunomide (Aubagio)® in NHS Scotland is restricted to use in patients with relapsing-remitting multiple sclerosis who do not have highly active disease, and only as an alternative to treatment with interferon beta or glatiramer acetate.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Aubagio** (Genzyme Therapeutics Ltd)
      - Teriflunomide 14 mg Aubagio 14mg tablets | 28 tablet (POM)
      - £1.037.84

Non-small cell lung cancer [as combination therapy] (specialist use only)

- **By intravenous infusion**
- **Adult:** (consult product literature)

- **Caution** Abnormal thyroid function—manufacturer advises to consider appropriate treatment—patients may need pre-medication to minimise the development of infusion-related reactions—consult product literature

- **Interactions** Appendix 1: monoclonal antibodies

- **Side-effects**
  - Common or very common Abdominal pain, appetite decreased, arthralgia, asthenia, chills, colitis, diarrhoea, dysphagia, dyspnoea, electrolyte imbalance, fever, hyperthyroidism, hypotension, hypothyroidism, hypoxia, influenza like illness, infusion related reaction, musculoskeletal pain, nasal congestion, nausea, pneumonia, skin reactions, thrombocytopenia, vomiting
  - Uncommon Adrenal insufficiency, diabetes mellitus, Guillain-Barre syndrome, hepatitis, meningitis, non-infective, pancreatitis
  - Rare or very rare Encephalitis non-infective, hypophysitis

- **Infusion-related reactions** Manufacturer advises permanently discontinue treatment in patients with severe infusion reactions.

- **Conception and contraception**
  - Manufacturer advises effective contraception in women of childbearing potential, during treatment and for 5 months after stopping treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **Pregnancy**
  - Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **Breast feeding**
  - Manufacturer advises avoid—no information available.

- **Monitoring requirements**
  - Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions—consult product literature.

- **Prescribing and dispensing information**
  - Manufacturer advises to record the brand name and batch number after each administration.
  - All prescribers should be familiar with the Physician Information and Management Guidelines provided by the manufacturer.

- **Handling and storage**
  - Manufacturer advises store in a refrigerator (2–8°C); consult product literature for storage conditions after dilution.

- **Patient and carer advice**
  - An alert card should be provided.

- **Missed doses**
  - Manufacturer advises if a dose is missed, it should be administered as soon as possible—administration schedule should be adjusted to maintain a 3-week interval between doses.

- **Driving and skilled tasks**
  - Manufacturer advises patients should be counselled on the effects on driving and performance of skilled tasks—increased risk of drowsiness.

- **National funding/access decisions**

- **Nice decisions**
  - Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (updated July 2018) NICE TA492
  - Atezolizumab (Tecentriq)® is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults, for whom cisplatin-based chemotherapy is unsuitable, only if:
Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after platinum-containing chemotherapy (June 2018) NICE TA520

Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and
- the company provides aetuzolizumab with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta492

- Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (June 2018) NICE TA525

Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- aetuzolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and
- the company provides aetuzolizumab with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta525

Scottish Medicines Consortium (SMC) decisions

SME No. 1336/18

The Scottish Medicines Consortium has advised (July 2018) that aetuzolizumab (Tecentriq) is accepted for restricted use within NHS Scotland for the treatment of adults with locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy, subject to a two-year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower. SMC No. SME2103

The Scottish Medicines Consortium has advised (November 2018) that aetuzolizumab (Tecentriq) is not recommended for use within NHS Scotland as monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, as the clinical and economic case was not demonstrated.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

- Tecentriq (Roche Products Ltd)
- Atezolizumab 60 mg per 1 ml Tecentriq 1200mg/20ml concentrate for solution for infusion vials | 1 vial | £807.69

Atezolizumab is recommended as an option for treating metastatic Merkel cell carcinoma in adults, only if they

- their tumours express PD-L1 at a level of 5% or more, and
- the conditions of the managed access agreement for aetuzolizumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

NICE TA517

The Scottish Medicines Consortium has advised (July 2018) that aetuzolizumab (Tecentriq) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma after prior chemotherapy, subject to a two-year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

NICE TA525

Atezolizumab is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer after platinum-containing chemotherapy (May 2018)

NICE TA520

Atezolizumab is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults who have had chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), only if:

- aetuzolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and
- the company provides aetuzolizumab with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta492

- Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (May 2018)

Antibody responsive malignancy

Avelumab

- DRUG ACTION

Avelumab is a monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor, thereby potentiating an immune response to tumour cells.

- INDICATIONS AND DOSE

Metastatic Merkel cell carcinoma (specialist use only)

- BY INTRAVENOUS INFUSION

- Adult: 10 mg/kg every 2 weeks, for information on dose delay or interruption due to side-effects and infusion-related reactions—consult product literature

- CAUTIONS

Patients should receive pre-medication to minimise the development of adverse reactions (consult product literature)

- INTERACTIONS

Appendix 1: monoclonal antibodies

- SIDE-EFFECTS

Common or very common Abdominal pain - anaemia - appetite decreased - arthralgia - asthenia - chills - constipation - cough - diarrhoea - diziness - dry mouth - dyspnoea - endocrine disorders - fever - headache - hypertension - hypotension - influenza like illness - infusion related reaction - lymphopenia - myalgia - myositis - nephritis - neuropathies - peripheral oedema - pneumonitis - skin reactions - vomiting - weight decreased


Rare or very rare Myocarditis

SIDE-EFFECTS, FURTHER INFORMATION

Infusion-related reactions

For treatment modifications in patients with grade 1 or 2 infusion-related reactions, consult product literature. Manufacturer advises permanently discontinue treatment in patients with grade 3 or 4 infusion-related reaction.

Immune-related reactions

Most immune-related adverse reactions are reversible and managed by temporarily stopping treatment and administration of a corticosteroid—consult product literature for further information.

CONCEPTION AND CONTRACEPTION

Manufacturer advises women of child-bearing potential should use effective contraception during treatment and for at least 1 month after stopping treatment.

PREGNANCY

Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid during treatment and for at least 1 month after stopping treatment—no information available.

MONITORING REQUIREMENTS

Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions.

DIRECTIONS FOR ADMINISTRATION

Manufacturer advises for intermittent intravenous infusion (Bavencio®), dilute requisite dose with Sodium Chloride 0.9%; give over 60 minutes via a separate line using a low-protein binding 0.2 micron filter.

HANDLING AND STORAGE

Manufacturer advises store in a refrigerator (2–8°C)—consult product literature for storage conditions after preparation of the infusion.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Avelumab for treating metastatic Merkel cell carcinoma (April 2018) NICE TA517

Avelumab is recommended as an option for treating metastatic Merkel cell carcinoma in adults, only if they

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www.getintopharma.com
have had 1 or more lines of chemotherapy for metastatic disease. Avelumab is recommended for use within the Cancer Drugs Fund as an option for treating metastatic Merkel cell carcinoma in adults, only if:

- they have not had chemotherapy for metastatic disease, and
- the conditions in the managed access agreement for avelumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta517

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (May 2018) that avelumab (Bavencio®) is accepted for use within NHS Scotland as monotherapy for treating adults with metastatic Merkel cell carcinoma.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion
- Bavencio (Merck Serono Ltd)
  - Avelumab 20 mg per 1 ml Bavencio 200mg/10ml concentrate for solution for infusion vials | 1 vial (£768.00)

Bevacizumab

DRUG ACTION Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor.

INDICATIONS AND DOSE Treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy | First-line treatment of metastatic breast cancer in combination with paclitaxel when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate | First-line treatment of metastatic breast cancer in combination with capetitabine when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate (patients who have received adjuvant taxane or anthracycline-containing regimens in the previous 12 months should not be treated with bevacizumab in combination with capetitabine) | Advanced or metastatic renal cell carcinoma in combination with interferon alpha-2a | First-line treatment of unsectarectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology (in combination with platinum-based chemotherapy) | First-line treatment of advanced (FIGO stages IIIB, IIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel) | First recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who have not been treated previously with bevacizumab or other drugs that target vascular endothelial growth factor (in combination with carboplatin and gencitabine)

- BY INTRAVENOUS INFUSION
- Adult: (consult local protocol)

CAUTIONS Elective surgery (withhold treatment and avoid for at least 28 days after major surgery or until wound fully healed) - history of arterial thromboembolism - history of cardiovascular disease (increased risk of cardiovascular events, especially in the elderly) - history of hypertension (increased risk of proteinuria—discontinue if nephrotic syndrome) - increased risk of fistulas (discontinue permanently if tachleo-oesophageal or grade 4 fistula develops) - increased risk of haemorrhage - increased risk of tumour-associated haemorrhage - intra-abdominal inflammation (risk of gastro-intestinal perforation and gall bladder perforation - uncontrolled hypertension - untreatmet CNS metastases

INTERACTIONS → Appendix 1: monoclonal antibodies

SIDE-EFFECTS
- Rare or very rare Encephalopathy - necrotising fasciitis (discontinue and initiate treatment promptly)
- Frequency not known Chest pain - chills - flushing - gallbladder perforation - hyperglycaemia - hypotension - nasal septum perforation - osteonecrosis of jaw - pulmonary hypertension - renal thrombotic microangiopathy

CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 6 months after treatment in women.

PREGNANCY Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING Manufacturer advises avoid breast-feeding during and for at least 6 months after treatment.

MONITORING REQUIREMENTS
- Monitor for necrotising fasciitis (usually secondary to wound healing complications, gastro-intestinal perforation or fistula formation)—discontinue and initiate treatment promptly.
- Monitor blood pressure.
- Monitor for congestive heart failure.
- Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without hypertension).
- Consider dental check-up before initiating treatment (risk of osteonecrosis of the jaw).
• **NICE decisions**

  **Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007)** NICE TA118  
  Bevacizumab in combination with fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer; see also NICE guidance Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy.  
  [www.nice.org.uk/guidance/TA118](http://www.nice.org.uk/guidance/TA118)

  **Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (December 2010)** NICE TA212  
  Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.  
  [www.nice.org.uk/guidance/TA212](http://www.nice.org.uk/guidance/TA212)

  **Bevacizumab, cetuximab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012)** NICE TA242  
  Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy; see also NICE guidance Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007).  
  [www.nice.org.uk/guidance/TA242](http://www.nice.org.uk/guidance/TA242)

  **Bevacizumab (first-line), sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009)** NICE TA178  
  Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced and/or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced and/or metastatic renal cell carcinoma.  
  [www.nice.org.uk/guidance/TA178](http://www.nice.org.uk/guidance/TA178)

  **Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011)** NICE TA214  
  Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer.  
  [www.nice.org.uk/guidance/TA214](http://www.nice.org.uk/guidance/TA214)

  **Bevacizumab in combination with capcitabine for the first-line treatment of metastatic breast cancer (August 2012)** NICE TA263  
  Bevacizumab in combinations with capcitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment in the previous 12 months.  
  [www.nice.org.uk/guidance/TA263](http://www.nice.org.uk/guidance/TA263)

  **Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013)** NICE TA284  
  Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).  
  [www.nice.org.uk/guidance/TA284](http://www.nice.org.uk/guidance/TA284)

  **Bevacizumab in combination with gemcitabine and carboplatin for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (May 2013)** NICE TA285  
  Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and peritoneal cancer) that has not been previously treated with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.  

  **Scottish Medicines Consortium (SMC) decisions**

  The Scottish Medicines Consortium has advised (May 2012) that bevacizumab (Avastin®) is not recommended for use within NHS Scotland for the first line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.  
  The Scottish Medicines Consortium has advised (September 2015) that bevacizumab (Avastin®) is accepted for restricted use within NHS Scotland in combination with paclitaxel for the treatment of advanced FIGO stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.  
  [www.nice.org.uk/guidance/TA212](http://www.nice.org.uk/guidance/TA212)

  **All Wales Medicines Strategy Group (AWMSG) decisions**

  The All Wales Medicines Strategy Group has advised (September 2015) that bevacizumab (Avastin®) is not recommended for use within NHS Wales in combination with paclitaxel and cisplatin, or alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adults with persistent, recurrent, or metastatic carcinoma of the cervix. The case for cost-effectiveness has not been proven.  
  [www.nice.org.uk/guidance/TA212](http://www.nice.org.uk/guidance/TA212)

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Avastin (Roche Products Ltd)**  
  Bevacizumab 25 mg per 1 ml Avastin 400mg/16ml solution for infusion vials | 1 vial | £242.66  
  (Hospital only)

**Blinatumomab**

- **DRUG ACTION** The anti-lymphocyte monoclonal antibodies cause lysis of B lymphocytes.

### INDICATIONS AND DOSE

**Relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukaemia (initiated by a specialist)**

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - **Adult**: (consult product literature)
  - **Philadelphia chromosome-negative acute lymphoblastic leukaemia in complete remission with minimal residual disease (initiated by a specialist)**
    - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - **Adult (body-weight 45 kg and above)**: (consult product literature)
Brentuximab vedotin

08-May-2019

- **INDICATIONS AND DOSE**
  - CD30 positive Hodgkin lymphoma (specialist use only)
  - Systemic anaplastic large cell lymphoma (specialist use only)

- **CAUTIONS**
  - Elevated BMI—risk of hyperglycaemia - high tumour burden—risk of tumour lysis syndrome - rapidly proliferating tumours—risk of tumour lysis syndrome

- **SIDE-EFFECTS**
  - Common or very common
  - Abdominal pain - alopecia - anaemia - arthralgia - back pain - chill - constipation - cough - diarrhoea - dizziness - dyspnoea - fatigue - fever - hyperglycaemia - increased risk of infection - infusion related reaction - myalgia - nausea - nerve disorders - neutropenia - sepsis - skin reactions - thrombocytopenia - vomiting - weight decreased
  - Uncommon
  - Cytomegalovirus infection reactivation - pancreatitis acute - tumour lysis syndrome
  - Rare or very rare
  - Severe cutaneous adverse reactions (SCARs)
  - Frequency not known

- **CONCEPTION AND CONTRACEPTION**
  - Effective contraception required during treatment and for 6 months after treatment in men and women
  - PRENANCY
  - Avoid unless potential benefit outweighs risk (toxicity in animal studies)
  - BREAST FEEDING
  - Avoid—no information available
**Brentuximab vedotin for treating CD13**

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (October 2017) NICE TA478
- Brentuximab vedotin is recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if:
  - they have an Eastern Cooperative Oncology Group performance status of 0 or 1, and
  - the manufacturer provides brentuximab vedotin according to the commercial access agreement with NHS England.

These recommendations are not intended to affect treatment that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta478

- Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (June 2018) NICE TA524
- Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults with relapsed or refractory disease, only if:
  - they have already had autologous stem cell transplant, or
  - they have already had at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy are not suitable, and
  - the manufacturer provides brentuximab vedotin according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta524

- Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma (April 2019) NICE TA577

Brentuximab vedotin (Adcetris®) is recommended as an option for treating CD30-positive cutaneous T-cell lymphoma (CTCL) after at least one systemic therapy in adults, only if:

- they have mycosis fungoides stage IIB or over, primary cutaneous anaplastic large cell lymphoma or Sézary syndrome, and
- the manufacturer provides brentuximab vedotin according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta577

**Cetuximab**

**INDICATIONS AND DOSE**

Treatment of wild-type RAS metastatic colorectal cancer in patients with tumours expressing epidermal growth factor receptor, as combination therapy, or as monotherapy if oxaliplatin- and irinotecan-based therapy has failed or if irinotecan is not tolerated |

Treatment of locally advanced squamous cell cancer of the head and neck (in combination with radiotherapy) |

Treatment of recurrent or metastatic squamous cell cancer of the head and neck (in combination with platinum-based chemotherapy) |

- BY INTRAVENOUS INFUSION
  - Adult (initiated by a specialist): (consult product literature or local protocols)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness.

Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

Patients must receive an antihistamine and a corticosteroid at least one hour before infusion. Resuscitation facilities should be available and treatment should be initiated by a specialist.

**CONTRA-INDICATIONS**

Combination of cetuximab with oxaliplatin-containing chemotherapy is contra-indicated in patients with metastatic colorectal cancer who have mutant or unknown RAS status. RAS mutated colorectal tumours (or if RAS tumour status unknown)

**CAUTIONS**

Cardiopulmonary disease · cardiovascular disease · history of keratitis · pulmonary disease—discontinue if interstitial lung disease · risk factors for keratitis · severe dry eye · ulcerative keratitis (including contact lens use)

**INTERACTIONS** → Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

- **Common or very common** Appetite decreased · cytokine release syndrome · dehydration · diarrhoea · electrolyte imbalance · eye inflammation · fatigue · headache · infusion related reaction · mucositis · nausea · skin eruption · vomiting

- **Uncommon** Embolism and thrombosis · interstitial lung disease

- **Rare or very rare** Severe cutaneous adverse reactions (SCARs)

- **Frequency not known** Meningitis aseptic · superinfection of skin lesions

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

EXCIPIENTS: May contain Polysorbates

ELECTROLYTES: May contain Sodium

- Adcetris (Takeda UK Ltd)

**Brentuximab vedotin 50 mg** Adcetris 50mg powder for concentrate for solution for infusion vials | 1 vial [POD] £2,500.00
Daratumumab

**DRUG ACTION** Daratumumab is a monoclonal antibody that binds to CD38, a cell-surface protein, resulting in tumour cell death by immune-mediated actions and apoptosis.

**INDICATIONS AND DOSE**

Multiple myeloma (as monotherapy after failure of a proteasome inhibitor and an immunomodulatory agent) (specialist use only)

Multiple myeloma (in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy) (specialist use only)

**By intravenous infusion**

Adult: 16 mg/kg once weekly for weeks 1 to 9, for week 1, dose can alternatively be divided over 2 consecutive days, then 16 mg/kg every 3 weeks for weeks 10 to 24, then 16 mg/kg every 4 weeks for week 25 onwards until disease progression, for dose interruption or infusion rate reduction due to infusion-related reactions or side-effects—consult product literature

**Newly diagnosed multiple myeloma (in combination with bortezomib, melphalan and prednisone) (specialist use only)**

**By intravenous infusion**

Adult: 16 mg/kg once weekly for weeks 1 to 9, for week 1, dose can alternatively be divided over 2 consecutive days, then 16 mg/kg every 3 weeks for weeks 10 to 24, then 16 mg/kg every 4 weeks for week 25 onwards until disease progression, for dose interruption or infusion rate reduction due to infusion-related reactions or side-effects—consult product literature

**CAUTIONS**

History of obstructive pulmonary disorder (consider additional post-medication—consult product literature) - patients may need pre-medication to minimise adverse reactions - risk of herpes zoster reactivation (consider antiviral prophylaxis)

**CAUTIONS, FURTHER INFORMATION**

Infusion-related reactions Serious infusion-related reactions can occur and daratumumab should only be administered when appropriately trained staff and resuscitation facilities are immediately available; manufacturer advises pre-medication with a corticosteroid, an antihistamine and an anti- pyretic and post-medication with oral corticosteroids—consult product literature. Manufacturer advises patients should be closely monitored for signs of infusion-related reactions during and after administration; in the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

**INTERACTIONS** → Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

Common or very common Anae mia - atrial fibrillation - chills - cough - diarrhoea - dyspnoea - fatigue - fever - headache - hypertension - hypoxia - increased risk of infection - infusion related reaction - lymphopenia - muscle spasms - nasal congestion - nausea - neutropenia - peripheral neuropathy - peripheral oedema - pulmonary

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- **CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **PREGNANCY** Use only if potential benefit outweighs risk—no information available. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **BREAST FEEDING** Avoid breast-feeding during and for 2 months after treatment—no information available.

- **PRE-TREATMENT SCREENING** Evidence of non-mutated (wild-type) RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before cetuximab is initiated for the treatment of metastatic colorectal cancer, and should be determined by an experienced laboratory using a validated test method.

- **DIRECTIONS FOR ADMINISTRATION** Resuscitation facilities should be available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **DIRECTIVE FOR ADMINISTRATION**

  - **PRE-TREATMENT SCREENING**

  - **PREGNANCY**

  - **CONCEPTION AND CONTRACEPTION**

  - **Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (June 2008) NICE TA145** Cetuximab in combination with radiotherapy is an option for the treatment of locally advanced squamous cell cancer of the head and neck in patients who have a Karnofsky performance status of 90% or greater and when all forms of platinum-based chemoradiotherapy treatment are contra-indicated.

  - [www.nice.org.uk/guidance/TA145](www.nice.org.uk/guidance/TA145)

  - **Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242** Cetuximab monotherapy or combination therapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy.

  - [www.nice.org.uk/guidance/TA242](www.nice.org.uk/guidance/TA242)

  - **Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (updated September 2017) NICE TA439** Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor-expressing, RAS wild-type metastatic colorectal cancer in patients in combination with:

    - 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX), or
    - 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

    This advice is contingent upon the manufacturer providing cetuximab with the discount agreed in the commercial access agreement.

    - [www.nice.org.uk/guidance/TA439](www.nice.org.uk/guidance/TA439)

  - **Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (August 2017) NICE TA473** Cetuximab in combination with platinum-based chemotherapy is recommended as an option for treating recurrent or metastatic squamous cell cancer of the head and neck in patients only:

    - if the cancer started in the oral cavity, and
    - when the company provides the drug in line with the commercial access agreement with NHS England.

    Patients currently receiving cetuximab whose disease does not meet the above criteria may continue treatment until they and their clinician consider it appropriate to stop.

    - [www.nice.org.uk/guidance/TA473](www.nice.org.uk/guidance/TA473)

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**

  - **Erbitux** (Merck Serono Ltd)

    - **Cetuximab 5 mg per 1 ml** Erbitux 100mg/20ml solution for infusion vials | 1 vial (P38) £178.10 (Hospital only)
    - Erbitux 500mg/100ml solution for infusion vials | 1 vial (P38) £890.50 (Hospital only)

www.getintopharma.com
Antibody responsive malignancy 867

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- **EXCIPIENTS:** May contain Polysorbates
- **ELECTROLYTES:** May contain Sodium
  - Darzalex (Janssen-Cilag Ltd) ▼
    - Daratumumab 20 mg per ml Darzalex 400mg/20ml concentrate for solution for infusion vials | 1 vial | £1,440.00
    - Darzalex 100mg/5ml concentrate for solution for infusion vials | 1 vial | £360.00

**Dinutuximab beta**

- **DRUG ACTION** Dinutuximab beta is a chimeric monoclonal antibody; it specifically targets the carbohydrate moiety of disialoganglioside 2, which is overexpressed on neuroblastoma cells.

- **INDICATIONS AND DOSE**
  - High-risk neuroblastoma (specialist use only)
    - By intravenous infusion
    - Adult: (consult product literature)

- **CONTRA-INDICATIONS** Acute grade 3 or 4, or extensive chronic graft-versus-host disease

- **CAUTIONS** Avoid vaccinations during and for at least 10 weeks after treatment cessation (increased risk of immune stimulation and neurological toxicity) - ensure absence of systemic infection — any other infection should be controlled before treatment initiation - pre-medication must be administered to minimise the risk of infusion-related reactions and neuropathic pain

- **CAUTIONS, FURTHER INFORMATION**
  - Pre-medication Severe infusion-related reactions can occur and dinutuximab beta should only be administered when appropriately trained staff and resuscitation facilities are immediately available; manufacturer advises pre-medication with an antihistamine, and to monitor closely, particularly during the first and second treatment course; discontinue immediately if reaction occurs and treat as indicated—consult product literature.

  - Manufacturer advises pre-medication with non-opioid analgesics, gabapentin and opioids—consult product literature.

- **INTERACTIONS** → Appendix 1: monoclonal antibodies

- **SIDE-EFFECTS**
  - Common or very common
  - Uncommon
    - Disseminated intravascular coagulation - eosinophilia - hepatocellular injury - hypovolaemic shock - intracranial pressure increased - peripheral vascular disease - posterior reversible encephalopathy syndrome (PRES)

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer advises women of childbearing potential should use contraception during and for 6 months after stopping treatment. See also

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oedema - respiratory disorders - throat irritation - thrombocytopenia - vomiting

- **Frequency not known**
  - Allergic rhinitis - chest discomfort - hypotension - pruritus

**SIDE-EFFECTS, FURTHER INFORMATION**

- Manufacturer advises effective contraception in women of childbearing potential during treatment and for 3 months after stopping treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk — no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Manufacturer advises avoid — no information available.

- **EFFECT ON LABORATORY TESTS**
  - Positive possible indirect Coombs test (may affect antibody screening).

- **HANDLING AND STORAGE**
  - Manufacturer advises store in a refrigerator at 2–8°C; consult product literature for storage advice following dilution.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (March 2018) NICE TA510 Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:
      - they have daratumumab after 3 previous therapies, and
      - the conditions in the managed access agreement are followed.

  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  - Daratumumab with bortezomib and dexethasone for previously treated multiple myeloma (April 2019) NICE TA573 Daratumumab (Darzalex®) plus bortezomib plus dexethasone is recommended for use within the Cancer Drugs Fund as an option for treating relapsed multiple myeloma in people who have had one previous treatment. It is recommended only if the conditions in the managed access agreement for daratumumab plus bortezomib plus dexethasone are followed.

  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

**Scottish Medicines Consortium (SMC) decisions**

- SMC No. 1205/17
  - The Scottish Medicines Consortium has advised (October 2017) that daratumumab (Darzalex®) is accepted for restricted use within NHS Scotland as monotherapy for use as a fourth-line treatment option for adults with relapsed and refractory multiple myeloma, only if a proteasome inhibitor and an immunomodulatory agent have been used as prior therapy and disease demonstrated progression on the last therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

www.getintopharma.com
Dinutuximab beta for treating neuroblastoma (August 2018)

**National Funding/Access Decisions**

- **Patient and Carer Advice**
  - Handling and storage: Manufacturer advises monitor circulatory and respiratory function — risk of capillary leak syndrome.
  - Handling and storage: Manufacturer advises monitor liver function and electrolytes regularly.
  - Handling and storage: Manufacturer advises store in a refrigerator (2–8°C) — consult product literature for further information regarding storage conditions outside refrigerator and after preparation of the infusion.
  - Patient and carer advice: Driving and skilled tasks: Manufacturer advises patients should not use or drive machines during treatment.
  - National funding/access decisions: NICE decisions

**NICE decisions**

- Dinutuximab beta for treating neuroblastoma (August 2018)
  - NICE TS38

  Dinutuximab beta (Qarziba®) is recommended as an option for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if:
  - they have not already had anti-GD2 immunotherapy; and
  - the manufacturer provides dinutuximab beta according to the commercial arrangement.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/ts38

Scottish Medicines Consortium (SMC) decisions

- SMC No. SMC2105

The Scottish Medicines Consortium has advised (November 2018) that dinutuximab beta (Qarziba®) is accepted for use within NHS Scotland for the treatment of high-risk neuroblastoma in patients aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease.

In patients with a history of relapsed or refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin-2.

This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**Pregnancy and Reproductive Function** in Cytotoxic drugs p. 888.

- **Pregnancy** Manufacturer advises avoid — no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- **Breast Feeding** Manufacturer advises avoid during treatment and for 6 months after the last dose — no information available.

**Monitoring Requirements**

- Manufacturer advises pre-treatment evaluation of pulse oximetry, bone marrow function, liver function and renal function — consult product literature for values required for treatment initiation.
- Manufacturer advises monitor circulatory and respiratory function — risk of capillary leak syndrome.
- Manufacturer advises monitor liver function and electrolytes regularly.

**Handling and Storage**

- Manufacturer advises store in a refrigerator (2–8°C) — consult product literature for further information regarding storage conditions outside refrigerator and after preparation of the infusion.

**Patient and Carer Advice**

- Driving and skilled tasks: Manufacturer advises patients should not use or drive machines during treatment.

**National Funding/Access Decisions**

- NICE decisions

**NICE decisions**

- Dinutuximab beta for treating neuroblastoma (August 2018)
  - NICE TS38

  Dinutuximab beta (Qarziba®) is recommended as an option for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if:
  - they have not already had anti-GD2 immunotherapy, and
  - the manufacturer provides dinutuximab beta according to the commercial arrangement.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  www.nice.org.uk/guidance/ts38

Scottish Medicines Consortium (SMC) decisions

- SMC No. SMC2105

The Scottish Medicines Consortium has advised (November 2018) that dinutuximab beta (Qarziba®) is accepted for use within NHS Scotland for the treatment of high-risk neuroblastoma in patients aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease.

In patients with a history of relapsed or refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin-2.

This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Qarziba (EUSA Pharma Ltd)
  - Dinutuximab beta 4.5 mg per 1 ml Qarziba 20mg/4.5ml concentrate for solution for infusion vials | 1 vial £7,610.00 (Hospital only)

**Durvalumab**

- **Drug Action** Durvalumab is a human monoclonal antibody that selectively binds to programmed cell death ligand-1 (PD-L1), blocking its interaction with the programmed death-1 (PD-1) receptor and with CD80, and thereby potentiating an immune response to tumour cells.

- **Indications and Dose**
  - Non-small cell lung cancer (initiated by a specialist)
    - Adult: 10 mg/kg every 2 weeks, consult product literature for information on dose adjustments based on individual patient safety and tolerability.

- **Interactions** → Appendix 1: monoclonal antibodies

- **Side-effects**
  - Common or very common: Cough, diarrhoea, dysphonia, dysuria, fever, flank pain, gastrointestinal discomfort, gastrointestinal disorders, hyperthyroidism, hypothyroidism, increased risk of infection, infusion related reaction, myalgia, night sweats, peripheral oedema, respiratory disorders, skin reactions — thyroditis
  - Uncommon: Adrenal insufficiency, glomerulonephritis, hepatic disorders, myopathy, nephritis — type 1 diabetes mellitus
  - Rare or very rare: Diabetes insipidus, hypopituitarism, hypopituitarism — myocardiits

**Side-effects, further information**

**Immune-related reactions**

- Manufacturer advises that most immune-related adverse reactions resolved with appropriate management, including initiation of immunosuppressive treatment and treatment modifications — consult product literature.

**Infusion-related reactions**

- Manufacturer advises to permanently discontinue treatment in patients with severe infusion reactions.

- **Conception and Contraception**
  - Manufacturer advises effective contraception in women of childbearing potential during treatment and for at least 3 months after stopping treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **Pregnancy**
  - Manufacturer advises avoid — no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **Breast Feeding**
  - Manufacturer advises avoid — no information available.

- **Monitoring Requirements**
  - Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions — consult product literature.

- **Directions for Administration**
  - Manufacturer advises for intravenous infusion, dilute to a concentration between 1 mg/mL and 15 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 60 minutes through a low-protein binding in-line filter (pore size 0.2 or 0.22 micron).

- **Handling and Storage**
  - Manufacturer advises store in a refrigerator (2–8°C) and protect from light — consult product literature for storage conditions after preparation of the infusion.

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- EXCipients: May contain Polysorbates
  - Imfinzi (AstraZeneca UK Ltd)

  **Imfinzi 50 mg per 1 ml** Imfinzi 220mg/2.4ml concentrate for solution for infusion vials | 1 vial £592.00
  - Imfinzi 500mg/10ml concentrate for solution for infusion vials | 1 vial £2,466.00

www.getintopharma.com
Elotuzumab

12-Apr-2019

DRUG ACTION Elotuzumab is a monoclonal antibody that targets the signalling lymphocytic activation molecule family member 7 (SLAMF7) protein, thereby activating natural killer cells and mediating myeloma cell death.

INDICATIONS AND DOSE

Multiple myeloma in patients who have received at least one prior therapy (in combination with lenalidomide and dexamethasone) (specialist use only)

- BY INTRAVENOUS INFUSION
  - Adult: 10 mg/kg every week, on days 1, 8, 15 and 22 of cycles 1 and 2, then 10 mg/kg every 2 weeks, on days 1 and 15 of subsequent cycles

CAUTIONS

Pre-medication must be administered to minimise the development of infusion-related reactions—consult product literature—secondary primary malignancies

CAUTIONS, FURTHER INFORMATION

Secondary primary malignancies Manufacturer advises to monitor for the development of secondary primary malignancy before and during treatment with elotuzumab.

INTERACTIONS

Appendix 1: monoclonal antibodies

SIDE-EFFECTS

- Common or very common Chest pain · cough · deep vein thrombosis · diarrhoea · fatigue · fever · headache · hypersensitivity · increased risk of infection · infusion related reaction · lymphopenia · mood altered · night sweats · numbness · oropharyngeal pain · weight decreased

SIDE-EFFECTS, FURTHER INFORMATION

Side-effects reported when used in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone.

Infusion-related reactions Manufacturer advises for mild-to-moderate infusion reactions interrupt treatment or reduce infusion rate, and monitor closely (consult product literature); permanently discontinue therapy in severe infusion reactions.

CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception in men and women of childbearing potential; male patients should continue effective contraception during treatment and for at least one month after the last dose if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

PREGNANCY

Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

HANDLING AND STORAGE

Manufacturer advises store in a refrigerator (2–8°C); consult product literature for storage conditions after preparation of the infusion.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion

EXCipients: May contain Polysorbates, sucrose

- Empliciti (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Elotuzumab 300 mg Empliciti 300mg powder for concentrate for solution for infusion vials | 1 vial | £3,085.00
  - Elotuzumab 400 mg Empliciti 400mg powder for concentrate for solution for infusion vials | 1 vial | £3,446.00

Gemtuzumab ozogamicin

17-Oct-2018

DRUG ACTION Gemtuzumab ozogamicin is a monoclonal antibody that binds to CD33-expressing tumour cells to induce cell cycle arrest and apoptotic cell death.

INDICATIONS AND DOSE

CD33-positive acute myeloid leukaemia (specialist use only)

- BY INTRAVENOUS INFUSION

- Adult: (consult product literature)

CAUTIONS

Adverse-risk cytogenetics (consider benefits and risks of treatment, consult product literature) · haematopoietic stem cell transplantation (increased risk of hepatotoxicity) · pre-medication recommended to minimise adverse reactions

CAUTIONS, FURTHER INFORMATION

Pre-medication Serious infusion-related reactions can occur and gemtuzumab ozogamicin should only be administered when appropriately trained staff and resuscitation facilities are immediately available; manufacturer advises pre-medication with a corticosteroid, paracetamol and antihistamine 1 hour prior to dosing, and to take appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia—consult product literature.

SIDE-EFFECTS

- Common or very common Anaemia · appetite decreased · ascites · chills · constipation · decreased leucocytes · diarrhoea · dyspnoea · fatigue · fever · gastrointestinal discomfort · gastrointestinal disorders · haemorrhage · headache · hepatic disorders · hyperbilirubinaemia · hyperglycaemia · hypertension · hypotension · infection · infusion related reaction (including fatal cases) · multi organ failure · nausea · neutropenia · oedema · pancytopenia · sinusoidal obstruction syndrome · skin reactions · stomatitis · tachycardia · thrombocytopenia · tumour lysis syndrome (including fatal cases) · vomiting

Frequency not known Interstitial pneumonia

SIDE-EFFECTS, FURTHER INFORMATION

Infusion-related reactions (including fatal cases) can occur during the first 24 hours after administration. Manufacturer advises interrupt treatment immediately and treat as clinically indicated (consult product literature); permanent discontinuation should be strongly considered in patients who develop signs and symptoms of anaphylaxis.

CONCEPTION AND CONTRACEPTION

Manufacturer advises women of childbearing potential should use 2 methods of effective contraception during treatment and for at least 7 months after the last dose; male patients should use 2 methods of effective contraception during treatment and for at least 4 months after the last dose if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid during treatment and for at least one month after the last dose—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises caution in moderate-to-severe impairment—increased risk of developing hepatotoxicity; postpone treatment if serum transaminases (ALT or AST) greater than 2.5 times the upper limit of normal or total bilirubin greater than 2 times the upper limit of normal.

MONITORING REQUIREMENTS

Manufacturer advises monitor complete blood counts prior to each dose as well as signs and symptoms of infection.

www.getintopharma.com
bleeding and other effects of myelosuppression during treatment; dose interruption or discontinuation of treatment may be required—consult product literature.

- Manufacturer advises monitor for signs and symptoms of infusion-related reactions—close clinical monitoring, including pulse, blood pressure and temperature, should be performed during infusion; monitor for signs and symptoms of tumour lysis syndrome.
- Manufacturer advises monitor for signs and symptoms of hepatotoxicity (including hepatic veno-occlusive disease); liver tests should be monitored prior to each dose—consult product literature.

### Prescribing and dispensing information

Gemtuzumab ozogamicin is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

### Handling and storage

Manufacturer advises store in a refrigerator (2–8°C) and protect from light—consult product literature for storage conditions after reconstitution and dilution.

### Patient and carer advice

- **Driving and skilled tasks** Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue and headache.

### National funding/access decisions

**NICE decisions**
- Gemtuzumab ozogamicin for untreated acute myeloid leukaemia (November 2018) NICE TAs545
  - Gemtuzumab ozogamicin (Mylotarg® 5), with daunorubicin and cytarabine, is recommended as an option for untreated de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over, only if:
    - they start induction therapy when either the cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available, and
    - they start consolidation therapy when their cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful), and
  - the manufacturer provides gemtuzumab ozogamicin according to the commercial arrangement.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

  [Website link](https://www.nice.org.uk/guidance/ta545)

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (October 2018) that gemtuzumab ozogamicin (Mylotarg® 5) is accepted for restricted use within NHS Scotland as combination therapy with daunorubicin and cytarabine for the treatment of previously untreated, de novo CD33-positive acute myeloid leukaemia in patients aged 15 years and above with a favourable, intermediate or unknown cytogenetic profile.

### Medicinal forms

- **Medication costs** There can be variation in the licensing of different medicines containing the same drug.
- **Powder for solution for infusion**
  - Mylotarg® (Pfizer Ltd) ▶

  Gemtuzumab ozogamicin 5 mg Mylotarg 5mg powder for concentrate for solution for infusion vials | 1 vial [GDP] £6,300.00 (Hospital only)

### Inotuzumab ozogamicin

#### Drug action

Inotuzumab ozogamicin is a monoclonal antibody that binds to CD22-expressing tumour cells to induce cell cycle arrest and apoptotic cell death.

#### Indications and dose

Monotherapy for relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (under expert supervision)
- By intravenous infusion
- Adult: (consult product literature)

#### Contra-indications

- Prior confirmed severe or ongoing sinusoidal obstruction syndrome

#### Caution

- History of, or predisposition to QT-interval prolongation (e.g. electrolyte disturbances, concomitant use of drugs that prolong the QT interval); patients may need pre-medication to minimise adverse reactions—patients undergoing haematopoietic stem cell transplantation (increased risk of hepatotoxicity)

#### Further information

- Pre-medication Manufacturer advises pre-medication with a corticosteroid, antipyretic and antihistamine prior to dosing in all patients and pre-medication to reduce uric acid levels and hydration in patients with a high tumour burden (increased risk of tumour lysis syndrome)—consult product literature.

#### Interactions

- Appendix 1: monoclonal antibodies

#### Side-effects

- Common or very common

#### Further information

Manufacturer advises interrupt treatment if an infusion related reaction occurs; depending on the severity, discontinuation of the infusion or administration of steroids and antihistamines should be considered (consult product literature); permanently discontinue treatment in severe or life-threatening infusion reactions.

#### Conception and contraception

Manufacturer advises effective contraception in women of childbearing potential during treatment and for at least 8 months after the last dose; male patients should use effective contraception during treatment and for at least 5 months after the last dose if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

#### Pregnancy

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

#### Breast feeding

Manufacturer advises avoid during treatment and for at least two months after the last dose—no information available.

#### Hepatic impairment

Manufacturer advises caution if bilirubin and transaminase levels are raised (limited information available); avoid in serious ongoing impairment.

#### Dose adjustments

Manufacturer advises dose interruption or discontinuation according to bilirubin and transaminase levels.

#### Pre-treatment screening

Manufacturer advises baseline CD22 positivity of greater than 0% is required prior to initiating treatment.
Inotuzumab ozogamicin is recommended only if the Scottish Medicines Consortium (SMC) decisions (2018) have advised (June 2018) that inotuzumab ozogamicin (Besponsa®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL) for whom the intent is to proceed to stem cell transplantation. Adults with Philadelphia chromosome positive relapsed or refractory B cell precursor ALL should have failed treatment with at least one tyrosine kinase inhibitor. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**DRUG ACTION**

Iplimumab is a monoclonal antibody which causes T-cell activation resulting in tumour cell death.

**INDICATIONS AND DOSE**

- **Melanoma (as monotherapy) (specialist use only)**
  - *By Intravenous infusion*
  - Adult: 3 mg/kg every 4 weeks for 4 doses, for dose interruption or discontinuation of treatment due to immune-related side-effects—consult product literature
- **Melanoma (in combination with nivolumab) (specialist use only)** Advanced renal cell carcinoma (in combination with nivolumab) (specialist use only)
  - *By Intravenous infusion*
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: IPILIMUMAB (YERVOY®): REPORTS OF CYTOMEGALOVIRUS (CMV) GASTROINTESTINAL INFECTION OR REACTIVATION (JANUARY 2019)

There have been post-marketing cases of gastrointestinal CMV infection or reactivation in iplimumab-treated patients reported to have corticosteroid-refractory immune-related colitis, including fatal cases.

Patients should be advised to contact their healthcare professional immediately at the onset of symptoms of colitis. Possible causes, including infections, should be investigated; a stool infection work-up should be performed and patients screened for CMV. For patients with corticosteroid-refractory immune-related colitis, use of an additional immunosuppressive agent should only be considered if other causes are excluded using viral PCR on biopsy, and eliminating other viral, bacterial, and parasitic causes.

**SIDE-EFFECTS**

- **Common or very common** Alopecia - anaemia - appetite decreased - arthralgia - asthma - cancer pain - chills - confusion - constipation - cough - dehydration - diarrhoea - dizziness - dyspnoea - electrolyte imbalance - eye discomfort - fever - gastrointestinal discomfort - gastrointestinal disorders - haemorrhage - headache - hepatic disorders - hypophysitis - hypopituitarism - hypotension - hypothyroidism - influenza like illness - lethargy - lymphopenia - mucositis - muscle complaints - nausea - nerve disorders - night sweats - oedema - pain - skin reactions - vasodilation - vision disorders - vomiting - weight decreased
- **Uncommon** Adrenal hypofunction - alkalosis - allergic rhinitis - amenorrhoea - arthrythmias - arthritis - brain oedema - depression - dysarthria - eosinophilia - eye inflammation - glomerulonephritis - haemolytic anaemia - hair colour changes - hyperthyroidism - hypogonadism - increased risk of infection - infusion related reaction - libido decreased - meningitis - movement disorders - multi organ failure - muscle weakness - myopathy - nephritis - autoimmunity - neutropenia - pancreatitis - paraneoplastic

**INTERACTIONS**

→ Appendix 1: monoclonal antibodies
**872 Antibody responsive malignancy**

**Immune system and malignant disease**

- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (December 2012) NICE TA268
  - Ipilimumab (Yervoy®) is recommended as an option for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

**Necitumumab**

- Necitumumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR).

**Indications and Dose**

- Necitumumab is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma in adults, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

**Scottish Medicines Consortium (SMC) decisions**

- The Scottish Medicines Consortium has advised (April 2013) that ipilimumab (Yervoy®) is accepted for use within NHS Scotland for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

- The Scottish Medicines Consortium has advised (November 2014) that ipilimumab (Yervoy®) is accepted for use within NHS Scotland for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**Side-effects**

- Common or very common: Conjunctivitis, dysuria, electrolyte imbalance, embolism and thrombosis, fever, haemorrhage, headache, hypomagnesaemia (severe), increased risk of infection, infusion related reaction, muscle spasms, oral disorders, skin reactions, taste altered, vomiting, weight decreased.
Antibody responsive malignancy 873

Melanoma (as monotherapy) (specialist use only) | Advanced renal cell carcinoma (as monotherapy) (specialist use only)

- **BY INTRAVENOUS INFUSION**
  - **Adult:** 400 mg every 2 weeks, consult product literature for information on dose adjustments based on individual patient safety and tolerability.

**Important Safety Information**

**MHRA/CHM Advice: Nivolumab (Opdivo®): Reports of Organ Transplant Rejection (July 2017)**

A European review of worldwide data concluded that nivolumab may increase the risk of rejection in organ transplant recipients. The MHRA recommends considering the benefit of treatment with nivolumab versus the risk of possible organ transplant rejection for each patient.

- **Caution** May increase risk of severe graft-versus-host reaction in patients who have had prior haematopoietic stem cell transplant (particularly in those with a prior history). patients may need pre-medication to minimise the development of infusion-related reactions.

**Interactions**

- **Common or very common** Abdominal pain - alopecia - anaemia - appetite decreased - arthralgia - constipation - cough - decreased leucocytes - diarrhoea - dizziness - dry mouth - dyspnoea - electrolyte imbalance - fatigue - fever - headache - hyperglycaemia - hypersensitivity - hypertension - hyperthyroidism - hypothyroidism - increased risk of infection - infusion related reaction - nausea - nerve disorders - neutropenia - oedema - pain - respiratory disorders - skin reactions - stomatitis - thrombocytopenia - vomiting - weight decreased


- **Rare or very rare** Dermatitis - diabetes mellitus - diabetic ketoacidosis - histiocytic necrotising lymphadenitis - myasthenic syndrome - myocardiitis - myopathy - severe cutaneous adverse reactions (SCARs) - vasculitis

- **Frequency not known** Solid organ transplant rejection

**Side-effects, Further Information**

**Immune-related reactions**

Manufacturer advises that most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications—consult product literature for further information.

### Nivolumab

**Drug Action**

Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor thereby potentiating an immune response to tumour cells.

**Indications and Dose**

Melanoma (in combination with ipilimumab) (specialist use only): Advanced renal cell carcinoma (in combination with ipilimumab) (specialist use only)

- **By Intravenous Infusion**
  - **Adult:** consult product literature

**Dosing Information**

**Solution for infusion**

- **ELECTROLYTES:** May contain Sodium
- **Portrazza (Eli Lilly and Company Ltd)**
  - **Necitumumab 16 mg per 1 ml** Portrazza 800mg/50ml concentrate for solution for infusion vials | 1 vial | £1,450.00 (Hospital only)

**BNF 78**

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Immune system and malignant disease

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Infusion-related reactions  Manufacturer advises that patients with mild or moderate infusion reactions may continue treatment with close monitoring and use of premedication according to local guidelines; discontinue treatment if severe infusion reactions occur.

- CONCEPTION AND CONTRACEPTION  Manufacturer advises effective contraception required during treatment and for at least 5 months after treatment in women of childbearing potential.
- PREGNANCY  Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.
- BREAST FEEDING  Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT  Manufacturer advises moderate to severe impairment (limited information available).
- MONITORING REQUIREMENTS  Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions, cardiac and pulmonary reactions, and electrolyte disturbances before and periodically during treatment. Patients should be monitored for adverse reactions for at least 5 months after the last dose.
- DIRECTIONS FOR ADMINISTRATION  Manufacturer advises for intermittent intravenous infusion, give undiluted or dilute to a concentration of not less than 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 30 or 60 minutes (depending on dose—consult product literature) through an in-line filter (pore size 0.2–1.2 micron).
- HANDLING AND STORAGE  Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for storage conditions after preparation of the infusion.
- PATIENT AND CARER ADVICE  Patients should be provided with a patient alert card with each prescription.
- NATIONAL FUNDING/ACCESS DECISIONS  

NICE decisions

- Nivolumab for treating advanced (unresectable or metastatic) melanoma (February 2016) NICE TA384
Nivolumab (Opdivo®) as monotherapy is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma in adults.

www.nice.org.uk/guidance/ta384

- Nivolumab in combination with ipilimumab for treating advanced melanoma (July 2016) NICE TA400
Nivolumab (Opdivo®) in combination with ipilimumab is recommended, within its marketing authorisation, as a treatment option for advanced (unresectable or metastatic) melanoma in adults, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta400

- Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (January 2019) NICE TA558
Nivolumab (Opdivo®) is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease. It is recommended only if the conditions in the managed access agreement are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta558

- Nivolumab for previously treated advanced renal cell carcinoma (updated November 2017) NICE TA417
Nivolumab (Opdivo®) is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults, when the manufacturer provides nivolumab in line with the commercial access agreement with NHS England.

www.nice.org.uk/guidance/ta417

- Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (updated November 2017) NICE TA462
Nivolumab (Opdivo®) is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin, when the manufacturer provides nivolumab in line with the commercial access agreement with NHS England.

www.nice.org.uk/guidance/ta462

- Nivolumab for previously treated squamous non-small-cell lung cancer (November 2017) NICE TA483
Nivolumab (Opdivo®) is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer in adults after chemotherapy, only if:

- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
- the conditions in the managed access agreement are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta483

- Nivolumab for previously treated non-squamous non-small-cell lung cancer (November 2017) NICE TA484
Nivolumab (Opdivo®) is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after chemotherapy, only if:

- their tumours are PD-L1 positive, and
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
- the conditions in the managed access agreement are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta484

- Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (November 2017) NICE TA490
Nivolumab (Opdivo®) is recommended for use within the Cancer Drugs Fund as an option for treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy, only if:

- the disease has progressed within 6 months of having chemotherapy, and
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and
- the conditions in the managed access agreement are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta490
arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta490

- Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (July 2018) NICE TA530

Nivolumab (Opdivo®) is not recommended, within its marketing authorisation, for treating locally advanced unresectable or metastatic urothelial carcinoma in adults who have had platinum-containing therapy.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta530

Scottish Medicines Consortium (SMC) decisions

SMC No. 1144/16
The Scottish Medicines Consortium has advised (July 2016) that nivolumab (Opdivo®) is accepted for use within NHS Scotland for the treatment of locally advanced or metastatic squamous non-small cell lung cancer after prior chemotherapy in adults. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1180/16
The Scottish Medicines Consortium has advised (October 2016) that nivolumab (Opdivo®) is accepted for restricted use within NHS Scotland for the treatment of locally advanced or metastatic squamous non-small cell lung cancer after prior chemotherapy in adults, subject to a two-year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1120/16
The Scottish Medicines Consortium has advised (August 2016) that nivolumab (Opdivo®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1187/16
The Scottish Medicines Consortium has advised (November 2016) that nivolumab (Opdivo®) is accepted for restricted use within NHS Scotland in combination with ipilimumab for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. SMC2112
The Scottish Medicines Consortium has advised (December 2018) that nivolumab (Opdivo®) is accepted for use within NHS Scotland as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1188/16
The Scottish Medicines Consortium has advised (June 2017) that nivolumab (Opdivo®) is accepted for use within NHS Scotland as monotherapy for treating adults with advanced uveal melanoma progressing after prior therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1240/17
The Scottish Medicines Consortium has advised (July 2017) that nivolumab (Opdivo®) is accepted for use within NHS Scotland for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1261/17
The Scottish Medicines Consortium has advised (September 2017) that nivolumab (Opdivo®) is accepted for restricted use within NHS Scotland as monotherapy, for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. Treatment with nivolumab is subject to a two year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1285/18
The Scottish Medicines Consortium has advised (January 2018) that nivolumab (Opdivo®) is not recommended for use within NHS Scotland as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy, as the economic case was not demonstrated.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

CAUTIONARY AND ADVISORY LABELS

3 ELECTROLYTES: May contain Sodium

Opdivo (Bristol-Myers Squibb Pharmaceuticals Ltd) ▼

Nivolumab 10 mg per 1 ml

Opdivo 40mg/4ml concentrate for solution for infusion vials | 1 vial (£633.00 (Hospital only)

Opdivo 100mg/10ml concentrate for solution for infusion vials | 1 vial (£11.097.00 (Hospital only)

Opdivo 240mg/24ml concentrate for solution for infusion vials | 1 vial (£32.633.00 (Hospital only)

Obinutuzumab

- INDICATIONS AND DOSE

Treatment of previously untreated chronic lymphocytic leukaemia in patients for whom full-dose fludarabine-based therapy is unsuccessful due to co-morbidities

Treatment of previously untreated advanced follicular lymphoma | Treatment of follicular lymphoma in patients who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen

- BY INTRAVENOUS INFUSION

Adult: (consult product literature or local protocols)

- CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION

For obinutuzumab contra-indications, consult product literature.

- CAUTIONS

CAUTIONS, FURTHER INFORMATION

For full details on the cautions of obinutuzumab, consult product literature.

- Hepatitis B infection and reactivation

Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking obinutuzumab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and
Immune system and malignant disease

Obinutuzumab for untreated advanced follicular lymphoma

Obinutuzumab with bendamustine for treating follicular lymphoma

Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (June 2015) NICE TA343

Olaratumab

**Drug action**

Olaratumab is a monoclonal antibody that binds to platelet-derived growth factor receptor alpha to inhibit tumour growth.

**Indications and dose**

Advanced soft tissue sarcoma (in combination with doxorubicin) in patients that are not amenable to curative treatment with surgery or radiotherapy, and who have not been previously treated with doxorubicin (specialist use only)

- By intravenous infusion

- Adult: 15 mg/kg once daily on days 1 and 8 of a 3-week cycle, for up to 8 cycles, patients whose disease has not progressed after combination therapy may continue with olaratumab monotherapy, for dose adjustments due to side-effects and infusion-related reactions—consult product literature

**Important safety information**

MHRA/CHM advice: Lartruvo® (Olaratumab): No new patients to be prescribed due to study showing no clinical benefit (February 2019)

Results from the clinical trial (ANNOUNCE) of olaratumab with doxorubicin in patients with advanced or metastatic soft tissue sarcoma showed no survival benefit compared with doxorubicin. No new patients should be prescribed Lartruvo®, but treatment may be continued in patients who experience clinical benefit while further assessment of study results is ongoing.

**Caution**

Patients should receive pre-medication to minimise the development of adverse reactions (consult product literature)

**Interactions**

- Appendix 1: monoclonal antibodies

**Side-effects**

- Common or very common

Arthralgia, diarrhoea, headache, infusion related reaction, lymphopenia, mucositis, muscle complaints, nausea, neutropenia, pain, vomiting
Panitumumab

02-Aug-2017

**Drug action** Panitumumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR).

**Indications and dose** Treatment of non-mutated RAS metastatic colorectal cancer (combination therapy): Treatment of non-mutated RAS metastatic colorectal cancer (monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens)

- By intravenous infusion
  - Adult: consult product literature

**Important safety information**

**MHRA/CHM advice: Severe skin reactions**

Severe skin reactions have been reported very commonly in patients treated with panitumumab. Patients receiving panitumumab who have severe skin reactions or develop worsening skin reactions should be monitored for the development of inflammatory or infectious sequelae (including cellulitis, sepsis, and necrotising fasciitis). Appropriate treatment should be promptly initiated and panitumumab withheld or discontinued.

**MHRA/CHM advice: Epidermal growth factor receptor (EGFR) inhibitors: serious cases of keratitis and ulcerative keratitis (May 2012)**

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib, and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

**Contra-indications** Interstitial pulmonary disease - the combination of panitumumab with oxaliplatin-containing chemotherapy is contra-indicated in patients with mutant RAS metastatic colorectal cancer or for whom RAS status is unknown.

**Caution** History of keratitis - history of severe dry eye - history of ulcerative keratitis - pulmonary disease - discontinue if interstitial lung disease develops - risk factors for keratitis - risk factors for severe dry eye - risk factors for ulcerative keratitis (including contact lens use).

**Interactions** → Appendix I: monoclonal antibodies
Antibody responsive malignancy

- **SIDE-EFFECTS**
  - **Common or very common** Alopecia - anaemia - anxiety - appetite decreased - asthenia - chest pain - chills - constipation - cough - dehydration - diarrhoea - dizziness - dry eye - dry mouth - dyspnoea - electrolyte imbalance - embolism and thrombosis - eye discomfort - eye disorders - eye inflammation - fever - flushing - gastrointestinal discomfort - gastrooesophageal reflux disease - haemorrhage - hair changes - headache - hyperglycaemia - hyperhidrosis - hypersensitivity (may be delayed) - hypertension - hypotension - increased risk of infection - insomnia - leucopenia - mucositis - nail disorders - nausea - oral disorders - pain - peripheral oedema - skin reactions - skin ulcer - tachycardia - vomiting - weight decreased
  - **Uncommon** Angioedema - cyanosis - infusion related reaction - nasal dryness - onycholysis - respiratory disorders
  - **Rare or very rare** Anaphylactic reaction - severe cutaneous adverse reactions (SCARs)
  - **INTERACTIONS**
    - Pembrolizumab may increase the risk of rejection in organ transplant recipients. The MHRA recommends considering the benefit of treatment with pembrolizumab versus the risk of possible organ transplant rejection for each patient.

- **PRE-TREATMENT SCREENING**
  - Evidence of non-mutated RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before panitumumab treatment is initiated, and should be determined by an experienced laboratory using a validated test method.

- **MONITORING REQUIREMENTS**
  - Monitor for hypomagnesaemia.
  - Monitor for hypocalcaemia.
  - Monitor for hypomagnesaemia.
  - Monitor for dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (consult product literature).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Cetuximab, bevazcizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242
    - Panitumumab monotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy.
    - www.nice.org.uk/guidance/TA242
  - **Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (updated September 2017) NICE TA439
    - Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:
      - 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX), or
      - 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).
    - This advice is contingent upon the manufacturer providing panitumumab with the discount agreed in the patient access scheme.
    - www.nice.org.uk/guidance/TA439

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**
  - **ELECTROLYTES**: May contain Sodium
    - **Vectibix (Amgen Ltd)**
      - **Panitumumab 20 mg per 1 ml** Vectibix 400mg/20ml concentrate for solution for infusion vials | 1 vial | £1,517.16 (Hospital only)
      - Vectibix 100mg/5ml concentrate for solution for infusion vials | 1 vial | £370.23 (Hospital only)

- **Pembrolizumab**
  - **DRUG ACTION** Pembrolizumab is a monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor, thereby potentiating an immune response to tumour cells.
  - **INDICATIONS AND DOSE**
    - Melanoma (specialist use only) | Non-small cell lung cancer (specialist use only) | Urothelial carcinoma (specialist use only) | Classical Hodgkin lymphoma (specialist use only) | Head and neck squamous cell carcinoma (specialist use only)
      - By intravenous infusion
        - Adult: 200 mg every 3 weeks, for dose adjustments due to side-effects or infusion-related reactions—consult product literature

- **IMPORTANT SAFETY INFORMATION**
  - **MHRA/CHM ADVICE: PEMBROLIZUMAB (KEYTRUDA®): REPORTS OF ORGAN TRANSPLANT REJECTION (JULY 2017)**
    - A European review of worldwide data concluded that pembrolizumab may increase the risk of rejection in organ transplant recipients. The MHRA recommends considering the benefit of treatment with pembrolizumab versus the risk of possible organ transplant rejection for each patient.

  **CAUTIONS**
  - Patients may need pretreatment to minimise the development of adverse reactions (consult product literature)

  **INTERACTIONS**
  - Appendix 1: monoclonal antibodies

  **SIDE-EFFECTS**

  **Uncommon**

  **Rare or very rare**
  - Erythema nodosum - haemolytic anaemia - myasthenic syndrome - sarcoidosis

  **Frequency not known**
  - Solid organ transplant rejection

  **SIDE-EFFECTS, FURTHER INFORMATION**
  - Immune-related reactions are reversible and managed by temporarily stopping treatment and administration of a corticosteroid—consult product literature for further information.

  **Infusion-related reactions**
  - Manufacturer advises to permanently discontinue treatment in patients with severe infusion reactions.

  **CONCEPTION AND CONTRACEPTION**
  - Manufacturer recommends effective contraception during treatment and for at least 4 months after treatment in women of childbearing potential.

  **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available

  **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

  **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor for signs and symptoms of infusion- and immune-related reactions.
Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (updated September 2017) NICE TA357

Pembrolizumab (Keytruda®) is recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only:

- after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor, and
- the manufacturer provides pembrolizumab in line with the commercial access agreement with NHS England.

www.nice.org.uk/guidance/ta357

Pembrolizumab for advanced melanoma not previously treated with ipilimumab (updated September 2017) NICE TA356

Pembrolizumab (Keytruda®) is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the manufacturer provides pembrolizumab in line with the commercial access agreement with NHS England.

www.nice.org.uk/guidance/ta356

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (December 2018) NICE TA553

Pembrolizumab (Keytruda®) is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of stage III melanoma with lymph node involvement in adults who have had complete resection. It is recommended only if the conditions in the managed access agreement for pembrolizumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta553

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (updated September 2017) NICE TA428

Pembrolizumab (Keytruda®) is recommended as an option for treating locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive tumour), only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and
- the manufacturer provides pembrolizumab in line with the commercial access agreement with NHS England. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they or their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta428

Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (July 2018) NICE TA531

Pembrolizumab (Keytruda®) is recommended as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults whose tumours express PD-L1 (with at least a 50% tumour proportion score) and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations, only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression, and
- the manufacturer provides pembrolizumab according to the commercial access agreement.

www.nice.org.uk/guidance/ta531

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (January 2019) NICE TA557

Pembrolizumab (Keytruda®), with pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund, as an option for untreated, metastatic, non-squamous non-small-cell lung cancer in adults whose tumours have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations. It is only recommended if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if disease progresses, and
- the manufacturer provides pembrolizumab according to the managed access agreement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta557

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (April 2018) NICE TA519

Pembrolizumab (Keytruda®) is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression, and
- the conditions in the managed access agreement for pembrolizumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta519

Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (updated July 2018) NICE TA522

Pembrolizumab (Keytruda®) is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if:

- their tumours express PD-L1 with a combined positive score of 10 or more, and
- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and
- the conditions of the managed access agreement for pembrolizumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta522

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (September 2018) NICE TA540

Pembrolizumab (Keytruda®) is not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin.
Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (September 2018) NICE TA540
Pembrolizumab (Keytruda®) is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have not received at least one prior chemotherapy regimen, subject to:
- pembrolizumab is stopped after 2 years of treatment or earlier if the person has a stem cell transplant or the disease progresses, and
- the conditions in the managed access agreement for pembrolizumab are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

The Scottish Medicines Consortium (SMC) has advised (December 2016) that pembrolizumab (Keytruda®) is not recommended for use within NHS Scotland as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab. The advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1087/15

Scottish Medicines Consortium (SMC) decisions
SMC No. 1086/15
The Scottish Medicines Consortium has advised (November 2015) that pembrolizumab (Keytruda®) is accepted for use within NHS Scotland as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab. The advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1087/15
The Scottish Medicines Consortium has advised (January 2017) that pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death ligand 1 (PD-L1) and who have received at least one prior chemotherapy regimen, subject to a two-year clinical stopping rule. The advice is contingent upon the continuing availability of pembrolizumab at the price agreed in the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1239/17
The Scottish Medicines Consortium has advised (July 2017) that pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death ligand 1 (PD-L1) with a ≥50% tumour proportion score with no epidermal growth factor receptor or anaplastic lymphoma kinase positive tumour mutations, subject to a two-year clinical stopping rule. The advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. SMCM217
The Scottish Medicines Consortium has advised (February 2019) that pembrolizumab (Keytruda®) is not recommended for use within NHS Scotland when used in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations, as the economic case was not demonstrated.

SMC No. 1291/18
The Scottish Medicines Consortium has advised (February 2018) that pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Treatment with pembrolizumab is subject to a two-year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1339/18
The Scottish Medicines Consortium has advised (September 2018) that pembrolizumab (Keytruda®) is not recommended for use within NHS Scotland as monotherapy, for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥10, as the economic case was not demonstrated.

SMC No. 1296/18
The Scottish Medicines Consortium has advised (March 2018) that pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of adults with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin, or who are transplant-ineligible and have failed brentuximab vedotin. Treatment with pembrolizumab is subject to a two-year clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Medications should be stored in a cool, dry place or a refrigerator, as instructed by the manufacturer. The patient should be advised to store their medications in a way that is childproof. Where applicable, the information should be presented in a concise and consistent manner, with clear instructions for use and storage.

Keytruda® is a recombinant humanised monoclonal antibody, and acts by inhibiting human epidermal growth factor receptor 2 protein (HER2) dimerisation.

Pertuzumab

Indications and dose
HER2-positive early stage breast cancer (in combination with trastuzumab and chemotherapy) | HER2-positive metastatic or locally recurrent unresectable breast cancer (in combination with trastuzumab and docetaxel) (specialist use only)
- by intravenous infusion
- Adult: consult product literature or local protocols

Caution
Conditions that could impair left ventricular function - history of congestive heart failure - impaired left ventricular function - prior anthracycline exposure - radiotherapy to the chest area - recent myocardial infarction - serious cardiac arrhythmia - uncontrolled hypertension

www.getintopharma.com
Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta569

Scottish Medicines Consortium (SMC) decisions

SMC No. 897/13

The Scottish Medicines Consortium has advised (June 2017) that pertuzumab (Perjeta®) is not recommended for use within NHS Scotland for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with trastuzumab and docetaxel, in adults who have not received previous anti-HER2 therapy or chemotherapy as the economic case was not sufficient to gain acceptance.

SMC No. SMC2119

The Scottish Medicines Consortium has advised (December 2018) that pertuzumab (Perjeta®) is accepted for use within NHS Scotland in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. SMC2120

The Scottish Medicines Consortium has advised (January 2019) that pertuzumab (Perjeta®) is accepted for use within NHS Scotland in combination with trastuzumab and docetaxel, in adults with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

Perjeta (Roche Products Ltd)

Pertuzumab 30 mg per 1 ml

Perjeta 420mg/14ml concentrate for solution for infusion vials 1 vial £2,395.00 (Hospital only)

Ramucirumab

31-May-2016

Drug action

Ramucirumab is a human monoclonal antibody that binds to the vascular endothelial growth factor receptor-2 (VEGFR-2), inhibiting VEGF–induced angiogenesis.

Indications and dose

Treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, in combination with paclitaxel, in patients with disease progression after prior platinum and fluoropyrimidine chemotherapy

By intravenous infusion

Adult: 8 mg/kg on days 1 and 15 of a 28 day cycle, dose to be administered prior to paclitaxel infusion, consult product literature for dose adjustments due to side-effects and infusion–related reactions continued
Treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, as monotherapy, in patients with disease progression after prior platinum or fluoropyrimidine chemotherapy, and for whom treatment in combination with paclitaxel is not appropriate

- **BY INTRAVENOUS INFUSION**
  - Adult: 8 mg/kg every 2 weeks, consult product literature for dose adjustments due to side-effects and infusion-related reactions

Treatment of metastatic colorectal cancer, in combination with FOLFIRI (irinotecan, fluorouracil and folinic acid), in patients with disease progression on, or after, prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine

- **BY INTRAVENOUS INFUSION**
  - Adult: 8 mg/kg every 2 weeks, dose to be administered prior to FOLFIRI administration, consult product literature for dose adjustments due to side-effects and infusion-related reactions

Treatment of locally advanced or metastatic non-small cell lung cancer, in combination with docetaxel, in patients with disease progression after platinum-based chemotherapy

- **BY INTRAVENOUS INFUSION**
  - Adult: 10 mg/kg on day 1 of a 21 day cycle, dose to be administered prior to docetaxel infusion, consult product literature for dose adjustments due to side-effects and infusion-related reactions

- **CAUTIONS**
  - Elective surgery—discontinue treatment for at least 4 weeks prior to surgery.
  - Hypertension—must be controlled before initiation.
  - Impaired wound healing—discontinue treatment until wound fully healed.
  - Pretreatment is recommended to minimise the development of adverse reactions (consult product literature) - risk of bleeding

- **INTERACTIONS**
  - Appendix 1: monoclonal antibodies

- **SIDE-EFFECTS**
  - Common or very common
    - Asthenia
    - Diarrhoea
    - Electrolyte imbalance
    - Gastrointestinal discomfort
    - Gastrointestinal perforation
    - Haemorrhage
    - Hand and foot syndrome
    - Headache
    - Hepatic pain
    - Hypertension
    - Hypoalbuminaemia
    - Leucopenia
    - Mucositis
    - Neutropenia
    - Peripheral oedema
    - Proteinuria
    - Seizure
    - Stomatitis
    - Thrombocytopenia
  - Frequency not known
    - Arterial thrombosis
    - Back pain
    - Back spasms
    - Cardiac arrest
    - Cerebrovascular insufficiency
    - Chest discomfort
    - Chills
    - Dyspnoea
    - Flushing
    - Hypersensitivity
    - Hypotension
    - Hypoxia
    - Infusion related reaction
    - Myocardial infarction
    - Parasthesia
    - Respiratory disorders
    - Supraventricular tachycardia
  - Rare or individual
    - Cardiac arrest
    - Cerebrovascular insufficiency
    - Chills
    - Diaphoresis
    - Hypertension
    - Hypotension
    - Infusion related reaction
    - Hypertension
    - Hypoxia
    - Proteinuria
    - Seizure
    - Stomatitis

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Infusion-related hypersensitivity reactions have been reported with ramucirumab, particularly during or following the first or second infusion; if the patient experiences a grade 1 or 2 infusion-related reaction, the manufacturer advises to reduce rate of infusion by 50% and give premedication for all subsequent infusions—consult product literature. Manufacturer advises to permanently discontinue treatment in the event of a grade 3 or 4 infusion-related reaction.

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer advises effective contraception during treatment and for up to 3 months after treatment in women of childbearing potential.

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING**
  - Manufacturer advises discontinue breast-feeding during treatment and for at least 3 months after treatment—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe cirrhosis, cirrhosis with hepatic encephalopathy, cirrhosis with clinically significant ascites, or hepatorenal syndrome (risk of progressive hepatic failure, no information available).

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor for signs of infusion-related hypersensitivity reactions; monitor blood pressure prior to each infusion; monitor for development or worsening of proteinuria during treatment—consult product literature; monitor blood counts and coagulation parameters in patients at risk of bleeding.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Cyramza®), give intermittently in Sodium chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and invert gently to mix. Do not exceed a rate of 25 mg/minute, and give over approximately 60 minutes via an infusion pump using a separate infusion line with a protein sparing 0.22 micron filter.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - For Cyramza®, each 10 mL vial contains sodium 17 mg (equivalent to Na+ 0.74 mmol).

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy (January 2016) NICE TA378
    - Ramucirumab alone or in combination with paclitaxel is not recommended for the treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy.
    - Patients whose treatment was started before this guidance was published, should have the option to continue treatment until they and their clinician consider it appropriate to stop.
    - NICE decisions for locally advanced or metastatic non-small cell lung cancer (August 2016) NICE TA403
    - Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **ELECTROLYTES**: May contain Sodium
  - **Cyramza®** (Eli Lilly and Company Ltd)
    - Ramucirumab 10 mg per 1 mL
      - Cyramza® 100mg/10ml concentrate for solution for infusion vials | 1 vial (£89.50 | Hospital only)
      - Cyramza® 500mg/50ml concentrate for solution for infusion vials | 1 vial (£9.50 | Hospital only)

**Rituximab**

- **INDICATIONS AND DOSE**
  - Rheumatoid arthritis (specialist use only)
  - **BY INTRAVENOUS INFUSION**
    - Adult: 1 g, then 1 g after 2 weeks, consult product literature for information on retreatment

www.getintopharma.com
Antibody responsive malignancy 883

Non-Hodgkin’s lymphoma (specialist use only) | Chronic lymphocytic leukaemia (specialist use only) | Granulomatosis with polyangiitis and microscopic polyangiitis (specialist use only)

- **BY INTRAVENOUS INFUSION**
- **Adult:** consult product literature.

Non-Hodgkin’s lymphoma (specialist use only)

- **BY SUBCUTANEOUS INJECTION**
- **Adult:** consult product literature.

Pemphigus vulgaris (specialist use only)

- **BY INTRAVENOUS INFUSION**
- **Adult:** 1 g then 1 g after 2 weeks; maintenance 0.5 g at months 12 and 18, and then every 6 months thereafter if needed, consult product literature for the treatment of relapse.

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**
Severe infection

**SPECIFIC CONTRA-INDICATIONS**
- When used for pemphigus vulgaris, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis: Severe heart failure, severe, uncontrolled heart disease.

**CONTRA-INDICATIONS, FURTHER INFORMATION**
For full details on contra-indications, consult product literature.

**CAUTIONS**

**GENERAL CAUTIONS**
History of cardiovascular disease; exacerbation of angina, arrhythmia, and heart failure have been reported - patients receiving cardiotoxic chemotherapy; exacerbation of angina, arrhythmia, and heart failure have been reported - pre-medication recommended to minimise adverse reactions (consult product literature) - predisposition to infection - transient hypotension occurs frequently during infusion (anti-hypertensives may need to be withheld for 12 hours before infusion).

**SPECIFIC CAUTIONS**
- When used for pemphigus vulgaris, granulomatosis with polyangiitis and microscopic polyangiitis: Pneumocystis jirovecii pneumonia - consult product literature for prophylaxis requirements.

**CAUTIONS, FURTHER INFORMATION**
For full details on cautions, consult product literature or local treatment protocol.

Hepatitis B infection and reactivation
- Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

**INTERACTIONS**
- Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**
- **Common or very common**
  - Angioedema
  - Anxiety
  - Appetite decreased
  - Arrhythmias
  - Bone marrow disorders
  - Bursitis
  - Cancer pain
  - Cardiac disorder
  - Chest pain
  - Chills
  - Conjunctivitis
  - Cough aggravated
  - Dizziness
  - Dysphagia
  - Dyspnoea
  - Ear pain
  - Gastrointestinal discomfort
  - Gastrointestinal disorders
  - Hepatitis B
  - Hypercholesterolaemia
  - Hypglycaemia
  - Hyperhidrosis
  - Hypocalcaemia
  - Hypotension
  - Insomnia
  - Lacrimation disorder
  - Malaise
  - Migraine
  - Multi organ failure
  - Muscle tone increased
  - Myalgia
  - Nausea
  - Nerve disorders
  - Oedema
  - Oral disorders
  - Oropharyngeal pain
  - Osteoarthritis
  - Pain
  - Respiratory disorders
  - Sensation abnormal
  - Sepsis
  - Skin reactions
  - Throat irritation
  - Tinnitus
  - Vasodilation
  - Weight decreased

- **Uncommon**
  - Asthma
  - Coagulation disorder
  - Haemolytic anaemia
  - Heart failure
  - Hypoxia
  - Ischaemic heart disease
  - Lymphadenopathy
  - Taste altered

- **Rare or very rare**
  - Cytokine release syndrome
  - Facial paralysis
  - Hepatitis B reactivation
  - Renal failure
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Transient hypertension
  - Vasculitis
  - Vision disorders

- **Frequency not known**
  - Hearing loss
  - Hypogammaglobulinaemia
  - Infective thrombosis
  - Irritability
  - Posterior reversible encephalopathy syndrome (PRES)
  - Psychiatric disorder
  - Seizure
  - Skin papilloma

**SIDE-EFFECTS, FURTHER INFORMATION**
Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

Progressive multifocal leuкоencephalopathy has been reported in association with rituximab; patients should be monitored for cognitive, neurological, or psychiatric signs and symptoms. If progressive multifocal leuкоencephalopathy is suspected, suspend treatment if this has been excluded.

**CONCEPTION AND CONTRACEPTION**
Effective contraception (in both sexes) required during and for 12 months after treatment.

**PREGNANCY**
Avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus.

**BREAST FEEDING**
Avoid breast-feeding during and for 12 months after treatment.

**MONITORING REQUIREMENTS**
For full details on monitoring requirements consult product literature.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use: For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to 1–4 mg/mL and gently invert bag to avoid foaming; for further information, consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**
Rituximab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

**PATIENT AND CARER ADVICE**
Alert card Patients should be provided with a patient alert card with each infusion.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- **Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis** (March 2014) NICE TA308
- With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener’s] and microscopic polyangiitis), only if:
  - further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose, or
  - cyclophosphamide is contra-indicated or not tolerated, or
  - the patient has not completed their family, and treatment with cyclophosphamide may materially affect their fertility, or
  - the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months or
  - the patient has had uroepithelial malignancy.
Immune system and malignant disease

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (August 2010) NICE TA195

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with methotrexate, is recommended as an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor (TNF) inhibitor. Repeat courses of rituximab should be given no more frequently than every 6 months, and should only be continued if an adequate response is achieved and maintained.

www.nice.org.uk/guidance/ta195

Rituximab for the first-line treatment of stage III-IV follicular lymphoma (January 2012) NICE TA243

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with:
- cyclophosphamide, vincristine and prednisolone (CVP);
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP);
- mitoxantrone, chlorambucil and prednisolone (MCP);
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alfa (CHVPi); or
- chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

www.nice.org.uk/guidance/ta243

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma (February 2008) NICE TA137

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with chemotherapy, is recommended as an option for the induction of remission in patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma. Rituximab monotherapy, as maintenance therapy, is recommended as an option for the treatment of patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma in remission induced with chemotherapy (with or without rituximab). Rituximab monotherapy is recommended as an option for the treatment of patients with relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

www.nice.org.uk/guidance/ta137

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (July 2010) NICE TA193

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for patients with relapsed or refractory chronic lymphocytic leukaemia except when the condition:
- is refractory to fludarabine (that is, it has not responded to fludarabine, or has relapsed within 6 months of treatment), or
- has previously been treated with rituximab, unless it was in the context of a clinical trial, at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or with chemotherapy other than fludarabine and cyclophosphamide.

Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for patients with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab, unless rituximab has been given as specified above.

www.nice.org.uk/guidance/ta193

Rituximab for the first-line maintenance treatment of follicular non-Hodgkin’s lymphoma (June 2011) NICE TA226

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab maintenance therapy is recommended as an option for the treatment of patients with follicular non-Hodgkin’s lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

www.nice.org.uk/guidance/ta226

Rituximab for the first-line treatment of chronic lymphocytic leukaemia (July 2009) NICE TA174

With intravenous use This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with fludarabine and cyclophosphamide, is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia.

www.nice.org.uk/guidance/ta174

Idelalisib for treating chronic lymphocytic leukaemia (October 2015) NICE TA359

Rituximab, in combination with idelalisib, is recommended as an option for treatment in adults:
- who have untreated chronic lymphocytic leukaemia or
- who have chronic lymphocytic leukaemia when the disease has been treated but has relapsed within 24 months and
- if the manufacturer provides idelalisib with the discount agreed in the simple discount agreement.

Patients who are already receiving idelalisib should continue treatment until they or their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta359

Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (February 2019) NICE TA561

Venetoclax (Venclyxto®) with rituximab is recommended, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy. It is recommended only if the manufacturer provides it according to the commercial arrangement.

www.nice.org.uk/guidance/ta561

Scottish Medicines Consortium (SMC) decisions

SMC No. 894/13

With intravenous use The Scottish Medicines Consortium has advised (August 2013) that Rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis. It is restricted to use in patients who have relapsed following treatment with cyclophosphamide or who are intolerant to or unable to receive cyclophosphamide.

SMC No. 975/14

With subcutaneous use The Scottish Medicines Consortium has advised (June 2014) that subcutaneous rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in accordance with UK licensing, except in the maintenance setting, where use is restricted to patients who have responded to induction therapy with rituximab plus chemotherapy.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- MabThera (Roche Products Ltd)

Rituximab 119.66 mg per 1 ml MabThera 1400mg/11.7ml solution for injection vials | 1 vial (with SMC No. 894/13 agreement) 11,344.65 (Hospital only)
Solution for infusion

**EXCIPIENTS:** May contain Polysorbates  
**ELECTROLYTES:** May contain Sodium

- **Rituximab** (Roche Products Ltd)
  - **Rituximab 100 mg per 1 ml** MabThera 100mg/10ml concentrate for solution for infusion vials | 2 vial (£349.25)  
  - **Rituximab 500 mg/50ml** concentrate for solution for infusion vials | 1 vial (£873.15)  

- **Rixathon** (Sandoz Ltd) ▼
  - **Rituximab 10 mg per 1 ml** Rituxan 100mg/10ml concentrate for solution for infusion vials | 2 vial (£314.33, Hospital only)  
  - **Rituximab 500mg/50ml** concentrate for solution for infusion vials | 1 vial (£785.84, Hospital only)  
  - **Rituximab 100 mg per 1 ml** Truxima 100mg/10ml concentrate for solution for infusion vials | 2 vial (£314.33)  
  - **Truxima 500mg/50ml** concentrate for solution for infusion vials | 1 vial (£785.84)

**Siltuximab**

- **DRUG ACTION** Siltuximab is a monoclonal antibody that inhibits interleukin-6 receptor binding.

**INDICATIONS AND DOSE**

**Treatment of multicentric Castleman’s disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative**

- **BY INTRAVENOUS INFUSION**
  - Adult: 11 mg/kg every 3 weeks

**CAUTIONS**

- Patients at increased risk of gastrointestinal perforation—promptly investigate those presenting with symptoms suggestive of gastrointestinal perforation - severe infection—withdraw treatment until resolved - treat infection prior to treatment

- **CAUTIONS, FURTHER INFORMATION**

Consult product literature for further information about siltuximab cautions.

- **Hypersensitivity reactions** Infusion-related side-effects are reported commonly with siltuximab; resuscitation facilities should be available during treatment.

**INTERACTIONS** ▶ Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - hypersensitivity - hypertension - hypertriglyceridaemia - increased risk of infection - infusion related reaction - localised oedema - neutropenia - renal impairment - skin reactions - thrombocytopenia - weight increased

**SIDE-EFFECTS, FURTHER INFORMATION** Siltuximab therapy should be discontinued permanently in the event of a severe infusion-related reaction, anaphylaxis, a severe allergic reaction, or the occurrence of cytokine-release syndrome. Mild to moderate infusion-related reactions may improve by temporarily reducing the rate or stopping the infusion. When restarting treatment, a reduced infusion rate and the administration of antihistamines, paracetamol, and corticosteroids may be considered. Consider discontinuation of siltuximab if more than 2 doses are delayed due to treatment-related toxicities during the first 48 weeks—for full details consult product literature.

**CONCEPTION AND CONTRAINDICATIONS**

- **Women** of childbearing potential should use effective contraception during and for 3 months after treatment.
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution (no information).

**MONITORING REQUIREMENTS**

- Monitor neutrophil and platelet count, and haemoglobin levels prior to each dose of siltuximab treatment for the first 12 months and thereafter prior to every third dosing cycle. Consider delaying treatment if required neutrophil, platelet, and haemoglobin levels not achieved—consult product literature for details.

- **Monitor for infection during treatment.**

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Sylvant®), give intermittently in Glucose 5%. Allow vials to reach room temperature over approximately 30 minutes, then reconstitute each 100 mg vial with 5.2 mL of water for injection, and each 400 mg vial with 20 mL of water for injection, to produce a 20 mg/mL solution. Gently swirl without shaking to dissolve. Further dilute to 250 mL with glucose 5% and gently mix. Use within 6 hours of dilution and give over 60 minutes using an administration set lined with polyvinyl chloride or polyurethane, through a low-protein binding in-line 0.2 micron filter.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
- **Powder for solution for infusion**
  - **Sylvant** (Janssen-Cilag Ltd) ▼
    - **Siltuximab 100 mg** Sylvant 100mg powder for concentrate for solution for infusion vials | 1 vial (£415.00, Hospital only)  
    - **Siltuximab 400 mg** Sylvant 400mg powder for concentrate for solution for infusion vials | 1 vial (£1,661.00, Hospital only)

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**Trastuzumab**

**INDICATIONS AND DOSE**

**Treatment of early breast cancer which overexpresses human epidermal growth factor receptor-2 (HER2) (initiated by a specialist)** Treatment of metastatic breast cancer in patients with HER2-positive tumours who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (in combination with paclitaxel) or docetaxel (initiated by a specialist) Treatment of metastatic breast cancer in postmenopausal patients with hormone-receptor positive HER2-positive tumours not previously treated with trastuzumab (in combination with an aromatase inhibitor) (initiated by a specialist)

- **BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION**
  - **Adult:** (consult product literature) or local protocols

Monotherapy for metastatic breast cancer in patients with tumours that overexpress HER2 who have received at least 2 chemotherapy regimens including, where appropriate, an aromatase inhibitor and a taxane (initiated by a specialist)

- **BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION**
  - **Adult:** (consult product literature or local protocols)

Treatment of metastatic gastric cancer in patients with HER2-positive tumours who have not received treatment for metastatic gastric cancer (in combination with capecitabine or fluorouracil and cisplatin) (initiated by a specialist)

- **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult product literature or local protocols)

**CONTRA-INDICATIONS**

- Severe dyspnoea at rest

**CAUTIONS**

- Coronary artery disease - history of hypertension - symptomatic heart failure - uncontrolled arrhythmias

**INTERACTIONS** ▶ Appendix 1: monoclonal antibodies

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**SIDE-EFFECTS**

- **Common or very common** Alopecia, anaemia, angioedema, anxiety, appetite decreased, arrhythmias, arthralgia, arthritis, asthenia, asthma, ataxia, breast abnormalities, cardiomyopathy, chest pain, chill, constipation, cough, cystitis, depression, diarrhoea, diziness, drowsiness, dry eye, dry mouth, dyspnoea, excessive tearing, eye inflammation, fever, gastrointestinal discomfort, haemorrhage, haemorrhoids, headache, heart failure, hepatic disorders, hyperhidrosis, hypersensitivity, hypotension, increased risk of infection, influenza like illness, infusion related reaction (may be delayed), insomnia, leucopenia, malaise, mucositis, muscle complaints, muscle tone increased, nail disorders, nausea, neutropenia, oedema, oral disorders, pain, palpitations, pancreatitis, paraesthesia, peripheral neuropathy, renal disorder, respiratory disorders, rhinorrhoea, sedation, skin reactions, speech altered, thinking abnormal, thrombocytopenia, tremor, vasodilation, vomiting, weight decreased
- **Uncommon** Deafness, pericardial effusion
- **Rare or very rare** Paresis
- **Frequency not known** Brain oedema, cancer progression, cardiogenic shock, glomerulonephritis, hyperkalaemia, hypoprotrombinaemia, hypothyroidism, pulmonary fibrosis (may be delayed), pulmonary oedema (may be delayed) - renal failure

**CONCEPTION AND CONCEPTION**

Manufacturer advises effective contraception in women of childbearing potential during and for 7 months after treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**

Manufacturer advises avoid—

- oligohydramnios reported. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Avoid breast-feeding during treatment and for 7 months afterwards.

**MONITORING REQUIREMENTS**

- Cardiotoxicity Monitor cardiac function before and during treatment for details of monitoring and managing cardiotoxicity, consult product literature.

**DIRECTIONS FOR ADMINISTRATION**

- Resuscitation facilities should be available during administration of trastuzumab.

**PRESCRIBING AND DISPENSING INFORMATION**

When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab is not interchangeable with trastuzumab emtansine. Trastuzumab is a biosimilar medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Guidance on the use of trastuzumab for the treatment of advanced breast cancer (March 2002) NICE TA34

Trastuzumab in combination with paacltaxel is recommended as an alternative for patients who have received prior chemotherapy for HER2-positive metastatic breast cancer, in whom anthracycline treatment is inappropriate.

Trastuzumab monotherapy is recommended as an alternative for patients who have received prior chemotherapy for HER2-positive metastatic breast cancer, in whom anthracycline treatment is inappropriate. Trastuzumab monotherapy is recommended as an alternative for patients with tumours expressing HER2 scored at levels of 3+ who have received prior anthracycline treatment.

**Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (August 2006) NICE TA107**

Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as an option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

www.nice.org.uk/guidance/ta107

- Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012) NICE TA257

Lapatinib or trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women of metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2). Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta257

- Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (March 2018) NICE TA509

Pertuzumab, in combination with trastuzumab and docetaxel, is recommended, within its marketing authorisation, for treating HER2-positive metastatic or locally recurrent unresectable breast cancer, in adults who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease, only if the manufacturer provides pertuzumab within the agreed commercial access arrangement.

www.nice.org.uk/guidance/ta509

- Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (November 2010) NICE TA208

Trastuzumab in combination with cisplatin and capecitabine or fluorouracil is recommended for human epidermal growth factor receptor-2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction in patients who:

- have not received treatment for metastatic disease and
- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3.

www.nice.org.uk/guidance/ta208

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 928/13

The Scottish Medicines Consortium has advised (January 2014) that subcutaneous trastuzumab injection (Herceptin®) is accepted for restricted use within NHS Scotland for the treatment of adults with HER2 positive metastatic breast cancer and early breast cancer, when used within licensed indications excluding use in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

SMC No. 623/10

The Scottish Medicines Consortium has advised (October 2015) that trastuzumab solution for infusion (Herceptin®) is accepted for restricted use within NHS Scotland in combination with capecitabine or fluorouracil and cisplatin for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, who have not received prior anticaner treatment for their metastatic disease. It is restricted to patients with metastatic gastric cancer whose tumours have HER2 over-expression, as determined by an accurate and validated assay.

www.getintopharma.com
Trastuzumab emtansine

02-Aug-2017

DRUG ACTION

Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have previously received trastuzumab and a taxane separately or in combination (initiated by a specialist) Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have developed disease recurrence during or within 6 months of completing adjuvant therapy (initiated by a specialist)

BY INTRAVENOUS INFUSION

Adult: (consult product literature or local protocols)

CAUTIONS

Dyspnoea at rest—increased risk of pulmonary events - history of congestive heart failure - patients over 75 years - peripheral neuropathy (temporarily discontinue treatment—consult product literature) - recent history of myocardial infarction - recent history of unstable angina - risk of left ventricular dysfunction—consult product literature for specific risks with trastuzumab treatment - serious arrhythmias

INTERACTIONS

Appendix 1: monoclonal antibodies

SIDE-EFFECTS

Common or very common

Uncommon
Hepatic disorders - nodular regenerative hyperplasia - pneumonitis

CONCEPTION AND CONTRACEPTION

Effective contraception must be used during and for 6 months after stopping treatment in women and men.

PREGNANCY

Manufacturer advises avoid—oligohydramnios reported with trastuzumab. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid breast-feeding during and for 6 months after treatment.

HEPATIC IMPAIRMENT

Consult product literature for initiating treatment and discontinuation in cases of abnormal liver function tests.

Dose adjustments

Consult product literature for dose modification in cases of abnormal liver function tests.

RENAL IMPAIRMENT

No information available—manufacturer advises caution in severe impairment.

MONITORING REQUIREMENTS

Monitor hepatic function before each dose.

Monitor for signs and symptoms of neurotoxicity.

Monitor closely for infusion-related and hypersensitivity reactions.

Monitor platelet count before each dose and as clinically indicated (consult product literature for treatment modification in thrombocytopenia).

Test cardiac function before treatment and regularly during treatment—delay or discontinue treatment in cases of left ventricular dysfunction.

Monitor for dyspnoea, cough, fatigue and pulmonary infiltrates—discontinue if interstitial lung disease or pneumonitis confirmed (fatal cases reported).

DIRECTIONS FOR ADMINISTRATION

Resuscitation facilities should be available during administration of trastuzumab emtansine.

PRESCRIBING AND DISPENSING INFORMATION

When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab emtansine and trastuzumab are not interchangeable.

NATIONAL FUNDING/ACCESS DECISIONS

Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (updated November 2017) NICE TA458

Trastuzumab emtansine is recommended, within its marketing authorisation, as an option for treating human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Trastuzumab emtansine is recommended only if the manufacturer provides it with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (April 2017) that trastuzumab emtansine (Kadcyla®) is accepted for use within NHS Scotland as monotherapy for the treatment of patients with human epidermal growth factor type 2 (HER2)-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination, and have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

www.getintopharma.com
2 Carcinoid syndrome

**ENZYME INHIBITORS**

**Telotristat ethyl**

**DRUG ACTION** Telotristat ethyl and its active metabolite inhibit L-tryptophan hydroxylases TPH-1 and TPH-2 which reduces the production of serotonin, thereby alleviating symptoms associated with carcinoid syndrome.

**INDICATIONS AND DOSE**

**Carcinoid syndrome diarrhoea (specialist use only)**

- **BY MOUTH**
  - Adult: 250 mg 3 times a day, review treatment if no response after 12 weeks

**SIDE-EFFECTS**

- Common or very common: Appetite decreased - constipation - fatigue - fever - flatulence - gastrointestinal discomfort - headache - peripheral oedema

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

**RENAL IMPAIRMENT** Manufacturer advises caution in mild-to-moderate impairment; avoid in severe impairment—no information available.

**MONITORING REQUIREMENTS** Manufacturer advises monitor liver function at initiation and during treatment as clinically indicated—discontinue if liver injury suspected.

**PATIENT AND CARER ADVICE** Manufacturer advises inform patients to report any symptoms of depression or decreased interest.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1237/18

The Scottish Medicines Consortium has advised (June 2018) that telotristat ethyl (Xermelo®) is accepted for restricted use within NHS Scotland for the treatment of carcinoid syndrome diarrhoea in adults who experience an average of four or more bowel movements a day. This recommendation applies only in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or where the list/contract price is equivalent or lower than the WPAS price.

**MEDIUM FORMS**

- **Powder for solution for infusion**
  - **Kadcyla** (Roche Products Ltd)
    - Trastuzumab emtansine 100 mg Kadcyla 100mg powder for concentrate for solution for infusion vials | 1 vial £641.01
    - Trastuzumab emtansine 160 mg Kadcyla 160mg powder for concentrate for solution for infusion vials | 1 vial £2,625.62

**3 Cytotoxic responsive malignancy**

**Cytotoxic drugs**

**Overview**

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential to damage normal tissue; most cytotoxic drugs are teratogenic. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of subclinical metastatic disease is known to be high). All cytotoxic drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Combinations of cytotoxic drugs, as continuous or pulsed cycles of treatment, are frequently more toxic than single drugs but have the advantage in certain tumours of enhanced response, reduced development of drug resistance and increased survival. However for some tumours, single-agent chemotherapy remains the treatment of choice.

Cytotoxic drugs fall into a number of classes, each with characteristic antitumour activity, sites of action, and toxicity. A knowledge of sites of metabolism and excretion is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

**Cytotoxic drug handling guidelines**

- Trained personnel should reconstitute cytotoxics
- Reconstitution should be carried out in designated pharmacy areas
- Protective clothing (including gloves, gowns, and masks) should be worn
- The eyes should be protected and means of first aid should be specified
- Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard)
- Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material
- Staff exposure to cytotoxic drugs should be monitored
Intrathecal chemotherapy

A Health Service Circular (HSC 2008/001) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered; written local guidance covering all aspects of national guidance should be available. Support for training programmes is also available. Copies, and further information may be obtained from: Department of Health PO Box 777 London SE1 6XH Fax: 01623 724524

It is also available from the Department of Health website (www.dh.gov.uk).

Safe systems for cytotoxic medicines

NHS cancer networks have been established across the UK to bring together all stakeholders in all sectors of care, to work collaboratively to plan and deliver high quality cancer services for a given population. NHS cancer networks have websites containing information on local chemotherapy services and treatment.

Safe system requirements:

- cytotoxic drugs for the treatment of cancer should be given as part of a wider pathway of care coordinated by a multidisciplinary team
- cytotoxic drugs should be prescribed, dispensed, and administered only in the context of a written protocol or treatment plan
- injectable cytotoxic drugs should only be dispensed if they are prepared for administration
- oral cytotoxic medicines should be dispensed with clear directions for use

Cytotoxic drugs: important safety information

Risk of incorrect dosing of oral anti-cancer medicines

The National Patient Safety Agency has advised (January 2008) that the prescribing and use of oral cytotoxic medicines should be carried out to the same standard as parenteral cytotoxic therapy.

- non-specialists who prescribe or administer on-going oral cytotoxic medication should have access to written protocols and treatment plans, including guidance on the monitoring and treatment of toxicity;
- staff dispensing oral cytotoxic medicines should confirm that the prescribed dose is appropriate for the patient. Patients should have written information that includes details of the intended oral anti-cancer regimen, the treatment plan, and arrangements for monitoring, taken from the original protocol from the initiating hospital. Staff dispensing oral cytotoxic medicines should also have access to this information, and to advice from an experienced cancer pharmacist in the initiating hospital.

Cytotoxic drug doses

Doses of cytotoxic drugs are determined using a variety of different methods including body-surface area or body-weight. Alternatively, doses may be fixed. Doses may be further adjusted following consideration of a patient’s neutrophil count, renal and hepatic function, and history of previous adverse effects to the cytotoxic drug. Doses may also differ depending on whether a drug is used alone or in combination.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from some of the drug entries in this chapter. However, even where dose statements have been provided, detailed specialist literature, individual hospital chemotherapy protocols, or local cancer networks should be consulted before prescribing, dispensing, or administering cytotoxic drugs.

Prescriptions should not be repeated except on the instructions of a specialist.

Cytotoxic drug side-effects

Side-effects common to most cytotoxic drugs are discussed below whilst side-effects characteristic of a particular drug or class of drugs (e.g. neurotoxicity with vinca alkaloids) are mentioned in the appropriate sections. Manufacturers’ product literature, hospital-trust protocols, and cancer-network protocols should be consulted for full details of side-effects associated with individual drugs and specific chemotherapy regimes.

Many side-effects of cytotoxic drugs often do not occur at the time of administration, but days or weeks later. It is therefore important that patients and healthcare professionals can identify symptoms that cause concern and can contact an expert for advice. Toxicities should be accurately recorded using a recognised scoring system such as the Common Toxicity Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute.

Extravasation of intravenous drugs

A number of cytotoxic drugs will cause severe local tissue necrosis if leakage into the extravascular compartment occurs. To reduce the risk of extravasation injury it is recommended that cytotoxic drugs are administered by appropriately trained staff. See information on the prevention and management of extravasation injury.

Oral mucositis

A sore mouth is a common complication of cancer chemotherapy; it is most often associated with fluorouracil p. 910, methotrexate p. 913, and the anthracyclines. It is best to prevent the complication. Good oral hygiene (rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2–3 times daily) is probably beneficial. For fluorouracil p. 910, sucking ice chips during short infusions of the drug is also helpful.

Once a sore mouth has developed, treatment is much less effective. Saline mouthwashes should be used but there is no good evidence to support the use of antiseptic or anti-inflammatory mouthwashes. In general, mucositis is self-limiting but with poor oral hygiene it can be a focus for blood-borne infection.

Tumour lysis syndrome

Tumour lysis syndrome occurs secondary to spontaneous or treatment-related rapid destruction of malignant cells. Patients at risk of tumour lysis syndrome include those with non-Hodgkin’s lymphoma (especially if high grade and bulky disease), Burkitt’s lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia (particularly if high white blood cell counts or bulky disease), and occasionally those with solid tumours. Pre-existing hyperuricaemia, dehydration, and renal impairment are also predisposing factors. Features include hyperkalaemia, hyperuricaemia (see below), and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow. Early identification of patients at risk, and initiation of prophylaxis or therapy for tumour lysis syndrome, is essential.

Hyperuricaemia

Hyperuricaemia, which may be present in high-grade lymphoma and leukaemia, can be markedly worsened by chemotherapy and is associated with acute renal failure. Allopurinol p. 1121 should be started 24 hours before treating such tumours and patients should be adequately hydrated. The dose of mercaptopurine p. 912 or azathioprine p. 836 should be reduced if allopurinol needs to be given concomitantly. Febuxostat p. 1121 may also be used and should be started 2 days before cytotoxic therapy is initiated. Rasburicase p. 542, a recombinant urate oxidase, is licensed for hyperuricaemia in patients with haematological malignancy. It rapidly reduces plasma-uric acid.
Cytotoxic responsive malignancy

Concentration and may be of particular value in preventing complications following treatment of leukaemias or bulky lymphomas.

**Bone-marrow suppression**

All cytotoxic drugs except vincristine sulfate p. 929 and bleomycin p. 919 cause bone-marrow suppression. This commonly occurs 7 to 10 days after administration, but is delayed for certain drugs, such as carmustine p. 893, lomustine p. 897, and melphalan p. 897. Peripheral blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone-marrow has not recovered.

Cytotoxic drugs may be contra-indicated in patients with acute infection; any infection should be treated before, or when starting, cytotoxic drugs.

Fever in a neutropenic patient (neutrophil count less than 1.06 x 10^9/litre) requires immediate broad-spectrum antibacterial therapy. Appropriate bacteriological investigations should be conducted as soon as possible.

Patients taking cytotoxic drugs who have signs or symptoms of infection should be advised to seek prompt medical attention. All patients should initially be investigated and treated under the supervision of the appropriate oncology or haematology specialist.

In selected patients, the duration and the severity of neutropenia can be reduced by the use of recombinant human granulocyte-colony stimulating factors.

Symptomatic anaemia is usually treated with red blood cell transfusions. For guidance on the use of erythropoietins in patients with cancer, see MHRA/CHM advice and NICE guidance.

**Alopecia**

Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients. No pharmacological methods of preventing this are available.

**Thromboembolism**

Venous thromboembolism can be a complication of cancer itself, but chemotherapy increases the risk.

**Cytotoxic drugs: effect on pregnancy and reproductive function**

Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

Exclude pregnancy before treatment with cytotoxic drugs. Contraceptive advice should be given before cytotoxic therapy begins; women of childbearing age should use effective contraception during and after treatment.

Regimens that do not contain an alkylating drug or procarbazine may have less effect on fertility, but those with an alkylating drug or procarbazine carry the risk of causing permanent male sterility (there is no effect on potency).

Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

**Cytotoxic drugs: nausea and vomiting**

Nausea and vomiting cause considerable distress to many patients who receive chemotherapy and to a lesser extent abdominal radiotherapy, and may lead to refusal of further treatment; prophylaxis of nausea and vomiting is therefore extremely important. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Patients vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, patients under 50 years of age, anxious patients, and those who experience motion sickness. Susceptibility also increases with repeated exposure to the cytotoxic drug.

Drugs may be divided according to their emetogenic potential and some examples are given below, but the symptoms vary according to the dose, to other drugs administered and to the individual's susceptibility to emetogenic stimuli.

- **Mildly emetogenic treatment**—fluorouracil, etoposide p. 923, methotrexate p. 913 (less than 100 mg/m^2, low dose in children), the vinca alkaloids, and abdominal radiotherapy.

- **Moderately emetogenic treatment**—the taxanes, doxorubicin hydrochloride p. 901, intermediate doses of cyclophosphamide p. 894, mitoxantrone p. 963, and high doses of methotrexate (0.1 – 1.2 g/m^2).

- **Highly emetogenic treatment**—cisplatin p. 921, dacarbazine p. 895, and high doses of cyclophosphamide.

**Prevention of acute symptoms**

For patients at low risk of emesis, pretreatment with dexamethasone p. 675 or lorazepam p. 339 may be used.

For patients at high risk of emesis, a 5HT3-receptor antagonist, usually given by mouth in combination with dexamethasone and the neurokinin receptor antagonist aprepitant p. 433 is effective.

**Prevention of delayed symptoms**

For delayed symptoms associated with moderately emetogenic chemotherapy, a combination of dexamethasone and 5HT3-receptor antagonist is effective; for highly emetogenic chemotherapy, a combination of dexamethasone and aprepitant is effective. Rolapitant p. 434 and metoclopramide hydrochloride p. 432 are also licensed for delayed chemotherapy-induced nausea and vomiting.

**Prevention of anticipatory symptoms**

Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesic, sedative, and anxiolytic effects.

**Treatment of cytotoxic-induced side-effects**

**Anthracycline side-effects**

**Anthracycline-induced cardiotoxicity**

The anthracycline cytotoxic drugs are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side-effects.

**Anthracycline extravasation**

Local guidelines for the management of extravasation should be followed or specialist advice sought.

See further information on the prevention and management of extravasation injury.

**Chemotherapy-induced mucositis and myelosuppression**

Folinic acid p. 941 (given as calcium folinate) is used to counteract the folate-antagonist action of methotrexate p. 913 and thus speed recovery from methotrexate-induced mucositis or myelosuppression ("folinic acid rescue").

Folinic acid is also used in the management of methotrexate overdose, together with other measures to maintain fluid and electrolyte balance, and to manage possible renal failure.

Folinic acid does not counteract the antibacterial activity of folate antagonists such as trimethoprim p. 574.

When folinic acid and fluorouracil p. 910 are used together in metastatic colorectal cancer the response-rate improves compared to that with fluorouracil alone.

The calcium salt of levofolinic acid p. 919 is used to increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.
The dose of calcium levofolinate is generally half that of calcium folinate.

The disodium salts of folic acid and levofolinic acid are also used for rescue therapy following methotrexate therapy, and for use with fluorouracil for colorectal cancer.

**Urothelial toxicity**

Haemorrhagic cystitis is a common manifestation of urothelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide p. 894 and ifosfamide p. 896; it is caused by the metabolite acrolein. Mesna p. 940 reacts specifically with this metabolite in the urinary tract, preventing toxicity. Mesna is used routinely (preferably by mouth) in patients receiving ifosfamide, and in patients receiving cyclophosphamide by the intravenous route at a high dose (e.g. more than 2 g) or in those who experienced urothelial toxicity when given cyclophosphamide previously.

**Anthracyclines and other cytotoxic antibiotics**

Drugs in this group are widely used. Many cytotoxic antibiotics act as radiomimetics and simultaneous use of radiotherapy should be avoided because it may markedly increase toxicity. Daunorubicin p. 900, doxorubicin hydrochloride p. 901, epirubicin hydrochloride p. 902 and idarubicin hydrochloride p. 903 are anthracycline antibiotics. Mitoxantrone p. 903 is an anthracycline derivative.

Doxorubicin hydrochloride is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable. Conventional doxorubicin hydrochloride is used to treat the acute leukaemias, Hodgkin’s and non-Hodgkin’s lymphomas, paediatric malignancies, and some solid tumours including breast cancer.

Epirubicin hydrochloride is structurally related to doxorubicin hydrochloride and can be used to treat breast cancer.

Idarubicin hydrochloride has general properties similar to those of doxorubicin hydrochloride; it is mostly used in the treatment of haematological malignancies.

Daunorubicin also has general properties similar to those of doxorubicin hydrochloride.

Mitoxantrone is structurally related to doxorubicin hydrochloride.

Pimonidazole p. 904 is licensed as monotherapy for the treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas, although the benefits of using it as a fifth-line or greater chemotherapy in refractory patients has not been established.

Bleomycin p. 919 is given intravenously or intramuscularly to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin’s lymphoma.

Daunomycin is principally used to treat paediatric cancers. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin p. 919 can be given intravenously to treat gastro-intestinal and breast cancers, and by bladder instillation for superficial bladder tumours. It causes delayed bone marrow toxicity.

**Vinca alkaloids**

The vinca alkaloids, vinblastine sulfate p. 929, vincristine sulfate p. 929, and vindesine sulfate p. 930, are used to treat a variety of cancers including leukaemias, lymphomas, and some solid tumours. Vinorelbine p. 931 is a semi-synthetic vinca alkaloid. See also, role of vinorelbine in the treatment of breast cancer.

**Antimetabolites**

Antimetabolites are incorporated into new nuclear material or combine irreversibly with cellular enzymes, preventing normal cellular division.

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**Alkylating drugs**

Extensive experience is available with these drugs, which are among the most widely used in cancer chemotherapy. They act by damaging DNA, thus interfering with cell replication.

Cyclophosphamide is used mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours. It is given by mouth or intravenously; it is inactive until metabolised by the liver.

Ifosfamide is related to cyclophosphamide and is given intravenously.

Melphanal p. 897 is licensed for the treatment of multiple myeloma, polycythaemia vera, childhood neuroblastoma, advanced ovarian adenocarcinoma, and advanced breast cancer. However, in practice, melphanal is rarely used for ovarian adenocarcinoma; it is no longer used for advanced breast cancer. Melphanal is also licensed for regional arterial perfusion in localised malignant melanoma of the extremities and localised soft-tissue sarcoma of the extremities.

Lomustine p. 897 is a lipid-soluble nitrosourea and the drug is given at intervals of 4 to 6 weeks.

Carmustine p. 893 has similar activity to lomustine; it is given to patients with multiple myeloma, non-Hodgkin’s lymphomas, and brain tumours. Carmustine implants are licensed for intralesional use in adults for the treatment of recurrent glioblastoma multiforme as an adjunct to surgery. Carmustine implants are also licensed for high-grade malignant glioma as adjunctive treatment to surgery and radiotherapy.

Estramustine phosphate p. 896 is a combination of an oestrogen and chlorimethine used predominantly in prostate cancer. It is given by mouth and has both an antimitotic effect and (by reducing testosterone concentration) a hormonal effect.

Mitobronitol is occasionally used to treat chronic myeloid leukaemia; it is available on a named-patient basis from specialist importing companies.

**ANTINEOPLASTIC DRUGS > ALKYLATING AGENTS**

**Bendamustine hydrochloride**

**INDICATIONS AND DOSE**

Treatment of chronic lymphocytic leukaemia | Treatment of non-Hodgkin’s lymphoma | Treatment of multiple myeloma

- By intravenous infusion
- Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**


Recent clinical trials have shown increased mortality when bendamustine was used in combination treatments outside its approved indications. In addition, a recent European review of post-marketing data has suggested that the risk of opportunistic infections for all patients receiving bendamustine treatment may be greater than previously recognised.

The MHRA recommends monitoring patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events; known carriers of hepatitis B virus (HBV) should be monitored for signs and symptoms of active HBV infection. Patients should be advised to report promptly new signs of infection; consider discontinuing bendamustine if there are signs of opportunistic infections.
**CONTRA-INDICATIONS** Jaundice • low leucocyte count • low platelet count • major surgery less than 30 days before start of treatment • severe bone marrow suppression

**CAUTIONS** Cardiac disorders—monitor serum potassium and ECG

**INTERACTIONS** → Appendix 3: alkylating agents

**SIDE-EFFECTS**
- Common or very common  Alopecia • amenorrhoea • anaemia • anorexia • appetite decreased • arrhythmias • cardiac disorder • chills • constipation • decreased leucocytes • dehydration • diarrhoea • dizziness • fatigue • fever • haemorrhage • headache • hepatitis B reaction • hypersensitivity • hypertension • hypokalaemia • hypotension • increased risk of infection • insomnia • mucusitis • nausea • neutropenia • pain • palpitations • respiratory disorders • skin reactions • stomatitis • thrombocytopenia • tumour lysis syndrome • vomiting
- Uncommon  Bone marrow disorders • heart failure • myocardial infarction • neoplasms • pericardial effusion
- Rare or very rare  Anticholinergic syndrome • ataxia • circulatory collapse • drowsiness • haemorrhage • hyperhidrosis • infertility • multi organ failure • nervous system disorder • paraesthesia • peripheral neuropathy • sepsis • taste altered
- Frequency not known  Extravasation necrosis • hepatic failure • necrosis • renal failure • severe cutaneous adverse reactions (SCARs)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Secondary malignancy** Use of bendamustine is associated with an increased incidence of acute leukaemias. **Infections** Serious and fatal infections are reported, including opportunistic infections such as Pneumocystis jiroveci pneumonia (PIP), varicella zoster virus (VZV) and cytomegalovirus (CMV)—manufacturer advises monitoring for respiratory signs and symptoms throughout treatment; patients should be advised to report new signs of infection, including fever or respiratory symptoms, promptly. Reactivation of hepatitis B is reported in patients who are chronic carriers of the virus—manufacturer advises monitoring for signs and symptoms of active hepatitis B during treatment and for several months after stopping treatment.

**CONCEPTION AND CONTRACEPTION** Effective contraception is required during treatment in men or women, and for 6 months after treatment in men. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid (teratogenic and mutagenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

**Dose adjustments** Manufacturer advises reduce dose by 30% in moderate impairment.

**RENAL IMPAIRMENT** No information available on use in patients with creatinine clearance less than 10 mL/minute.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- *Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (February 2011)* NICE TA216  Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. www.nice.org.uk/guidance/TA216
- *Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (August 2017)* NICE TA472  Bendamustine in combination with obinutuzumab followed by obinutuzumab maintenance, is recommended for use within the Cancer Drugs Fund as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, only if the conditions in the managed access agreement for obinutuzumab are followed. www.nice.org.uk/guidance/TA472

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (April 2011) that bendamustine (Levact®) is accepted for use within NHS Scotland for first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- *Bendamustine hydrochloride (Non-proprietary)*
  - Bendamustine hydrochloride 25 mg Bendamustine 25mg powder for concentrate for solution for infusion vials | 1 vial £6.85–£65.98 | 5 vial Painter £312.53–£347.26 (Hospital only) | 20 vial Painter £1,241.14 (Hospital only)
  - Bendamustine hydrochloride 100 mg Bendamustine 100mg powder for concentrate for solution for infusion vials | 1 vial Painter £262.02 | 5 vial Painter £1,241.14–£1,379.04 (Hospital only)
  - Levact  (Napp Pharmaceuticals Ltd)  Bendamustine hydrochloride 25 mg Levact 25mg powder for concentrate for solution for infusion vials | 5 vial Painter £347.26 (Hospital only)
  - Levact 100mg powder for concentrate for solution for infusion vials | 5 vial Painter £1,379.04 (Hospital only)

**Busulfan** *(Busulphan)*

**INDICATIONS AND DOSE**

Chronic myeloid leukaemia, induction of remission
- **BY MOUTH**
  - Adult: 60 micrograms/kg daily (max. per dose 4 mg); maintenance 0.5–2 mg daily

**Conditioning treatment before haematopoietic progenitor cell transplantation**
- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

**Conditioning treatment before haematopoietic progenitor cell transplantation in patients who are candidates for a reduced-intensity conditioning (RIC) regimen**
- **BY INTRAVENOUS INFUSION**
  - Adult: (consult local protocol)

**DOSES AT EXTREMES OF BODY-WEIGHT**
- Dose may need to be calculated based on body surface area or adjusted ideal body weight in obese patients—consult product literature.

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 888.

**CAUTIONS** Avoid in Acute porphyrias p. 1058; high dose (antiepileptic prophylaxis required) • history of seizures (antiepileptic prophylaxis required) • ineffective once in blast crisis phase • previous progenitor cell transplant (increased risk of hepatic veno-occlusive disease) • previous radiation therapy (increased risk of hepatic veno-occlusive disease) • risk of second malignancy • three or
**INTERACTIONS** → Appendix 1: alkylating agents

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Alopecia, diarrhoea, hepatic disorders, nausea, respiratory disorders, sinusoidal obstruction syndrome, skin reactions, thrombocytopenia, vomiting
- **Uncommon** Seizure
- **Rare or very rare** Cataract, eye disorders

**SPECIFIC SIDE-EFFECTS**

- **Common or very common** With intravenous use: Anaemia, anxiety, appetite decreased, arrhythmia, arthralgia, ascites, asthenia, asthma, cardiomegaly, chest pain, chills, confusion, constipation, cough, depression, dizziness, dysphoria, dysuria, electrolyte imbalance, embolism and thrombosis, fever, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, headache, hiccups, hyperglycaemia, hypersensitivity, hypertension, hypoalbuninaemia, hypotension, increased risk of infection, insomnia, mucositis, myalgia, nervous system disorder, neutropenia, oedema, pain, pancytopenia, pericardial effusion, pericarditis, reactivation of infections, renal disorder, renal impairment, stomatitis, vasodilatation, weight increased
- **Uncommon** With oral use: Amenorrhoea (may be reversible), azoospermia, bone marrow disorders, cardiac tamponade, delayed puberty, hyperbilirubinaemia, infertility male, leucopenia, leukaemia, menopausal symptoms, oral disorders, ovarian and fallopian tube disorders, testicular atrophy
- **Rare or very rare** With oral use: Dry mouth, erythema nodosum, gynaecomastia, myasthenia gravis, radiation injury, Sjögren’s syndrome
- **Frequency not known** With intravenous use: Hypogonadism, ovarian failure, premature menopause, sepsis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Lung toxicity** Discontinue if lung toxicity develops.

**Secondary malignancy** Use of busulfan is associated with an increased incidence of secondary malignancy.

**CONCEPTION AND CONTRACEPTION** Manufacturers advise effective contraception during and for 6 months after treatment in men or women. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid (teratogenic in animals). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**Monitoring** In patients with hepatic impairment, manufacturer advises regular liver function tests → consult product literature.

**MONITORING REQUIREMENTS**
- Monitor cardiac and liver function.
- Frequent blood tests are necessary because excessive myelosuppression may result in irreversible bone-marrow aplasia.

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**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

<table>
<thead>
<tr>
<th>Tablet</th>
<th><strong>Busulfan (Non-proprietary)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Busulfan 2 mg</strong></td>
<td>Busulfan 2mg tablets</td>
</tr>
</tbody>
</table>

**Solution for infusion**

<table>
<thead>
<tr>
<th><strong>Busulfan (Non-proprietary)</strong></th>
<th><strong>Busulfan 6 mg per 1 ml</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Busulfan 6 mg per 1 ml</strong></td>
<td>Busulfan 60mg/10ml concentrate for solution for infusion vials</td>
</tr>
<tr>
<td><strong>Busilvex (Pierre Fabre Ltd)</strong></td>
<td><strong>Busulfan 6 mg per 1 ml</strong></td>
</tr>
<tr>
<td><strong>Busulfan 6 mg per 1 ml</strong></td>
<td>Busilvex 60mg/10ml concentrate for solution for infusion ampoules</td>
</tr>
</tbody>
</table>

**CAUTIONS** Avoid in Acute porphyrias p. 1058

**INTERACTIONS** → Appendix 1: alkylating agents

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Alopecia, anaemia, ataxia, constipation, diarrhoea, dizziness, headache, nausea, seizures, vomiting

**SPECIFIC SIDE-EFFECTS**

- **Common or very common** With intravenous use: Abdominal pain, abscess, anxiety, asthenia, chest pain, coma, confusion, conjunctival oedema, depression, diabetes mellitus, drowsiness, dysphagia, electrolyte imbalance, embolism and thrombosis, eye pain, faecal incontinence, fever, gait abnormal, haemorrhage, hallucination, healing impaired, hydrocephalus, hyperglycaemia, hypersensitivity, hypertension, hypotension, increased risk of infection, injury, insomnia, intracranial pressure increased, leucocytosis, memory loss, meningitis, oedema, pain, paralysis, paraesthesia, peripheral neuropathy, personality disorder, rash, sensation abnormal, sepsis, speech impairment, stupor, thinking abnormal, thrombocytopenia, tremor, urinary incontinence, vision disorders
- **Uncommon** With intravenous use: Acute leukaemia, appetite decreased, bone marrow depression, encephalopathy (with high doses), hepatotoxicity, myelodysplastic syndrome (following long term use) — ocular toxicity, respiratory disorders, retinal haemorrhage, stomatitis
- **Rare or very rare** With intravenous use: Gynaecomastia, nephrotoxicity (cumulative), peripheral vascular disease (with high doses)
- **Frequency not known** With intravenous use: Infertility, myalgia

**SIDE-EFFECTS, FURTHER INFORMATION**

**Pulmonary toxicity** Lung infiltration, pulmonary fibrosis, pneumonitis, and interstitial lung disease have been
reported, some of which have been fatal. These appear to be dose-related, cumulative, and may be delayed.

**Hepatotoxicity** Hepatotoxicity has been reported to occur with high doses, and may be delayed up to 60 days after administration; usually reversible.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**NATIONAL FUNDING/ACCESS DECISIONS**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

**IMPORTANT SAFETY INFORMATION**

**SIDE-EFFECTS, FURTHER INFORMATION** Secondary malignancy Use of chlorambucil is associated with an increased incidence of acute leukaemia, particularly with prolonged use.

**Skin reactions** Manufacturer advises assessing continued use if rash occurs—has been reported to progress to Stevens-Johnson syndrome and toxic epidermal necrolysis.

**CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution—monitor for signs and symptoms of toxicity.

**Dose adjustments** Manufacturer advises consider dose reduction in severe impairment—limited information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (June 2015) NICE TA343**

Obinutuzumab, in combination with chlorambucil, is an option for untreated chronic lymphocytic leukaemia in patients who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if:

- bendamustine-based therapy is not suitable, and
- the manufacturer provides obinutuzumab with the discount agreed in the patient access scheme.

Patients currently receiving obinutuzumab that is not recommended according to the above criteria should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

**Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (June 2015) NICE TA344**

Ofatumumab in combination with chlorambucil is an option for untreated chronic lymphocytic leukaemia only if:

- the patient is ineligible for fludarabine-based therapy, and
- bendamustine is not suitable, and
- the manufacturer provides ofatumumab with the discount agreed in the patient access scheme.

Patients currently receiving ofatumumab that is not recommended according to the above criteria should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Implant**

- Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007) NICE TA121

Carmustine implants are an option for the treatment of newly diagnosed high-grade (Grade 3 or 4) glioma only for patients in whom at least 90% of the tumour has been resected. Carmustine implants should only be used within specialist centres.

[www.nice.org.uk/guidance/ta121](http://www.nice.org.uk/guidance/ta121)

**INDICATIONS AND DOSE**

**Some lymphomas and chronic leukaemias (used either alone or in combination therapy)**

- **BY MOUTH**
- **Adult:** (consult local protocol)

**IMMUNE SYSTEM AND MALIGNANT DISEASE**

**Chlorambucil**

**INDICATIONS AND DOSE**

**Some lymphomas and chronic leukaemias (used either alone or in combination therapy)**

- **BY MOUTH**
- **Adult:** (consult local protocol)

**IMPORANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**CAUTIONS** Children with nephrotic syndrome (increased seizure risk) - history of epilepsy (increased seizure risk)

**INTERACTIONS**

- Appendix 1: alkylating agents

**SIDE-EFFECTS**

- **Common or very common** Anaemia - bone marrow disorders - diarrhoea - gastrointestinal disorder - leucopenia - nausea - neoplasms - neutropenia - oral ulceration - seizures - thrombocytopenia - vomiting

- **Uncommon** Skin reactions

- **Rare or very rare** Cystitis - fever - hepatic disorders - movement disorders - muscle twitching - peripheral neuropathy - respiratory disorders - severe cutaneous adverse reactions (SCARs) - tremor

- **Frequency not known** Amenorrhoea - azoospermia

**SIDE-EFFECTS, FURTHER INFORMATION** Secondary malignancy Use of chlorambucil is associated with an increased incidence of acute leukaemia, particularly with prolonged use.

**Skin reactions** Manufacturer advises assessing continued use if rash occurs—has been reported to progress to Stevens-Johnson syndrome and toxic epidermal necrolysis.

**CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Cyclophosphamide**

**INDICATIONS AND DOSE**

**Rheumatoid arthritis with severe systemic manifestations**

- **BY MOUTH**
- **Adult:** 1–1.5 mg/kg daily

**Severe systemic rheumatoid arthritis Other connective tissue diseases (especially with active vasculitis)**

- **BY INTRAVENOUS INJECTION**
- **Adult:** 0.5–1 g every 2 weeks, then reduced to 0.5–1 g every month, frequency adjusted according to clinical response and haematological monitoring. To be given with prophylactic mesna

**Used, mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours**

- **BY MOUTH, OR BY INTRAVENOUS INFUSION**
- **Adult:** (consult local protocol)
Cytotoxic responsive malignancy

**BREAST FEEDING** Discontinue breast-feeding during and for 36 hours after stopping treatment.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of decreased cyclophosphamide activation and increased risk of veno-occlusive liver disease).

**Dose adjustments** Manufacturer advises consider dose adjustment in severe impairment—consult product literature.

**RENAL IMPAIRMENT**

Dose adjustments Reduce dose if serum creatinine concentration greater than 120 micromol/litre.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (cyclophosphamide injection; Baxter) give via drip tubing in Glucose 5% or Sodium chloride 0.9%; reconstitute 500 mg with 25 mL sodium chloride 0.9%; reconstitute 1 g with 50 mL sodium chloride 0.9%.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution, solution for injection, solution for infusion.

**Tablet**

- **Cyclophosphamide (Non-proprietary)**
  - Cyclophosphamide (as Cyclophosphamide monohydrate) 500 mg Cyclophosphamide 50mg tablets 100 tablet £39.00  
    - **Cytoxan** (Imported (United States))
      - Cyclophosphamide 25 mg Cytoxan 25mg tablets | 100 tablet £66.99

**Powder for solution for injection**

- **Cyclophosphamide (Non-proprietary)**
  - Cyclophosphamide (as Cyclophosphamide monohydrate) 500 mg Cyclophosphamide 50mg powder for solution for injection vials | 1 vial £34.12
    - **Cytoxan** (Imported (United States))
      - Cyclophosphamide 25 mg Cytoxan 25mg powder for solution for injection vials | 1 vial £34.12

Dacarbazine

- **INDICATIONS AND DOSE**
  - Metastatic melanoma | Soft-tissue sarcomas (combination therapy) | Hodgkin's disease (combination therapy)
  - **BY INTRAVENOUS INFUSION, OR BY INTRAVENOUS INJECTION**
  - Adult: (consult local protocol)

**SIDE-EFFECTS**

- **Common or very common** Anaemia - appetite decreased - leucopenia - nausea - thrombocytopenia - vomiting
- **Uncommon** Alopecia - infection - influenza like illness - photosensitivity reaction - skin reactions
- **Rare or very rare** Agranulocytosis - confusion - diaphoresis - flushing - headache - hepatic disorders - lethargy - pancytopenia - paraesthesia - renal impairment - seizure - visual impairment

**CONCEPTION AND CONTRACEPTION** Ensure effective contraception during and for at least 6 months after treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid (carcinogenic and teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.
Cytotoxic responsive malignancy

**Dose adjustments**
Dose reduction may be required in combined renal and hepatic impairment.

**RENAL IMPAIRMENT**
Avoid in severe impairment.

**Dose adjustments**
Dose reduction may be required in combined renal and hepatic impairment.

**PRESCRIBING AND DISPENSING INFORMATION**
Dacarbazine is a component of a commonly used combination for Hodgkin’s disease (ABVD—doxorubicin previously *Adriamycin*), bleomycin, vinblastine, and dacarbazine.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
CAUTIONARY AND ADVISORY LABELS 5, 23

- Estracyt (Pfizer Ltd)
- Estramustine phosphate (as Estramustine sodium phosphate) 140 mg Estracyt 140mg capsules | 100 capsule £171.28

**Ifosfamide**

**INDICATIONS AND DOSE**

- Malignant disease
  - BY INTRAVENOUS INFUSION
  - Adult: (consult local protocol)

**CONTRA-INDICATIONS**
Acute infection - urinary-tract infection - urinary-tract obstruction - urothelial damage

**CAUTIONS**
Avoid in Acute porphyrias p. 1058 - diabetes mellitus

**INTERACTIONS**
→ Appendix 1: alkylating agents

**SIDE-EFFECTS**
- Common or very common
  - Alopecia - appetite decreased - bone marrow disorders - haemorrhage - hepatic disorders - infection - leucopenia - nausea - reactivation of infection - renal impairment - thrombocytopenia - vomiting
- Uncommon
  - Cardiotoxicity - diarrhoea - hypertension - oral disorders
- Rare or very rare
  - Skin reactions
- Frequency not known

**SIDE-EFFECTS, FURTHER INFORMATION**
Urothelial toxicity
Mesna is routinely given with ifosfamide to reduce urothelial toxicity.

**Secondary malignancy**
Use of ifosfamide is associated with an increased incidence of acute leukaemia.

**Conception and Contraception**
Manufacturer advises adequate contraception during and for at least 6 months after treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Pregnancy**
Avoid (teratogenic and carcinogenic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Breast Feeding**
Discontinue breast-feeding.

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**Estramustine phosphate**

**INDICATIONS AND DOSE**

- Prostate cancer
  - BY MOUTH
  - Adult: Initially 560–840 mg daily in divided doses; maintenance 140–1400 mg daily in divided doses

**CONTRA-INDICATIONS**
Peptic ulceration - severe cardiovascular disease - thromboembolic disorders

**CAUTIONS**
Cardiovascular disease - cerebrovascular disease - conditions which might be aggravated by fluid retention (such as epilepsy or migraine) - congestive heart failure - diabetes - hypercalcemia - hypertension

**INTERACTIONS**
→ Appendix 1: alkylating agents

**SIDE-EFFECTS**
- Common or very common
- Frequency not known
  - Allergic dermatitis - angioedema - confusion - depression - erectile dysfunction - hypertension - muscle weakness - myocardiopathy
- **CONCEPTION AND CONTRACEPTION**
  - Men should use effective contraceptive methods during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution—monitor hepatic function; avoid in severe impairment.
- **RENAI IMPAIRMENT**
  - Manufacturer advises caution.
- **DIRECTIONS FOR ADMINISTRATION**
  - Each dose should be taken not less than 1 hour before or 2 hours after meals and should not be taken with products containing calcium, magnesium or aluminium, including dairy products and antacid medication.
- **PATIENT AND CARER ADVICE**
  - Patients should be given advice on how to administer estramustine capsules.

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**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Estracyt (Pfizer Ltd)
- Estramustine phosphate (as Estramustine sodium phosphate) 140 mg Estracyt 140mg capsules | 100 capsule £171.28

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**Immune system and malignant disease**

**RENAL IMPAIRMENT**
Frequency not known

**SIDE-EFFECTS**

**INTERACTIONS**

**CAUTIONS**

**MEDICINAL FORMS**

- Adriamycin
  - Dose adjustments
  - Manufacturer advises caution
  - Men should use
  - confusion
  - thrombocytopenia
- **diabetes**
- **Cardiovascular disease**
- **Prostate cancer**
- **Hodgkin disease (ABVD)**
- **Secondary malignancy**
- **Urothelial toxicity**
- **Cytotoxic drugs**
**HEPATIC IMPAIRMENT**  Manufacturer advises avoid.

**RENAL IMPAIRMENT**  Avoid if serum creatinine concentration greater than 120 micromol/litre.

**MONITORING REQUIREMENTS**  Ensure satisfactory electrolyte balance and renal function before each course (risk of tubular dysfunction, Fanconi’s syndrome or diabetes insipidus if renal toxicity not treated promptly).

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Ifosfamide (Non-proprietary)
  - Ifosfamide 1 gram: £115.79-
  - Ifosfamide 2 gram: £228.09-

**SIDE-EFFECTS**

**CONTRA-INDICATIONS**

**Monitoring Requirements**

**Renal Impairment**

**Contraception and Contraception**

**Breast Feeding**

**Pregnancy**

**Conception and Contraception**

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- Melphalan (Non-proprietary)
  - Melphalan (as Melphalan hydrochloride) 50 mg: £137.37
- Melphalan 100 mg: £234.94
- Melphalan 500 mg: £228.09-

**Tablet**
- Melphalan (Non-proprietary)
  - Melphalan 2 mg: £45.38
- Melphalan 100 mg: £228.09-

**IMPORTANT SAFETY INFORMATION**

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines**

See Cytotoxic drugs p. 888.

**INTERACTIONS**

- Appendix 1: alkylating agents

**SIDE-EFFECTS**

**General Side-Effects**

- Common or very common
  - Alopecia
  - Anaemia
  - Bone marrow depression (delayed)
  - Diarrhoea
  - Nausea
  - Stomatitis
  - Thrombocytopenia
  - Vomiting

- Rare or very rare
  - Haemolytic anaemia
  - Hepatic disorders
  - Respiratory disorders
  - Skin reactions

**Specific Side-Effects**

- Common or very common
  - With oral use
    - Leucopenia
  - With parental use
    - Feeling hot
    - Myalgia
    - Myopathy
    - Paraesthesia

- Rare or very rare
  - Peripheral vascular disease

**Side-Effects, Further Information**

Secondary malignancy

Use of melphalan is associated with an increased incidence of acute leukaemias.

**Conception and Contraception**

Manufacturer advises adequate contraception during treatment in men or women. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Pregnancy**

Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Breast Feeding**

Discontinues breast-feeding.

**Renal Impairment**

Dose adjustments

Reduce dose initially (consult product literature).

**Monitoring Requirements**

Monitor full blood count before and throughout treatment.

**Melphalan**

**Indications and Dose**

- Multiple myeloma
  - Adult: 150 micrograms/kg daily for 4 days, dose to be repeated every 6 weeks, dose may vary according to regimen
  - By intravenous injection, or by intravenous infusion
  - Adult: (consult product literature)

**Polycythaemia Vera**

- Adult: Initially 6–10 mg daily for 5–7 days, then reduced to 2–4 mg daily until satisfactory response, then reduced to 2–6 mg once weekly

**Localised malignant melanoma of the extremities**

**Localised soft-tissue sarcoma of the extremities**

- By regional arterial perfusion
  - Adult: (consult local protocol)

**Drug Action**

Lomustine is a lipid-soluble nitrosourea.

**Indications and Dose**

Hodgkin’s disease resistant to conventional therapy

- Malignant melanoma
  - Certain solid tumours

- By Mouth
  - Adult: 120–130 mg/m² every 6–8 weeks, dose is for when lomustine is used alone

**Hepatic Impairment**

Manufacturer advises avoid.

**Renal Impairment**

Avoid if serum creatinine concentration greater than 120 micromol/litre.

**Monitoring Requirements**

Ensure satisfactory electrolyte balance and renal function before each course (risk of tubular dysfunction, Fanconi’s syndrome or diabetes insipidus if renal toxicity not treated promptly).

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Ifosfamide (Non-proprietary)
  - Ifosfamide 1 gram: £115.79-
  - Ifosfamide 2 gram: £228.09-

**Side-Effects**

**Contra-Indications**

**Monitoring Requirements**

**Renal Impairment**

**Conception and Contraception**

**Breast Feeding**

**Pregnancy**

**Conception and Contraception**

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- Melphalan (Non-proprietary)
  - Melphalan (as Melphalan hydrochloride) 50 mg: £137.37
  - Melphalan powder and solvent for solution for injection vials: £228.09-

**Tablet**
- Melphalan (Non-proprietary)
  - Melphalan 2 mg: £45.38
  - Melphalan 100 mg: £228.09-
**Streptozocin**

**DRUG ACTION** Streptozocin is an antibiotic antineoplastic nitrosoare.

**INDICATIONS AND DOSE**
- Neuroendocrine tumours of pancreatic origin (specialist use only)
  - By intravenous infusion
  - Adult: (consult product literature)

**CAUTIONS**
- Antiemetic pre-medication recommended—avoid extravasation (risk of tissue necrosis) elderly—hyperhydration required (consult product literature)

**INTERACTIONS** → Appendix 1: streptozocin

**SIDE-EFFECTS**
- Common or very common: Acute kidney injury—diarrhoea—nausea—nephropathy—renal tubular injury—urinary disorder—urine abnormalities—vomiting
- Frequency not known: Confusion—depression—extravasation necrosis—fever—glucose tolerance impaired—hepatotoxicity—hypoalbuminaemia—lacthary

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises caution in women of childbearing potential that they are of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
- Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
- Manufacturer advises caution.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution.

**Dose adjustments**
- Manufacturer advises consider dose reduction.

**RENAL IMPAIRMENT**
- Manufacturer advises caution: evaluate benefit/risk ratio if eGFR 30—45 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

**Dose adjustments**
- Manufacturer advises reduce dose if eGFR 46—60 mL/minute/1.73 m²—consult product literature.

**MONITORING REQUIREMENTS**
- Manufacturer advises monitor renal function (plasma creatinine and eGFR derived from the MDRD formula) immediately before treatment initiation and 2 weeks after each course of therapy; proteinuria and serum electrolytes should also be monitored before treatment initiation and 2—4 weeks after the last cycle of treatment.

**HANDLING AND STORAGE**
- Manufacturer advises store in a refrigerator (2—8°C) and protect from light—consult product literature for storage conditions after reconstitution and dilution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- Zanosar (intrapharm Laboratories Ltd)

| Streptozocin 1 gram | Zanosar 1g powder for concentrate for solution for infusion vials | 1 vial | £570.00 |

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**Temozolomide**

**DRUG ACTION** Temozolomide is structurally related to dacarbazine.

**INDICATIONS AND DOSE**
- Newly diagnosed glioblastoma multiforme in adults (in combination with radiotherapy) and subsequently as monotherapy | Second-line treatment of malignant glioma in adults
  - BY MOUTH
  - Adult: (consult product literature)

**CAUTIONS**
- Pneumocystis jiroveci pneumonia—consult product literature for monitoring and prophylaxis requirements

**INTERACTIONS** → Appendix 1: alkylating agents

**SIDE-EFFECTS**

**Uncommon**

**Rare or very rare**
- Neoplasms—respiratory disorders—secondary malignancy—severe cutaneous adverse reactions (SCARs)

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises adequate contraception during treatment. Men should avoid fathering a child during and for at least 6 months after treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
- Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in severe impairment (no information available).

**RENAL IMPAIRMENT**
- Manufacturer advises caution—no information available.

**MONITORING REQUIREMENTS**
- Monitor liver function before treatment initiation, after each treatment cycle and midway through 42-day treatment cycles—consider the balance of benefits and risks of treatment if results are abnormal at any point (fatal liver injury reported).
Monitor for myelodysplastic syndrome.

Monitor for secondary malignancies.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    Temozolomide may be considered for the treatment of recurrent malignant glioma, which has not responded to first-line chemotherapy.  
    www.nice.org.uk/TA23
  - Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007) NICE TA121
    Temozolomide is an option for the treatment of newly diagnosed glioblastoma multiforme in patients with a WHO performance status of 0 or 1.  
    www.nice.org.uk/TA121

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 23, 25
    - Temozolomide (Non-proprietary) 23
      - Temozolomide 5 mg: Temozolomide 5mg capsules | 5 capsule (PO) £10.06–16.00
      - Temozolomide 20 mg: Temozolomide 20mg capsules | 5 capsule (PO) £40.23–66.50
      - Temozolomide 100 mg: Temozolomide 100mg capsules | 5 capsule (PO) £201.18–325.00
      - Temozolomide 140 mg: Temozolomide 140mg capsules | 5 capsule (PO) £296.47–446.00
      - Temozolomide 180 mg: Temozolomide 180mg capsules | 5 capsule (PO) £381.18–586.00
      - Temozolomide 250 mg: Temozolomide 250mg capsules | 5 capsule (PO) £529.42–814.00
  - **Temodal** (Merck Sharp & Dohme Ltd)
    - Temozolomide 5 mg: Temozolomide 5mg capsules | 5 capsule (PO) £10.59 (Hospital only)
    - Temozolomide 20 mg: Temozolomide 20mg capsules | 5 capsule (PO) £42.35 (Hospital only)
    - Temozolomide 100 mg: Temozolomide 100mg capsules | 5 capsule (PO) £211.77 (Hospital only)
    - Temozolomide 140 mg: Temozolomide 140mg capsules | 5 capsule (PO) £296.48 (Hospital only)
    - Temozolomide 180 mg: Temozolomide 180mg capsules | 5 capsule (PO) £381.19 (Hospital only)
    - Temozolomide 250 mg: Temozolomide 250mg capsules | 5 capsule (PO) £529.43 (Hospital only)

### Thiotepa

- **INDICATIONS AND DOSE**
  - Conditioning treatment before haematopoietic stem cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy
    - **BY INTRAVENOUS INFUSION**
    - **Adults:** (consult local protocol)

- **CAUTIONS**
  - Avoid in Acute porphyrias p. 1058

- **INTERACTIONS**
  - Appendix 1: alkylating agents

- **SIDE-EFFECTS**
  - **Common or very common**
    - Alopecia
    - anaemia
    - anxiety
    - appetite decreased
    - arthralgia
    - asthenia
    - azoospermia
    - cataract
    - chills
    - cognitive disorder
    - confusion
    - conjunctivitis
    - constipation
    - cough
    - cystitis
    - delirium
    - diarrhoea
    - dizziness
    - dysuria
    - embolism
    - eunuchoidism
    - extrapyramidal symptoms
    - fever
    - gastrointestinal discomfort
    - gastrointestinal disorders
    - generalised oedema
    - graft versus host disease
    - haemorrhage
    - headache
    - hearing impairment
    - heart failure
    - hepatic disorders
    - hyperglycaemia
    - hypersensitivity
    - hypertension
    - hypopituitarism
    - increased risk of infection
    - infertility
    - intracranial aneurysm
    - intracranial haemorrhage
    - leucopenia
    - lymphoedema
    - menopausal symptoms
    - mucositis
    - multi organ failure
    - myalgia
    - nausea
    - neutropenia
    - otoxicity
    - pain
    - pancytopenia
    - paraesthesia
    - psychiatric disorder
    - pulmonary oedema
    - renal impairment
    - respiratory disorders
    - secondary malignancy
    - sepsis
    - sinusal obstruction syndrome
    - skin reactions
    - stomatitis
    - thrombocytopenia
    - toxic shock syndrome
    - vision blurred
    - vomiting
    - weight increased

- **Uncommon**
  - Cardiomyopathy
  - hallucination
  - hypoxia
  - myocarditis

- **Frequency not known**
  - Severe cutaneous adverse reactions (SCARs)

### Conception and Contraception

- Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) decisions**
    - SMC No. 790/12
      - The Scottish Medicines Consortium has advised (June 2012) that thiotepa (Temapina®) is not recommended for use within NHS Scotland in combination with other chemotherapy as conditioning treatment in adults or children with haematological diseases, or solid tumours prior to haematopoietic stem cell transplantation.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for infusion**
  - **Temapina** (Adienne Pharma & Biotech)
    - Thiotepa 15 mg: Tepadin 15mg powder for concentrate for solution for infusion vials | 1 vial (PO) £
    - Thiotepa 100 mg: Tepadin 100mg powder for concentrate for solution for infusion vials | 1 vial (PO) £

### Treosulfan

- **INDICATIONS AND DOSE**
  - Ovarian cancer
    - **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAPERITONEAL INSTILLATION**
    - **Adult:** (consult product literature)

### IMPORTANT SAFETY INFORMATION

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CAUTIONS**
  - Avoid in Acute porphyrias p. 1058

- **INTERACTIONS**
  - Appendix 1: alkylating agents

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Common or very common**
      - Alopecia
      - anaemia
      - bone marrow disorders
      - increased risk of infection
      - leucopenia
      - nausea
      - skin reactions
      - thrombocytopenia
      - vomiting
    - **Uncommon**
      - Neoplasms
        - treatment related secondary malignancy
    - **Rare or very rare**
      - Addison’s disease
      - cardiomyopathy
      - cystitis haemorrhagic
      - hypoglycaemia
      - influenza like illness
      - paraesthesia
      - respiratory disorders
      - scleroderma
      - sepsis

- **SPECIFIC SIDE-EFFECTS**
  - **Uncommon**
  - **With oral use** Stomatitis
Daunorubicin with cytarabine

The properties listed below are those particular to the combination only. For the properties of the components please consider, daunorubicin above, cytarabine p. 908.

- **INDICATIONS AND DOSE**
  - **Acute myelogenous leukaemia**
    - **BY INTRAVENOUS INFUSION**
      - Adult: (consult local protocol)
  - **Advanced AIDS-related Kaposis sarcoma (liposomal formulation only)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  - Myocardial insufficiency · previous treatment with maximum cumulative doses of daunorubicin or other anthracyclines · recent myocardial infarction · severe arrhythmia

- **CAUTIONS**
  - Caution in handling · irritant to tissues

- **INTERACTIONS**
  - Appendix 1: anthracyclines

- **SIDE-EFFECTS**
  - Abdominal pain · alopecia · amnorrhoea · anaemia · arrhythmias · ascites · ativoventricular block · azosperma · bone marrow disorders · cardiac inflammation · cardiomyopathy · chills · congestive heart failure · cyanosis · death · dehydration · diarrhoea · dyspnœa · extravasation necrosis · fever · flushing · gastrointestinal disorders · haemorrhage · hepatomegaly · hyperpyrexia · hyperuricaemia · hypoxia · infection · ischaemic heart disease · leucopenia · mucositis · myocardial infarction · nail discolouration · nausea · nephropathy · neutropenia · oedema · pain · paraesthesia · pleural effusion · radiation injuries · shock · skin reactions · stomatitis · thrombocytopenia · thrombophlebitis · urine red · venous sclerosis · vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Cardiotoxicity is cumulative and may be irreversible, however responds to treatment if detected early.

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Avoid (teratogenic and carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**
  - For solution for infusion
  - Manufacturer advises caution. For powder for solution for infusion manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- **Dose adjustments**
  - Manufacturer advises dose reduction according to serum bilirubin concentration—consult product literature.

- **RENAL IMPAIRMENT**
  - Avoid in severe impairment.

- **Dose adjustments**
  - Reduce dose by 25% if serum creatinine 105–265 micromol/litre.
  - Reduce dose by 50% if serum creatinine greater than 265 micromol/litre.

- **MONITORING REQUIREMENTS**
  - Cardiac monitoring essential.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 25

  - **Treosulfan (Non-proprietary)**
    - Treosulfan 250 mg
      - 100 capsule Pack £65.20
  - **Powder for solution for injection**
    - **Treosulfan (Non-proprietary)**
      - Treosulfan 1 gram
        - 5 vial Pack £269.17
      - Treosulfan 5 gram
        - 5 vial Pack £1,040.17

- **ANTINEOPLASTIC DRUGS**

- **Daunorubicin**

  - **INDICATIONS AND DOSE**
    - Acute myelogenous leukaemia · Acute lymphocytic leukaemia
      - **BY INTRAVENOUS INFUSION**
        - Adult: (consult local protocol)
    - **Advanced AIDS-related Kaposis sarcoma (liposomal formulation only)**
      - **BY INTRAVENOUS INFUSION**
        - Adult: (consult product literature)

  - **CONTRA-INDICATIONS**
    - Myocardial insufficiency · previous treatment with maximum cumulative doses of daunorubicin or other anthracyclines · recent myocardial infarction · severe arrhythmia

  - **CAUTIONS**
    - Caution in handling · irritant to tissues

  - **INTERACTIONS**
    - Appendix 1: anthracyclines

  - **SIDE-EFFECTS**
    - Abdominal pain · alopecia · amnorrhoea · anaemia · arrhythmias · ascites · ativoventricular block · azosperma · bone marrow disorders · cardiac inflammation · cardiomyopathy · chills · congestive heart failure · cyanosis · death · dehydration · diarrhoea · dyspnœa · extravasation necrosis · fever · flushing · gastrointestinal disorders · haemorrhage · hepatomegaly · hyperpyrexia · hyperuricaemia · hypoxia · infection · ischaemic heart disease · leucopenia · mucositis · myocardial infarction · nail discolouration · nausea · nephropathy · neutropenia · oedema · pain · paraesthesia · pleural effusion · radiation injuries · shock · skin reactions · stomatitis · thrombocytopenia · thrombophlebitis · urine red · venous sclerosis · vomiting

  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Cardiotoxicity is cumulative and may be irreversible, however responds to treatment if detected early.

  - **CONCEPTION AND CONTRACEPTION**
    - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

  - **PREGNANCY**
    - Avoid (teratogenic and carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

  - **BREAST FEEDING**
    - Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**
  - For solution for infusion
  - Manufacturer advises caution. For powder for solution for infusion manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

  - **Dose adjustments**
    - Manufacturer advises dose reduction according to serum bilirubin concentration—consult product literature.

- **RENAL IMPAIRMENT**
  - Avoid in severe impairment.

  - **Dose adjustments**
    - Reduce dose by 25% if serum creatinine 105–265 micromol/litre.
    - Reduce dose by 50% if serum creatinine greater than 265 micromol/litre.

- **MONITORING REQUIREMENTS**
  - Cardiac monitoring essential.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for infusion**
    - DaunoXome (Galen Ltd)
      - Daunorubicin (as Daunorubicin hydrochloride citrate liposomal pegylated) 2 mg per 1 ml
        - DaunoXome 50mg/25ml concentrate for solution for infusion vials | 1 vial (Pack) £250.00
    - **Powder for solution for infusion**
      - Daunorubicin (Non-proprietary)
        - Daunorubicin (as Daunorubicin hydrochloride)
          - 20 mg
            - Daunorubicin 20mg powder for solution for infusion vials | 10 vial (Pack) £715.00 (Hospital only)
Doxorubicin hydrochloride

INDICATIONS AND DOSE

Acute leukaemias | Hodgkin’s lymphoma | Non-Hodgkin’s lymphoma | Some solid tumours including breast cancer | Advanced soft-tissue sarcoma

- BY INTRAVENOUS INJECTION
  - Adults: (consult product literature)

Some papillary bladder tumours (bladder instillation) | Recurrent superficial bladder tumours (bladder instillation) | Transitional cell carcinoma (bladder instillation) | Carcinoma in situ (bladder instillation)

- BY INTRAVESICAL INSTILLATION
  - Adults: (consult product literature)

CAELYX®

For AIDS-related Kaposi’s sarcoma in patients with low CD4 count and extensive mucocutaneous or visceral disease | Advanced ovarian cancer when platinum-based chemotherapy has failed | Progressive multiple myeloma (in combination with bortezomib) in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone-marrow transplantation | Monotherapy for metastatic breast cancer in patients with increased cardiac risk

- BY INTRAVENOUS INFUSION
  - Adults: (consult product literature)

MYOCET®

For use with cyclophosphamide for metastatic breast cancer

- Adults: (consult product literature)

CONTRA-INDICATIONS | CAUTIONS | INTERACTIONS | SIDE-EFFECTS

- Common or very common
  - Alopecia | anaemia | anxiety | appetite decreased | arthralgias | asthenia | bone marrow depression | breast pain | cachexia | cardiovascular disorder | chest discomfort | chills | constipation | cough | decreased leucocytes | dehydration | depression | diarrhoea | dizziness | drowsiness | dry mouth | dysphagia | dyspnoea | dysuria | electrolyte imbalance | epistaxis | eye inflammation | fever | gastrointestinal discomfort | gastrointestinal disorders | headache | hyperhidrosis | hypersensitivity | hypertension | hyperthermia | hypotension | increased risk of infection | influenza like illness | infusion related reaction | insomnial | malaise | mucosal abnormalities | muscle complaints | muscle tone increased | muscle weakness | nail disorder | nausea | nerve disorders | neutropenia | oedema | oral disorders | pain | scrotal erythema | sensation abnormal | sepsis | skin reactions | skin ulcer | syncope | taste altered | thrombocytopenia | vasodilation | vision blurred | vomiting | weight decreased

- Uncommon
  - Confusion | embolism and thrombosis

- Rare or very rare
  - Secondary oral neoplasms | severe cutaneous adverse reactions (SCARs)

FURTHER INFORMATION

SIDE-EFFECTS, FURTHER INFORMATION

Extravasation can cause tissue necrosis.

Cardiomyopathy: Higher cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450 mg/m².

Liposomal formulations: Liposomal formulations of doxorubicin may reduce the incidence of cardiotoxicity and lower the potential for local necrosis, but infusion reactions, sometimes severe, may occur. Hand-foot syndrome (painful, macular reddening skin eruptions) occurs commonly with liposomal doxorubicin and may be dose limiting. It can occur after 2–3 treatment cycles and may be prevented by cooling hands and feet and avoiding socks, gloves, or tight-fitting footwear. It may also occur with non-liposomal formulations.

Elevated bilirubin concentrations: Doxorubicin is largely excreted in the bile and an elevated bilirubin concentration is an indication for reducing the dose.

CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

PREGNANCY

Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

For liposomal formulation, manufacturer advises caution. For solution for injection or infusion, manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

Dose adjustments: Manufacturer advises dose reduction according to bilirubin concentration.

RENAL IMPAIRMENT

Consult product literature in severe impairment.

MONITORING REQUIREMENTS

Patients should be assessed before treatment, by echocardiography. Cardiac monitoring during treatment may assist in determining safe dosage.

DIRECTIONS FOR ADMINISTRATION

Conventional doxorubicin is given by injection into a fast-running infusion, commonly at 21-day intervals.

PRESCRIBING AND DISPENSING INFORMATION

Doxorubicin is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389

Pegylated liposomal doxorubicin hydrochloride (PLDH) monotherapy or in combination with platinum, is recommended as an option for treating recurrent ovarian cancer.

PLDH, in combination with trabectedin, is not recommended for treating the first recurrence of platinum-sensitive ovarian cancer.

Patients currently receiving PLDH in combination with trabectedin should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA389

Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma (August 2017) NICE TA465

Doxorubicin, in combination with olaratumab, is recommended for use within the Cancer Drugs Fund as an option for advanced soft tissue sarcoma in patients, only if:

www.getintopharma.com
Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

Solution for injection

- Doxorubicin hydrochloride (Non-proprietary)
  - Doxorubicin hydrochloride 2 mg per 1 ml
    - Doxorubicin 10mg/5ml solution for injection vials | 1 vial (POD) £18.54 (Hospital only)
    - Doxorubicin 50mg/25ml solution for injection Cytosafe vials | 1 vial (POD) £103.00 (Hospital only)
  - Doxorubicin 10mg/5ml solution for infusion vials | 1 vial (POD) £103.00 (Hospital only)
  - Doxorubicin 10mg/5ml solution for infusion vials | 1 vial (POD) £20.60 (Hospital only)
  - Doxorubicin 10mg/ml concentrate for solution for infusion vials | 1 vial (POD) £13.12 (Hospital only) 1 vial (POD) £13.57
  - Doxorubicin 10mg/5ml solution for infusion vials | 1 vial (POD) £20.60 (Hospital only)
  - Doxorubicin 50mg/25ml solution for infusion vials | 1 vial (POD) £39.10
  - Doxorubicin 50mg/25ml solution for infusion vials | 1 vial (POD) £36.03 Vial

- Caelyx (Janssen-Cilag Ltd)
  - Doxorubicin hydrochloride (as Doxorubicin hydrochloride liposomal pegylated) 2 mg per 1 ml
    - Caelyx 50mg/25ml concentrate for solution for infusion vials | 1 vial (POD) £12.49
  - Caelyx 20mg/10ml concentrate for solution for infusion vials | 1 vial (POD) £36.03 Vial

Powder and solvent for suspension for infusion

Electrolytes: May contain Sodium

- Myocet (Teva UK Ltd)
  - Doxorubicin hydrochloride liposomal pegylated 50 mg
    - Myocet 50mg powder and solvent for suspension for infusion vials | 2 vial (POD) £912.26 (Hospital only)

Solution for infusion

- Doxorubicin hydrochloride (Non-proprietary)
  - Doxorubicin hydrochloride 2 mg per 1 ml
    - Doxorubicin 100mg/100ml solution for infusion vials | 1 vial (POD) £142.00 (Hospital only)
    - Doxorubicin 20mg/10ml concentrate for solution for infusion vials | 1 vial (POD) £142.00 (Hospital only)
    - Doxorubicin 100mg/100ml concentrate for solution for infusion vials | 1 vial (POD) £142.00 (Hospital only)
    - Doxorubicin 200mg/100ml solution for infusion vials | 1 vial (POD) £142.00 (Hospital only)
    - Doxorubicin 200mg/100ml solution for infusion vials | 1 vial (POD) £391.40

- Caelyx (Janssen-Cilag Ltd)
  - Doxorubicin hydrochloride (as Doxorubicin hydrochloride liposomal pegylated) 2 mg per 1 ml
    - Caelyx 50mg/25ml concentrate for solution for infusion vials | 1 vial (POD) £12.49
  - Caelyx 20mg/10ml concentrate for solution for infusion vials | 1 vial (POD) £36.03 Vial

Indications and dose

Treatment of breast cancer | Treatment and prophylaxis of certain forms of superficial bladder cancer

- By intravenous infusion, or by intravesical instillation

Contra-Indications

Bladder inflammation or contraction (when used as a bladder instillation) - catheterisation difficulties (when used as a bladder instillation) - haematuria (when used as a bladder instillation) - invasive tumours penetrating the bladder (when used as a bladder instillation) - myocardopathy - previous treatment with maximum cumulative doses of epirubicin or other anthracycline - recent myocardial infarction - severe arthrythmia - severe myocardial insufficiency - unstable angina - urinary tract infections (when used as a bladder instillation)

Caution

Caution in handling—irritant to tissues

Interactions

Appendix 1: anthracyclines

Side-effects

General side-effects

- Common or very common Paraesthesia, urinary frequency increased

Specific side-effects

- Common or very common
  - With intravesical use Chemical cystitis
  - With parenteral use Alopecia, anaemia, appetite decreased, bone marrow depression, dehydration, diarrhoea - increased risk of infection, leucopenia, mucositis, nausea, neutropenia, oesophagitis, stomatitis, urine red - vasodilation, vomiting
  - Uncommon
  - With parenteral use Embolism and thrombosis - thrombocytopenia
  - Rare or very rare
  - With parenteral use Amenorrhoea, arthrythmias, asites, asthenia, azospermia, cardiac conduction disorders, cardiomyopathy, cardio toxicity, chill, congestive heart failure, dizziness, dyspnoea, fever, hepatomegaly, hyperuricaemia, malaise, neoplasms, oedema, pleural effusion, pulmonary oedema, skin reactions

Frequency not known

- With intravesical use Cystitis bacterial
- With parenteral use Eye inflammation, haemorrhage, hypoxia, nail discoulouration, photosensitivity reaction - radiation injuries - sepsis - shock

Side-effects, further information

Manufacturer advises extreme caution with cumulative doses exceeding 900 mg/m² — risk of congestive heart failure increased.

Conception and contraception

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

Pregnancy

Avoid (carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

Breast feeding

Discontinue breast-feeding.

Hepatic impairment

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment. Dose adjustments

Manufacturer advises dose reduction according to bilirubin level.

Renal impairment

Dose adjustments.

Dose reduction may be necessary in severe impairment.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

Solution for injection

- Epirubicin hydrochloride (Non-proprietary)
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Epirubicin 10mg/5ml solution for injection vials | 1 vial (POD) £17.38 - £20.18
    - Epirubicin 50mg/25ml solution for injection vials | 1 vial (POD) £100.88

- Pharmorubicin (Pfizer Ltd)
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Pharmorubicin 50mg/25ml solution for injection Cytosafe vials | 1 vial (POD) £106.19 (Hospital only)
    - Pharmorubicin 10mg/5ml solution for injection Cytosafe vials | 1 vial (POD) £21.24 (Hospital only)

Solution for infusion

- Epirubicin hydrochloride (Non-proprietary)
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Epirubicin 100mg/100ml solution for infusion vials | 1 vial (POD) £366.85
    - Epirubicin 100mg/50ml solution for infusion vials | 1 vial (POD) £201.76

- Pharmorubicin (Pfizer Ltd)
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Pharmorubicin 200mg/100ml solution for infusion Cytosafe vials | 1 vial (POD) £386.16 (Hospital only)
### Idarubicin hydrochloride

**04-May-2017**

#### INDICATIONS AND DOSE

**Acute non-lymphocytic leukaemias monotherapy**
- **BY MOUTH**
  - Adult: 30 mg/m² daily for 3 days; maximum 400 mg/m² per course

**Acute non-lymphocytic leukaemia in combination therapy**
- **BY MOUTH**
  - Adult: 15–30 mg/m² daily for 3 days; maximum 400 mg/m² per course

**Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)—monotherapy**
- **BY MOUTH**
  - Adult: 45 mg/m² for 1 dose, repeat treatment every 3–4 weeks, alternatively 15 mg/m² daily for 3 consecutive days, repeat treatment every 3–4 weeks; maximum 400 mg/m² per course

**Acute leukaemias: Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)**
- **BY INTRAVENOUS INJECTION**
- Adult: (consult product literature)

#### IMPORTANT SAFETY INFORMATION

**RISKS OF INCORRECT DOSE**

*See Cytotoxic drugs p. 888.*

- **CONTRA-INDICATIONS**
  - Previous treatment with maximum cumulative dose of idarubicin or other anthracycline
  - Recent myocardial infarction
  - Severe arrhythmias
  - Severe myocardial insufficiency

- **CAUTIONS**
  - Caution in handling—irritant to tissues

- **INTERACTIONS**
  - Appendix 1: anthracyclines

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common
      - Alopecia
      - Anaemia
      - Appetite decreased
      - Arthralgias
      - Cardiomyopathy
      - Chills
      - Congestive heart failure
      - Diarrhoea
      - Embolism and thrombosis
      - Fever
      - Haemorrhage
      - Headache
      - Increased risk of infection
      - Leucopenia
      - Nausea
      - Neutropenia
      - Skin reactions
      - Stomatitis
      - Thrombocytopenia
      - Urine red-vomiting
    - Uncommon
      - Dehydration
      - Gastrointestinal disorders
      - Hyperuricaemia
      - Leukaemia secondary
      - Myocardial infarction
      - Nail discolouration
      - Sepsis
      - Shock
      - Soft tissue necrosis
    - Rare or very rare
      - Cardiac conduction disorders
      - Cardiac inflammation
      - Flushing
      - Intracranial haemorrhage
    - Frequency not known
      - Bone marrow disorders
      - Tumour lysis syndrome

- **SPECIFIC SIDE-EFFECTS**
  - Common or very common
    - With intravenous use
      - Abdominal pain
      - Mucosal abnormalities
      - Parasthesia
      - Radiation injuries
    - With oral use
      - Gastrointestinal discomfort
      - Mucositis
      - Radiation skin sensitivity

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Avoid. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- **Dose adjustments**
  - Manufacturer advises consider dose reduction in mild to moderate impairment—consult product literature.

- **MUSCULOSKELETAL**
  - Arthralgias
  - Myalgias

- **RESPIRATORY**
  - Hypostatic pneumonia
  - Pulmonary oedema

- **SKIN**
  - Alopecia
  - Pruritus

- **THERAPEUTIC EFFECT**
  - Decreased

#### MEDICATION FORMS

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS**
  - 25
    - **Zavedos (Pfizer Ltd)**
      - Idarubicin hydrochloride 5 mg Zavedos 5mg capsules | 1 capsule [PO] £1.47
      - Idarubicin hydrochloride 10 mg Zavedos 10mg capsules | 1 capsule [PO] £9.12

**Powder for solution for injection**
- **Zavedos (Pfizer Ltd)**
  - Idarubicin hydrochloride 5 mg Zavedos 5mg powder for solution for injection vials | 1 vial [PO] £87.36 (Hospital only)
  - Idarubicin hydrochloride 10 mg Zavedos 10mg powder for solution for injection vials | 1 vial [PO] £174.72 (Hospital only)

### Mitoxantrone

(Mitoxantrone)

#### INDICATIONS AND DOSE

**Metastatic breast cancer**
- Non-Hodgkin’s lymphoma
- Adult acute non-lymphocytic leukaemia
- Non-resectable primary hepatocellular carcinoma
- **BY INTRAVENOUS INFUSION**
- Adult: (consult local protocol)

#### CAUTIONS

- Intrathecal administration not recommended

#### INTERACTIONS

- Appendix 1: anthracyclines

#### SIDE-EFFECTS

**GENERAL SIDE-EFFECTS**
- Abdominal pain
- Alopecia
- Anxiety
- Appetite decreased
- Arthralgias
- Cardiomyopathy
- Chills
- Congestive heart failure
- Diarrhoea
- Embolism and thrombosis
- Fever
- Haemorrhage
- Headache
- Increased risk of infection
- Leucopenia
- Nausea
- Neutropenia
- Skin reactions
- Stomatitis
- Thrombocytopenia
- Urine red-vomiting

**COMMON OR VERY COMMON SIDE-EFFECTS**
- Alopecia
- Anaemia
- Appetite decreased
- Arthralgias
- Cardiomyopathy
- Chills
- Congestive heart failure
- Diarrhoea
- Embolism and thrombosis
- Fever
- Haemorrhage
- Headache
- Increased risk of infection
- Leucopenia
- Nausea
- Neutropenia
- Skin reactions
- Stomatitis
- Thrombocytopenia
- Urine red-vomiting

**RARE OR VERY RARE SIDE-EFFECTS**
- Cardiac conduction disorders
- Cardiac inflammation
- Flushing
- Intracranial haemorrhage

**FREQUENCY NOT KNOWN SIDE-EFFECTS**
- Bone marrow disorders
- Tumour lysis syndrome

#### MEDICATION FORMS

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- **Mitoxantrone (Non-proprietary)**
  - Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Mitoxantrone 20mg/10ml concentrate for solution for infusion vials | 1 vial [PFS] £121.85 (Hospital only) | 1 vial [PFS] £51.43
  - **Onkotrone (Baxter Healthcare Ltd)**
    - Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Onkotrone 20mg/10ml solution for infusion vials | 1 vial [PFS] £103.57
    - Onkotrone 25mg/12.5ml solution for infusion vials | 1 vial [PFS] £129.48

www.getintopharma.com
Pixantrone
07-Feb-2009

**INDICATIONS AND DOSE**
Treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas (monotherapy)

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS**
Active severe infection - risk factors for severe infection

**CAUTIONS**
Active cardiovascular disease - cardiac risk factors - caution in handling—irritant to tissues - concurrent radiotherapy to the mediastinal area - history of cardiovascular disease - previous radiotherapy to the mediastinal area - previous therapy with anthracyclines - previous therapy with anthracyclines

**INTERACTIONS**
Appendix 1: anthracyclines

**SIDE-EFFECTS**
- Common or very common
  - Uncommon
- Rare or very rare

**CONCEPTION AND CONTRACEPTION**
Ensure effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY**
Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**
No information available—manufacturer advises caution.

**MONITORING REQUIREMENTS**
Baseline investigations should include a full blood count, assessment of cardiac function measured by left ventricular ejection fraction, and measurement of serum concentrations of total bilirubin and total creatinine.

Full blood count and cardiac function should be monitored throughout treatment.

**PATIENT AND CARER ADVICE**
Photosensitivity Photosensitivity is a theoretical risk and patients should be advised to follow sun protection strategies.

**NATIONAL FUNDING/ACCESS DECISIONS**
NICE decisions
- Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin’s B-cell lymphoma (February 2014) NICE TA306

Pixantrone (Pixuvri®) monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin’s B-cell lymphoma in patients:
- who have previously been treated with rituximab, and
- who are receiving third- or fourth-line treatment, and
- if the manufacturer provides pixantrone with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta306

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
ELECTROLYTES: May contain Sodium

- Pixuvri (Servier Laboratories Ltd)

Pixantrone (as Pixantrone dimaleate) 29 mg

| 1 vial | £553.50 |

**ANTINEOPLASTIC DRUGS**
Azacitidine
14-Feb-2019

**INDICATIONS AND DOSE**
Treatment of intermediate-2 and high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, in adults who are not eligible for haematopoietic stem cell transplantation

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult local protocol)

**CONTRA-INDICATIONS**
Advanced malignant hepatic tumour

**CAUTIONS**
History of severe congestive heart failure - unstable cardiac disease (consider cardiopulmonary assessment before and during treatment) - unstable pulmonary disease (consider cardiopulmonary assessment before and during treatment)

**INTERACTIONS**
Appendix 1: azacitidine

**SIDE-EFFECTS**
- Common or very common

- Uncommon
  - Hepatic coma - hepatic failure - pyoderma gangrenosum - renal tubular acidosis

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

**PREGNANCY**
Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment (no information available)—monitor for adverse drug reactions.
Cytotoxic responsive malignancy

Stage III colon cancer, adjuvant following surgery (combination therapy)

- **BY MOUTH**
  - Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, recommended duration of treatment is 6 months, adjust dose according to tolerability—consult product literature

Metastatic colorectal cancer (monotherapy)

- **BY MOUTH**
  - Adult: 1.25 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Metastatic colorectal cancer (combination therapy)

- **BY MOUTH**
  - Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Advanced gastric cancer (first-line treatment in combination with a platinum based regimen)

- **BY MOUTH**
  - Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, alternatively 625 mg/m² twice daily given continuously, adjust dose according to tolerability—consult product literature

Locally advanced or metastatic breast cancer (second-line treatment as monotherapy after failure of a taxane and anthracycline regimen or where further anthracycline treatment is not indicated) Locally advanced or metastatic breast cancer (second-line treatment, in combination with docetaxel, where previous therapy included an anthracycline)

- **BY MOUTH**
  - Adult: 1.25 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 886.

- **CONTRA-INDICATIONS** Dihydropyrimidine dehydrogenase deficiency

- **CAUTIONS** Diabetes mellitus - diarrhoea or dehydration—consult product literature for guidance on dose modification and treatment interruption - electrolyte disturbances -history of angina pectoris - history of arrhythmias - history of significant cardiovascular disease - nervous system disease

- **INTERACTIONS** → Appendix 1: capecitabine

- **SIDE-EFFECTS**

Immune system and malignant disease

Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes’ C) colon cancer (April 2006) NICE TA100
Capecitabine alone or oxaliplatin combined with fluorouracil and folinic acid are options for adjuvant treatment following surgery for stage III (Dukes’ C) colon cancer.

www.nice.org.uk/TA100

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Tablet

Capecitabine (Non-proprietary)

- Capecitabine 150 mg tablets | 60 tablet (Roche Products Ltd) £40.02 DT = £30.00
- Capecitabine 300 mg tablets | 60 tablet (Roche Products Ltd) £76.04

- Capecitabine 500 mg tablets | 120 tablet (Roche Products Ltd) £240.00 DT + £225.72 | 120 tablet (Roche Products Ltd) £265.55 DT + £225.72 (Hospital only)

- Xeloda (Roche Products Ltd) £40.02 DT = £30.00
- Xeloda 500 mg tablets | 120 tablet (Roche Products Ltd) £265.55 DT + £225.72

Cladribine

Drug action
Cladribine is a nucleoside analogue that is cytotoxic particularly to lymphocytes and monocytes, inhibiting both DNA synthesis and repair. Its effect on B- and T-lymphocytes is thought to interrupt the cascade of immune events central to multiple sclerosis.

Indications and dose

Hairy cell leukaemia (specialist use only)
- By subcutaneous injection, or by intravenous infusion
  - Adult: (consult product literature or local protocols)

B-cell chronic lymphocytic leukaemia (specialist use only)
- By intravenous infusion
  - Adult: (consult product literature or local protocols)

Highly active relapsing-remitting multiple sclerosis (specialist use only)
- By mouth
  - Adult: (consult product literature or local protocols)

Important safety information

MHRA/ChM advice: Cladribine for leukaemia: reports of progressive multifocal encephalopathy (PML): stop treatment if PML suspected (December 2017)

The MHRA is aware of 3 confirmed cases of progressive multifocal encephalopathy (PML) that developed 6 months to several years after cladribine treatment for haematological conditions. An association between cladribine and prolonged lymphopenia has been reported.

PML should be considered in the differential diagnosis for patients with new or worsening neurological signs or symptoms. Patients should be monitored for signs and symptoms of new neurological dysfunction, and advised to seek urgent medical attention if they experience symptoms—stop treatment immediately if PML is suspected and ensure specialist investigation is received.

Contra-indications
- With oral use Active chronic hepatitis - active chronic tuberculosis - active malignancy - HIV infection - immunocompromised patients

Caution
General cautions
Acute infection - use irradiated blood only (haematology consultation advised)
Cytotoxic responsive malignancy 907

SPECIFIC CAUTIONS
- With intravenous use or subcutaneous use High tumour burden—consult product literature • symptomatic or severe bone marrow depression
- With oral use No prior exposure to varicella zoster virus • prior malignancy (consider if potential benefit outweighs risk)

CAUTIONS, FURTHER INFORMATION
- Immunosuppressive effect of cladribine
- With intravenous use or subcutaneous use Cladribine has potent and prolonged myelosuppressive and immunosuppressive effects. Patients treated with cladribine are more prone to serious bacterial, opportunistic infections, and viral infections, and prophylactic therapy should be considered in those at risk. Acute infections should be treated before initiating cladribine.
To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.
- Varicella zoster virus
- With oral use Manufacturer advises vaccination prior to initiation of therapy in patients who have no history of exposure to varicella zoster virus; delay treatment for 4–6 weeks after vaccination.

INTERACTIONS → Appendix 1: cladribine

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Common or very common Increased risk of infection

SPECIFIC SIDE-EFFECTS
- Common or very common
- With intravenous use Anaemia • anxiety • appetite decreased • arrhythmias • arthralgia • arthritis • ashenha • chest pain • chills • confusion • conjunctivitis • constipation • cough • diarrhoea • dizziness • dyspnoea • fever • flatulence • gastrointestinal discomfort • haemolytic anaemia • headache • hyperhidrosis • hypersensitivity • insomnia • joint disorders • malaise • muscle weakness • myalgia • myocardial ischaemia • nausea • neoplasms • oedema • pain • renal impairment • respiratory disorders • secondary malignancy • septic shock • skin reactions • thrombocytopenia • vomiting
- With oral use Alopecia • lymphopenia • rash
- With subcutaneous use Anaemia • anxiety • appetite decreased • arrhythmias • arthralgia • arthritis • ashenha • bone marrow disorders • chills • constipation • cough • diarrhoea • dizziness • dyspnoea • fever • gastrointestinal disorders • gastrointestinal pain • haemorrhage • headache • hyperhidrosis • hypotension • immunosuppression • insomnia • lymphopenia • malaise • miosis • myalgia • myocardial ischaemia • nausea • neutropenia • oedema • pain • respiratory disorders • secondary malignancy • sepsis • skin reactions • thrombocytopenia • vomiting

Uncommon
- With intravenous use Bone marrow disorders • hypereosinophilia • level of consciousness decreased • nerve disorders • neurotoxicity (with high doses) • paralysis • paraparesis • Stevens-Johnson syndrome • tumour lysis syndrome
- With subcutaneous use Ataxia • cachexia • confusion • drowsiness • eye inflammation • haemolytic anaemia • paraesthesia • polyneuropathy

Rare or very rare
- With intravenous use Heart failure
- With subcutaneous use Amyloidosis • cholelithiasis • depression • dysphagia • epilepsy • graft versus host disease • heart failure • hepatic failure • hypereosinophilia • pulmonary embolism • renal failure • severe cutaneous adverse reactions (SCARs) • speech disorder • tumour lysis syndrome

□ Frequency not known
- With oral use Malignancy

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during treatment and for at least 6 months after the last dose in men and women of childbearing potential.
- With oral use Manufacturer advises exclude pregnancy before each treatment course; if using a hormonal contraceptive, a barrier method should also be used for at least 4 weeks after the last dose of each course.

PREGNANCY Manufacturer advises avoid—teratogenic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

- With intravenous use or subcutaneous use Manufacturer advises avoid during treatment and for 6 months after the last dose—no information available.
- With oral use Manufacturer advises avoid during treatment and for 1 week after the last dose—no information available.

HEPATIC IMPAIRMENT
- With intravenous use Manufacturer advises caution (limited information available).
- With subcutaneous use Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment (no information available).
- With oral use Manufacturer advises avoid in moderate to severe impairment (no information available).

RENAL IMPAIRMENT
- With subcutaneous use Manufacturer advises caution in mild impairment; avoid in moderate-to-severe impairment.
- With intravenous use Manufacturer advises avoid in moderate-to-severe impairment—no information available.

PRE-TREATMENT SCREENING
- With oral use Manufacturer advises exclude HIV infection, active or latent tuberculosis and active or latent hepatitis before starting each treatment course—delay treatment until infection adequately treated.

MONITORING REQUIREMENTS
- Manufacturer advises monitor for malignancy—follow routine cancer screening guidelines.
- Manufacturer advises monitor for progressive multifocal leucoencephalopathy—perform a baseline MRI.
- Manufacturer advises monitor for haemolysis in patients who are or who become Coombs’ positive.
- Manufacturer advises haematological monitoring required—consult product literature.
- With intravenous use or subcutaneous use Renal and hepatic function should be monitored periodically as clinically indicated.

DIRECTIONS FOR ADMINISTRATION Litak® for subcutaneous use only—no dilution required; manufacturer advises patients may self-administer, after appropriate training. 
Leustat® for infusion use only.

HANDLING AND STORAGE
- Litak® Manufacturer advises store in a refrigerator (2–8°C).
- Leustat® Manufacturer advises store in a refrigerator (2–8°C).

PATIENT AND CARER ADVICE
Driving and skilled tasks
- With intravenous use or subcutaneous use Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and drowsiness.
Cytotoxic responsive malignancy

- NATIONAL FUNDING/ACCESS DECISIONS
  - NICE decisions
    - Cladribine tablets for treating relapsing–remitting multiple sclerosis (December 2017) NICE TA493
      - Cladribine tablets are recommended as an option for treating highly active multiple sclerosis in adults, only if the person has:
        - rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI, or
        - relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.
      - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
      - www.nice.org.uk/guidance/ta493

- Scottish Medicines Consortium (SMC) decisions
  - The Scottish Medicines Consortium has advised (February 2018) that cladribine ([Mavenclad](#)) is accepted for restricted use within NHS Scotland for the treatment of adults with:
    - rapidly evolving severe relapsing–remitting multiple sclerosis: patients with two or more relapses in the prior year whether on treatment or not, and at least one T1 gadolinium-enhancing lesion, or
    - sub-optimal therapy relapsing–remitting multiple sclerosis: patients with one or more relapses in the previous year while on disease modifying therapy, and at least one T1 gadolinium-enhancing lesion or nine T2 lesions.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - Litak (Lipomed GmbH)
      - Cladribine 2 mg per 1 ml Lipak 10mg/5ml solution for injection vials | 1 vial (PO) £165.00 (hospital only)
  - Solution for infusion
    - Leustat (Janssen-Cilag Ltd)
      - Cladribine 1 mg per 1 ml Leustat 10mg/10ml solution for infusion vials | 1 vial (PO) £159.70
    - Tableau
      - Mavenclad (Merck Serono Ltd)
        - Cladribine 10 mg Mavenclad 10mg tablets | 1 tablet (PO) £188.97 | 6 tablet (PO) £1,283.46

- Clofarabine

  - INDICATIONS AND DOSE
    - Relapsed or refractory acute lymphoblastic leukaemia in patients who have received at least two previous regimens
      - By intravenous infusion
    - Adult 18-20 years: (consult local protocol)

  - CAUTIONS
    - Cardiac disease

  - INTERACTIONS
    - Appendix 1: clofarabine

  - SIDE-EFFECTS
    - Common or very common
      - Alopecia, anaemia, appetite decreased, consciousness impaired, diarrhoea, dysphagia, eye disorders, eye inflammation, eye stinging, fever, gastrointestinal discomfort, gastritis, haematological disorders, haemorrhagic conjunctivitis (consider prophylactic corticosteroid eye drops), hyperuricaemia, leucopenia, myalgia, oral disorders, renal impairment, skin reactions, thrombocytopenia, urinary retention, vasculitis, visual disorders, vomiting
    - Uncommon
      - Arthralgia, dysphonia, headache, increased risk of infection, myalgia, nerve disorders, pain, paralysis, pericarditis, paresis, skin ulcer, throat pain
    - Rare or very rare
      - Arrhythmias

  - FREQUENCY NOT KNOWN
    - Antibiotic associated colitis, gastrointestinal disorders, hypernatraemia, pancreatitis, severe cutaneous adverse reactions (SCARs)

- CONCEPTION AND CONTRACEPTION
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- PREGNANCY
  - Manufacturer advises avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- BREAST FEEDING
  - Discontinue breast-feeding.

- HEPATIC IMPAIRMENT
  - Manufacturer advises use with caution in mild-to-moderate impairment; avoid in severe impairment—no information available.

- RENAL IMPAIRMENT
  - Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for infusion
    - ELECTROLYTES: May contain Sodium
      - Clofarabine (Non-proprietary)
        - Clofarabine 1 mg per 1 ml Clofarabine 20mg/20ml concentrate for solution for infusion vials | 1 vial (PO) £1,259.87–£1,326.18 (Hospital only)
      - Evoltra (Sanofi)
        - Clofarabine 1 mg per 1 ml Evoltra 20mg/20ml concentrate for solution for infusion vials | 1 vial (PO) £1,326.18 (Hospital only)

  - IMPORTANT SAFETY INFORMATION
    - Not all cytarabine preparations can be given by intrathecal injection—consult product literature.

- Cytarabine

  - DRUG ACTION
    - Cytarabine acts by interfering with pyrimidine synthesis.

  - INDICATIONS AND DOSE
    - Induction of remission of acute myeloblastic leukaemia
      - By intravenous infusion, or by intravenous injection, or by subcutaneous injection
      - Adult: (consult local protocol)

  - Lymphomatous meningitis
    - By intrathecal injection
      - Adult: (consult local protocol)

  - INTERACTIONS
    - Appendix 1: cytarabine

  - SIDE-EFFECTS
    - Common or very common
      - Alopecia, anaemia, appetite decreased, consciousness impaired, diarrhoea, dysphagia, eye disorders, eye inflammation, eye stinging, fever, gastrointestinal discomfort, gastrointestinal disorders, haemorrhagic conjunctivitis (consider prophylactic corticosteroid eye drops), hyperuricaemia, leucopenia, myalgia, oral disorders, renal impairment, skin reactions, thrombocytopenia, urinary retention, vasculitis, visual disorders, vomiting
    - Uncommon
      - Arthralgia, dysphonia, headache, increased risk of infection, myalgia, nerve disorders, pain, paralysis, pericarditis, paresis, skin ulcer, throat pain
    - Rare or very rare
      - Arrhythmias
    - Frequency not known
      - Acute respiratory distress syndrome (ARDS), amenorrhea, ataxia, azoospermia, bone marrow disorders, cardiomyopathy, cerebellar dysfunction, chest...

www.getintopharma.com

**CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Dose adjustments Reduce dose—consult product literature.

**MONITORING REQUIREMENTS**

Haematological monitoring. Cytarabine is a potent myelosuppressant and requires careful haematological monitoring.

**NATIONAL FUNDING/ACCESS DECISIONS**

**DEPOCYTE ®**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (July 2007) that liposomal cytarabine suspension (DepoCyte®) is not recommended for use within NHS Scotland for the intrathecal treatment of lymphomatous meningitis.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- **Cytarabine (Non-proprietary)**
  - Cytarabine 20 mg per 1 ml Cytarabine 100mg/5ml solution for injection Cytosafe vials | 5 vial | £20.48 (Hospital only)
  - Cytarabine 50mg/25ml solution for injection Cytosafe vials | 1 vial | £13.50
  - Cytarabine 100mg/5ml solution for injection vials | 5 vial | £30.00 (Hospital only) | 5 vial | £20.98
  - Cytarabine 100mg/5ml solution for injection vials | 1 vial | £13.50 (Hospital only)
  - Cytarabine 100 mg per 1 ml Cytarabine 1g/10ml solution for injection Cytosafe vials | 1 vial | £39.00 (Hospital only)
  - Cytarabine 1g/10ml solution for injection vials | 1 vial | £40.00-£49.78 (Hospital only) | 1 vial | £37.05-£39.00
  - Cytarabine 500mg/5ml solution for injection vials | 5 vial | £100.00 (Hospital only) | 5 vial | £89.78
  - Cytarabine 100mg/1ml solution for injection vials | 5 vial | £26.93
  - Cytarabine 2g/20ml solution for injection Cytosafe vials | 1 vial | £77.50
  - Cytarabine 2g/20ml solution for injection vials | 1 vial | £79.00-£88.92 (Hospital only) | 1 vial | £73.63-£77.50

**Suspension for injection**

- **DepoCyte** (Napp Pharmaceuticals Ltd)
  - Cytarabine liposomal pegylated 10 mg per 1 ml DepoCyte 50mg/5ml suspension for injection vials | 1 vial | £1,123.75 (Hospital only)

**Combinations available:** *Daunorubicin with cytarabine*, p. 900

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**Decitabine**

**DRUG ACTION** Decitabine is a pyrimidine analogue.

**INDICATIONS AND DOSE**

**Treatment of newly diagnosed acute myeloid leukaemia in patients over 65 years of age who are not candidates for standard induction chemotherapy**

- **BY INTRAVENOUS INFUSION**
  - Elderly: (consult local protocol)

**CAUTIONS** History of severe congestive heart failure - history of unstable cardiac disease

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**Fludarabine phosphate**

**INDICATIONS AND DOSE**

Initial treatment of advanced B-cell chronic lymphocytic leukaemia (CLL) or after first line treatment in patients with sufficient bone-marrow reserves

- **BY MOUTH**
  - Adult: 40 mg/m² for 5 days every 28 days, usually given for 6 cycles
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**CONTRA-INDICATIONS** Haemolytic anaemia

**CAUTIONS** Increased susceptibility to skin cancer - worsening of existing skin cancer

**CAUTIONS, FURTHER INFORMATION**

Immunosuppression Fludarabine has a potent and prolonged immunosuppressive effect. Patients treated with fludarabine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in those at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.

Co-trimoxazole is used to prevent pneumocystis infection.

**INTERACTIONS** → Appendix 1: fludarabine

**SIDE-EFFECTS**

**COMMON SIDE-EFFECTS**

- Common or very common Anaemia - diarrhoea - epistaxis - fever - headache - hypersensitivity - increased risk of infection - leucopenia - nausea - neutropenia - sepsis - stomatitis - thrombocytopenia - vomiting

- Uncommon Acute febrile neutrophilic dermatosis - pancytopenia

- Frequency not known Gastrointestinal disorders - interstitial lung disease

**CONCEPTION AND CONTRACEPTION** Men must avoid fathering a child during and for 3 months after treatment.

**PREGNANCY** Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available.

**RENAL IMPAIRMENT** Manufacturer advises caution if creatinine clearance less than 30 mL/minute—no information available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

**ELECTROLYTES:** May contain Potassium, sodium

- **Dacogen** (Janssen-Cilag Ltd)
  - Decitabine 50 mg Dacogen 50mg powder for concentrate for solution for infusion vials | 1 vial | £97.06

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**BNF 78**

**Cytotoxic responsive malignancy 909**

**Fludarabine phosphate**

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- **BY MOUTH**
  - Adult: 40 mg/m² for 5 days every 28 days, usually given for 6 cycles
  - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

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- Uncommon Acute febrile neutrophilic dermatosis - pancytopenia

- Frequency not known Gastrointestinal disorders - interstitial lung disease

**CONCEPTION AND CONTRACEPTION** Men must avoid fathering a child during and for 3 months after treatment.

**PREGNANCY** Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available.

**RENAL IMPAIRMENT** Manufacturer advises caution if creatinine clearance less than 30 mL/minute—no information available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

**ELECTROLYTES:** May contain Potassium, sodium

- **Dacogen** (Janssen-Cilag Ltd)
  - Decitabine 50 mg Dacogen 50mg powder for concentrate for solution for infusion vials | 1 vial | £97.06

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**Decitabine**

**DRUG ACTION** Decitabine is a pyrimidine analogue.

**INDICATIONS AND DOSE**

**Treatment of newly diagnosed acute myeloid leukaemia in patients over 65 years of age who are not candidates for standard induction chemotherapy**

- **BY INTRAVENOUS INFUSION**
  - Elderly: (consult local protocol)

**CAUTIONS** History of severe congestive heart failure - history of unstable cardiac disease

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**www.getintopharma.com**
Cytotoxic responsive malignancy

Fludarabine monotherapy for the first-line treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of progressive disease.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Fludarabine phosphate (Non-proprietary)
      - Fludarabine phosphate 25 mg per 1 ml Fludarabine phosphate 50mg/2ml concentrate for solution for injection vials | 1 vial | £155.00 (Hospital only)
    - **Tablet**
      - Fludara (Sanofi)
        - Fludarabine phosphate 10 mg Fludara 10mg tablets | 15 tablet | £302.48 (Hospital only) | 20 tablet | £403.31 (Hospital only)
    - Fludarabine phosphate 50 mg Fludarabine phosphate 50mg powder for solution for injection vials | 5 vial | £735.34 (Hospital only)

### Fluorouracil

**INDICATIONS AND DOSE**

Treatment of some solid tumours including gastrointestinal tract cancers and breast cancer \(^1\) in combination with folinic acid in advanced colorectal cancer

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRA-ARTERIAL INFUSION**
- **Adult** (consult product literature)

**CONTRA-INDICATIONS** Bone marrow depression (after treatment with radiotherapy or other antineoplastic agents) - complete or near complete absence of dihydouracil dehydrogenase activity (increased risk of severe, life-threatening, or fatal toxicity)—consult product literature - serious infections

**CAUTIONS** History of heart disease - partial dihydouracil dehydrogenase deficiency—consult product literature

**INTERACTIONS** → Appendix 1: fluorouracil

**SIDE-EFFECTS**

- **Common or very common** Agranulocytosis, alopecia, anaemia, anal inflammation, appetite decreased, asthenia, bone marrow disorders, bronchospasm, diarrhoea, gastrointestinal disorders, haemorrhage, hand and foot syndrome (long term use), healing impaired, immunosuppression, increased risk of infection, ischaemic heart disease, leucopenia, malaise, mucositis, nausea, neutropenia, skin reactions, stomatitis, thrombocytopenia, vomiting
- **Uncommon** Arrhythmias, cardiac inflammation, cardiogenic shock, cardiomyopathy congestive, dehydration, diziness, drowsiness, euphoric mood, eye disorders, eye inflammation, headache, heart failure, hepatic disorders, hypotension, movement disorders, myocardial infarction, nail discoloration, nail disorders, nerve disorders, ovulation disorder, parkinsonism, photosensitivity reaction, seizures, spermatogenesis disorder, vision disorders
- **Rare or very rare** Biliary sclerosis, cardiac arrest, cerebral ischaemia, cholecytitis, coma, confusion, embolism and thrombosis, encephalopathy, fever, muscle weakness, peripheral vascular disease, renal failure, seizure, speech impairment, sudden cardiac death
- **Frequency not known** Vein discolouration

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**Fludarabine**

- **Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (February 2007)** NICE TA119
  - Fludarabine monotherapy is **not** recommended for the first-line treatment of chronic lymphocytic leukaemia.
  - www.nice.org.uk/TA119
- **Fludarabine for the treatment of B-cell chronic lymphocytic leukaemia (September 2001)** NICE TA29
  - Oral fludarabine is recommended for the second-line treatment of B-cell chronic lymphocytic leukaemia in patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combined chemotherapy of either:
    - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
    - cyclophosphamide, doxorubicin and prednisolone (CAP)
    - cyclophosphamide, vincristine and prednisolone (CVP)
  - Intraocular fludarabine should only be used when oral fludarabine is contra-indicated.
  - www.nice.org.uk/TA29
- **Scottish Medicines Consortium (SMC) decisions**
  - The Scottish Medicines Consortium has advised (October 2006) that fludarabine is accepted for restricted use for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of progressive disease.

- **Immune system and malignant disease**
- **Monitor for signs of haemolysis.**
- **RENAL IMPAIRMENT**
- **BREAST FEEDING**
- **PREGNANCY** Avoid (embryotoxic and teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- **BREAST FEEDING** Discontinue breast-feeding.
- **FLUSHING**
- **INTERACTIONS**
- **CONTRA-INDICATIONS** Bone marrow depression (after treatment with radiotherapy or other antineoplastic agents) - complete or near complete absence of dihydouracil dehydrogenase activity (increased risk of severe, life-threatening, or fatal toxicity)—consult product literature - serious infections
- **CAUTIONS** History of heart disease - partial dihydouracil dehydrogenase deficiency—consult product literature
- **INTERACTIONS** → Appendix 1: fluorouracil
  - **SIDE-EFFECTS**
    - **Common or very common** Agranulocytosis, alopecia, anaemia, anal inflammation, appetite decreased, asthenia, bone marrow disorders, bronchospasm, diarrhoea, gastrointestinal disorders, haemorrhage, hand and foot syndrome (long term use), healing impaired, immunosuppression, increased risk of infection, ischaemic heart disease, leucopenia, malaise, mucositis, nausea, neutropenia, skin reactions, stomatitis, thrombocytopenia, vomiting
    - **Uncommon** Arrhythmias, cardiac inflammation, cardiogenic shock, cardiomyopathy congestive, dehydration, diziness, drowsiness, euphoric mood, eye disorders, eye inflammation, headache, heart failure, hepatic disorders, hypotension, movement disorders, myocardial infarction, nail discoloration, nail disorders, nerve disorders, ovulation disorder, parkinsonism, photosensitivity reaction, seizures, spermatogenesis disorder, vision disorders
    - **Rare or very rare** Biliary sclerosis, cardiac arrest, cerebral ischaemia, cholecytitis, coma, confusion, embolism and thrombosis, encephalopathy, fever, muscle weakness, peripheral vascular disease, renal failure, seizure, speech impairment, sudden cardiac death
    - **Frequency not known** Vein discolouration

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**Fludara**

- **Fludara (Sanofi)**
- **Fludara phosphate 10 mg Fludara 10mg tablets | 15 tablet | £302.48 (Hospital only) | 20 tablet | £403.31 (Hospital only)
- **Fludara phosphate 50 mg Fludara 50mg powder for solution for injection vials | 5 vial | £735.34 (Hospital only)
Gemcitabine

23-Jul-2018

● INDICATIONS AND DOSE

First-line treatment for locally advanced or metastatic non-small cell lung cancer (as monotherapy in elderly patients and in palliative treatment; otherwise in combination with cisplatin) | Treatment of locally advanced or metastatic pancreatic cancer | Treatment of advanced or metastatic bladder cancer (in combination with cisplatin) | Treatment of locally advanced or metastatic epithelial ovarian cancer which has relapsed after a recurrence-free interval of at least 6 months following previous platinum-based therapy (in combination with carboplatin) | Treatment of metastatic breast cancer which has relapsed after previous chemotherapy including an anthracycline (in combination with paclitaxel)

▶ BY INTRAVENOUS INFUSION

▶ Adults: (consult local protocol)

● INTERACTIONS | Appendix 1: gemcitabine

● SIDE-EFFECTS

▶ Common or very common Alopecia - anaemia - appetite decreased - asthenia - back pain - bone marrow depression - chills - constipation - cough - diarrhoea - drowsiness - dyspnoea - fever - haematuria - headache - hyperhidrosis - influenza like illness - insomnia - leucopenia - myalgia - nausea - neutropenia - oedema - oral disorders - proteinuria - rhiinitis - skin reactions - thrombocytopenia - vomiting

▶ Uncommon Respiratory disorders

▶ Rare or very rare Capillary leak syndrome - hypotension - myocardial infarction - posterior reversible encephalopathy syndrome (PRES) - severe cutaneous adverse reactions (SCARs) - skin ulcer - thrombocytopenia

▶ Frequency not known Arrhythmias - coagulopathy - cyanosis - drug reaction with eosinophilia and systemic symptoms (DRESS) - fever - hypotension - infusional reactions - neutropenia - pericarditis - pyrexia - rash - tachycardia - urticaria

SIDE-EFFECTS, FURTHER INFORMATION Gemcitabine should be discontinued if signs of microangiopathic haemolytic anaemia occur.

● CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during treatment. Men must avoid fathering a child during and for 6 months after treatment.

● PREGNANCY Avoid (teratogenic). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

● BREAST FEEDING Discontinue breast-feeding.

● HEPATIC IMPAIRMENT Manufacturer advises caution

● RENAL IMPAIRMENT Manufacturer advises caution

● PRE-TREATMENT SCREENING Manufacturer advises caution

● MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for injection

▶ Fluorouracil (Non-proprietary) Fluorouracil (as Fluorouracil sodium) 25 mg per 1 ml Fluorouracil 500mg/20ml solution for injection vials | 10 vial (PPO) £64.00 (Hospital only) Fluorouracil 250mg/10ml solution for injection vials | 5 vial (PPO) £24.00 (Hospital only) Fluorouracil (as Fluorouracil sodium) 50 mg per 1 ml Fluorouracil 1g/20ml solution for injection vials | 1 vial (PPO) £12.16-£12.80 Fluorouracil 500mg/10ml solution for injection vials | 1 vial (PPO) £6.08-£6.40 | 5 vial (PPO) £32.00 (Hospital only)

Solution for infusion

▶ Fluorouracil (Non-proprietary) Fluorouracil (as Fluorouracil sodium) 25 mg per 1 ml Fluorouracil 2.5g/100ml solution for infusion vials | 1 vial (PPO) £32.00 (Hospital only) | 1 vial (PPO) £32.00 Fluorouracil (as Fluorouracil sodium) 50 mg per 1 ml Fluorouracil 5g/100ml solution for infusion vials | 1 vial (PPO) £64.00 (Hospital only) | 1 vial (PPO) £64.00-£64.00 Fluorouracil 2.5g/50ml solution for infusion vials | 1 vial (PPO) £32.00 (Hospital only) | 1 vial (PPO) £32.00 (Hospital only)

www.getintopharma.com
Patients currently receiving gemcitabine in combination with carboplatin should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA476

- Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer (September 2017)
  NICE TA476

Gemcitabine with paclitaxel as albumin-bound nanoparticles (nab-paclitaxel) is recommended as an option for untreated metastatic adenocarcinoma of the pancreas in adults, only if:
- other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy, and
- the manufacturer provides nab-paclitaxel with the discount agreed in the patient access scheme.

Patients whose treatment with nab-paclitaxel was started before this guidance was published, should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA476

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2006) that gemcitabine (Gemzar®) is accepted for restricted use within NHS Scotland for the treatment of metastatic breast cancer, which has relapsed following previous chemotherapy including an anthracycline (unless contra-indicated).

### MEDICINAL FORMS

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<thead>
<tr>
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<td>Gemcitabine 1g/26.3ml concentrate for solution for infusion vials</td>
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<td>Gemcitabine (as Gemcitabine hydrochloride) 2 gram</td>
<td>Gemcitabine 2g/20ml concentrate for solution for infusion vials</td>
</tr>
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<td>Gemcitabine 2g/52.6ml concentrate for solution for infusion vials</td>
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<tbody>
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</tbody>
</table>

### Mercaptopurine

(6-Mercaptopurine)

#### INDICATIONS AND DOSE

**Severe acute Crohn’s disease** | **Maintenance of remission of Crohn’s disease** | **Ulcerative colitis**

- **BY MOUTH**
  - Adult: 1–1.5 mg/kg daily, some patients may respond to lower doses

**Acute leukaemias** | **Chronic myeloid leukaemia**

- **BY MOUTH USING TABLETS**
  - Adult: Initially 2.5 mg/kg daily, adjusted according to response, alternatively initially 50–75 mg/m² daily, adjusted according to response

- **BY MOUTH USING ORAL SUSPENSION**
  - Adult: Initially 25–75 mg/m² daily, adjusted according to response

#### DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Manufacturer advises reduce dose to one-quarter of the usual dose with concurrent use of allopurinol.

#### DOSE EQUIVALENT AND CONVERSION

- Mercaptopurine tablets and Xaluprine® oral suspension are not bioequivalent, haematological monitoring is advised when switching formulations.

#### UNLICENSED USE

Not licensed for use in severe ulcerative colitis and Crohn’s disease.

### IMPORTANT SAFETY INFORMATION

#### SAFE PRACTICE

Mercaptopurine has been confused with mercaptamine; care must be taken to ensure the correct drug is prescribed and dispensed.

#### RISKS OF INCORRECT DOING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

#### CONTRA-INDICATIONS

Absent thiopurine methyltransferase activity

#### CAUTIONS

Reduced thiopurine methyltransferase activity

#### CAUTIONS, FURTHER INFORMATION

Thiopurine methyltransferase. The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, thioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

#### INTERACTIONS

→ Appendix 1: mercaptopurine

#### SIDE-EFFECTS

- **Common or very common** Anaemia - appetite decreased - bone marrow depression - diarrhoea - hepatic disorders - hepatotoxicity (more common at high doses) - leucopenia - nausea - oral disorders - thrombocytopenia - vomiting

- **Uncommon** Arthralgia - fever - increased risk of infection - neutropenia - pancreatitis - rash

- **Rare or very rare** Alopecia - face oedema - intestinal ulcer - neoplasms - oligozoospermia

- **Frequency not known** Photosensitivity reaction

#### CONCEPTION AND CONCEPTION

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

#### PREGNANCY

Avoid (teratogenic). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

#### BREAST FEEDING

Discontinue breast-feeding.
**Methotrexate**

**01-Feb-2019**

**DRUG ACTION** Methotrexate inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines.

**INDICATIONS AND DOSE**

**Severe Crohn’s disease**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 25 mg once weekly until remission induced; maintenance 15 mg once weekly

**Maintenance of remission of severe Crohn’s disease**
- **BY MOUTH**
  - Adult: 10–25 mg once weekly

**Moderate to severe active rheumatoid arthritis**
- **BY MOUTH**
  - Adult: 7.5 mg once weekly, adjusted according to response; maximum 20 mg per week

**Severe active rheumatoid arthritis**
- **BY INTRAMUSCULAR INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 7.5 mg once weekly, then increased in steps of 2.5 mg once weekly, adjusted according to response; maximum 25 mg per week

**Neoplastic diseases**
- **BY MOUTH, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION, OR BY INTRA-ARTERIAL INFUSION, OR BY INTRAMUSCULAR INJECTION, OR BY INTRATHecal INJECTION**
- Adult: (consult product literature)

**Severe psoriasis unresponsive to conventional therapy (specialist use only)**
- **BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 2.5–10 mg once weekly, then increased in steps of 2.5–5 mg, adjusted according to response, dose to be adjusted at intervals of at least 1 week; usual dose 7.5–15 mg once weekly, stop treatment if inadequate response after 3 months at the optimum dose; maximum 30 mg per week

**SIDE-EFFECTS**
- **Common or very common**
  - With intrathecal use: Nocrotising demyelinating leukoencephalopathy; neuropathy
  - With oral use: Anaemia; appetite decreased; diarrhoea; drowsiness; fatigue; gastrointestinal discomfort; headache; increased risk of infection; leucopenia; nausea; oral disorders; respiratory disorders; skin reactions; throat ulcer; thrombocytopenia; vomiting
  - With parenteral use: Anaemia; appetite decreased; chest pain; cough; diarrhoea; drowsiness; dyspnoea; fatigue; fever; gastrointestinal discomfort; headache; leucopenia; malaise; nausea; oral disorders; respiratory disorders; skin reactions; throat complaints; thrombocytopenia; vomiting

**UNLICENSED USE** Not licensed for use in severe Crohn’s disease.

**IMPORTANT SAFETY INFORMATION**

Note that the dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:

- the patient is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

**CONTRA-INDICATIONS** Active infection (in non-malignant conditions); ascites; immunodeficiency syndromes (in non-malignant conditions); significant pleural effusion

**CAUTIONS** Photosensitivity—psoriasis lesions aggravated by UV radiation (skin ulceration reported); diarrhoea—extreme caution in blood disorders (avoid if severe); peptic ulceration—risk of accumulation in pleural effusion or ascites—dren before treatment; ulcerative colitis—ulcerative stomatitis

**INTERACTIONS** → Appendix 1: methotrexate

**UNLICENSED USE** Not licensed for use in severe Crohn’s disease.
osteoporosis · photosensitivity reaction · rheumatoid arthritis aggravated · seizure · severe cutaneous adverse reactions (SCARs) · vasculitis · vertigo · vulvovaginal disorders

- With parenteral use Agranulocytosis · alopecia · arthralgia · bone marrow disorders · confusion · cystitis · depression · diabetes mellitus · drug toxicity · dysuria · gastrointestinal disorders · haemorrhage · healing impaired · hepatic disorders · increased risk of infection · lipatropathy · local reaction · myalgia · neoplasms · osteoporosis · pain · paraesthesia · photosensitivity reaction · rheumatoid arthritis aggravated · seizure · severe cutaneous adverse reactions (SCARs) · sterile abscess · vasculitis · vertigo · vulvovaginal disorders

- Rare or very rare

- With oral use Azotemia · brain oedema · cognitive impairment · conjunctivitis · cough · dyspnoea · eosophagitis · gynaecomastia · hypertension · immune deficiency · infertility · insomnia · lymphadenopathy · meningitis aseptic · menstrual disorder · mood altered · muscle weakness · nail discoulouration · neutropenia · oligozoospermia · pain · pancreatitis · paresis · pericardial disorders · pericarditis · proteinuria · psychosis · radiation injuries · renal impairment · retinopathy · sensation abnormal · sepsis · sexual dysfunction · speech impairment · stress fracture · taste metallic · telangiectasia · tinnitus · visual impairment

- With parenteral use Aproea · asthma-like conditions · azotemia · conjunctivitis · embolism and thrombosis · eosophagitis · gynaecomastia · hypertension · immune deficiency · infertility · influenza like illness · insomnia · lymphadenopathy · meningitis · meningitis aseptic · menstrual disorder · mood altered · muscle weakness · nail discoulouration · necrosis · neutropenia · paralysis · pericardial disorders · pericarditis · proteinuria · reactivation of infection · renal impairment · retinopathy · sepsis · sexual dysfunction · sperm abnormalities · stress fracture · taste altered · telangiectasia · vision disorders

- Frequency not known

- With oral use Encephalopathy

- With parenteral use Aphihasia · chills · cognitive disorder · defective coagulation · dizziness · hangnails · leukemia · leukoencephalopathy · metabolic change · mucositis · nephropathy · pancreatitis · pulmonary oedema · skin ulcer · sudden death · tinnitus

SIDE-EFFECTS, FURTHER INFORMATION

Give folic acid to reduce side-effects. Folic acid decreases mucosal and gastrointestinal side-effects of methotrexate and may prevent hematotoxicity; there is no evidence of a reduction in haematological side-effects.

Withdraw treatment if ulcerative stomatitis develops—may be first sign of gastro-intestinal toxicity.

Treatment with folic acid (as calcium folinate) may be required in acute toxicity.

- CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception during and for at least 6 months after treatment in men and women.

- PREGNANCY

Avoid (teratogenic; fertility may be reduced during therapy but this may be reversible).

- BREAST FEEDING

Discontinue breast-feeding—present in milk.

- HEPATIC IMPAIRMENT

When used for malignancy, avoid in severe hepatic impairment—consult local treatment protocol for details. Avoid with hepatic impairment in non-malignant conditions—dose-related toxicity.

- RENAL IMPAIRMENT

Risk of nephrotoxicity at high doses. Avoid in severe impairment.

Dose adjustments Reduce dose.

- PRE-TREATMENT SCREENING

Exclude pregnancy before treatment.

Patients should have full blood count and renal and liver function tests before starting treatment.

- MONITORING REQUIREMENTS

- In view of reports of blood dyscrasias (including fatalities) and liver cirrhosis with low-dose methotrexate patients should:

  - have full blood count and renal and liver function tests repeated every 1–2 weeks until therapy stabilised, thereafter patients should be monitored every 2–3 months.

  - be advised to report all symptoms and signs suggestive of infection, especially sore throat

- Local protocols for frequency of monitoring may vary.

- Treatment with folic acid (as calcium folinate) may be required in acute toxicity.

- PRESCRIBING AND DISPENSING INFORMATION

Folic acid following methotrexate administration helps to prevent methotrexate-induced mucositis and myelosuppression.

The licensed routes of administration for parenteral preparations vary—further information can be found in the product literature for the individual preparations.

- PATIENT AND CARER ADVICE

Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).

Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.

Patients should be counselled on the dose, treatment booklet, and the use of NSAIDs.

Methotrexate treatment booklets Methotrexate treatment booklets should be issued where appropriate.

In England, Wales, and Northern Ireland, they are available for purchase from:

- Gorse Street, Chadderton
- Oldham
- OLS 9QH
- Tel: 0845 610 1112

GP practices can obtain supplies through their Local Area Team stores.

NHS Hospitals can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com.

In Scotland, treatment booklets can be obtained by emailing stockholders.dppas@raps.org.uk or by fax on 0131 629 9967.

These booklets include advice for adults taking oral methotrexate for inflammatory conditions, and a section for recording results of blood tests and dosage information.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection.

- Tablet

<table>
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<tr>
<th>Methotrexate (Non-proprietary)</th>
<th>Methotrexate 2.5 mg</th>
<th>Methotrexate 2.5mg tablets</th>
<th>24 tablet</th>
<th>£1.52–£3.75</th>
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- Solution for injection

- Methotrexate (Non-proprietary)

Methotrexate (as Methotrexate sodium) 2.5 mg per 1 ml Methotrexate 5mg/2ml solution for injection vials | 5 vial | £36.00 (Hospital only) |
Nelarabine

- INDICATIONS AND DOSE
  - T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma in patients who have relapsed or who are refractory after receiving at least two previous regimens
  - BY INTRAVENOUS INFUSION
  - Adult: (consult local protocol)

- CAUTIONS
  - Previous or concurrent craniospinal irradiation (increased risk of neurotoxicity) prior or concurrent intrathecal chemotherapy (increased risk of neurotoxicity)

- INTERACTIONS
  - Appendix 1: nelarabine

- SIDE-EFFECTS
  - Common or very common
  - Rare or very rare
    - Rhabdomyolysis

- Frequency not known
  - Progressive multifocal leukoencephalopathy (PML)

- SIDE-EFFECTS, FURTHER INFORMATION
  - If neurotoxicity occurs, treatment should be discontinued.

- CONCEPTION AND CONTRACEPTION
  - Manufacturer advises effective contraception during and for at least 3 months after treatment in men and women.

- PREGNANCY
  - Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- BREAST FEEDING
  - Discontinue breast-feeding.

- MONITORING REQUIREMENTS
  - Neurotoxicity Close monitoring for neurological events is strongly recommended—discontinue if neurotoxicity occurs.
Pemetrexed for the treatment of non-small cell lung cancer

**INDICATIONS AND DOSE**

Treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (in combination with cisplatin). First-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (in combination with cisplatin). Second-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (monotherapy). Maintenance treatment in locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology that has not progressed immediately following platinum-based chemotherapy (monotherapy).

**DRUG ACTION**
Pemetrexed inhibits thymidylate transferase and other folate-dependent enzymes.

**CAUTIONS**
- Diabetes - history of cardiovascular disease - prophylactic folic acid supplementation required (consult product literature).
- Renal disorder - mucositis - nausea - neuropathy sensory - oedema - pain - renal disorder - skin reactions - stomatitis - vomiting

**SIDE-EFFECTS**
- Common or very common Appetite decreased - fatigue - mucositis - nausea - neuropathy sensory - oedema - pain - renal disorder - skin reactions - stomatitis - vomiting
- Conception and contraception Manufacturer advises effective contraception during treatment. Men must avoid fathering a child during and for 6 months after treatment.
- Pregnancy Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- Breast feeding Discontinue breast-feeding.
- Renal impairment Manufacturer advises avoid if creatinine clearance less than 45 mL/minute — no information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium has advised (March 2008) that the use of nelerabine (Atriance®) within NHS Scotland is restricted to bridging treatment before stem cell transplantation.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Electrolytes**: May contain Sodium
- Atriance® (Novartis Pharmaceuticals UK Ltd) ▼
  - NERELABINE 5 mg per 1 ml
  - Atriance 250mg/50mL solution for infusion
  - 6 vial £1,332.00

**Pemetrexed**

**DRUG ACTION**
Pemetrexed inhibits thymidylate transferase and other folate-dependent enzymes.

**INDICATIONS AND DOSE**

Treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (in combination with cisplatin).

First-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (in combination with cisplatin).

Second-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (monotherapy).

Maintenance treatment in locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology that has not progressed immediately following platinum-based chemotherapy (monotherapy).

- by intravenous infusion
- Adult: (consult local protocol)

**CAUTIONS**
- Diabetes - history of cardiovascular disease - prophylactic folic acid supplementation required (consult product literature).
- Renal disorder - mucositis - nausea - neuropathy sensory - oedema - pain - renal disorder - skin reactions - stomatitis - vomiting

**SIDE-EFFECTS**
- Common or very common Appetite decreased - fatigue - mucositis - nausea - neuropathy sensory - oedema - pain - renal disorder - skin reactions - stomatitis - vomiting
- Conception and contraception Manufacturer advises effective contraception during treatment. Men must avoid fathering a child during and for 6 months after treatment.
- Pregnancy Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- Breast feeding Discontinue breast-feeding.
- Renal impairment Manufacturer advises avoid if creatinine clearance less than 45 mL/minute — no information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Pemetrexed for the treatment of non-small cell lung cancer (August 2007) NICE TA124
  - Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small cell lung cancer which has previously been treated with chemotherapy.
  - www.nice.org.uk/TA124
- Pemetrexed for the first-line treatment of non-small cell lung cancer (September 2009) NICE TA181
  - Pemetrexed, in combination with cisplatin, is an option for the first-line treatment of locally advanced or metastatic non-small cell lung cancer only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.
  - www.nice.org.uk/TA181
- Pemetrexed for the maintenance treatment of non-small cell lung cancer (updated August 2017) NICE TA190
  - Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.
  - www.nice.org.uk/TA190
- Pemetrexed maintenance treatment for non-squamous non-small cell lung cancer after pemetrexed and cisplatin (August 2016) NICE TA402
  - Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in patients when:
    - their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy
    - their Eastern Cooperative Oncology Group performance status is 0 or 1 at the start of maintenance treatment, and,
    - the company provides the drug according to the terms of the commercial access agreement as agreed with NHS England.
  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA402
- Pemetrexed for the treatment of malignant pleural mesothelioma (January 2008) NICE TA135
  - Pemetrexed is an option for the treatment of malignant pleural mesothelioma only in patients who have a WHO performance status of 0 or 1 [WHO performance status is a measure of the ability to perform ordinary tasks], who are considered to have advanced disease and for whom surgical resection is considered inappropriate.
  - www.nice.org.uk/TA135

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium has advised (September 2008) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland as monotherapy for the second-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. It is restricted for use in patients with good performance status who would otherwise be eligible for docetaxel treatment.

The Scottish Medicines Consortium has advised (February 2010) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland in combination with cisplatin for the first-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. It is restricted to patients in whom histology has been confirmed as adenocarcinoma or large cell carcinoma.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Pemetrexed (Non-proprietary)
  - Pemetrexed (as Pemetrexed ditroremo) 25 mg per 1 mL
  - Pemetrexed 100mg/4mL concentrate for solution for infusion 1 vial £140.00
  - Pemetrexed 500mg/20mL concentrate for solution for infusion 1 vial £700.00
  - Pemetrexed 1000mg/40mL concentrate for solution for infusion 1 vial £1,400.00

www.getintopharma.com
Powder for solution for infusion

**ELECTROLYTES:** May contain Sodium

- **Pemetrexed (Non-proprietary)**
  - Pemetrexed (as Pemetrexed disodium) 100 mg: Pemetrexed 100mg powder for concentrate for solution for infusion vials | 1 vial | £160.00–£245.00 (Hospital only)
  - Pemetrexed (as Pemetrexed disodium) 500 mg: Pemetrexed 500mg powder for concentrate for solution for infusion vials | 1 vial | £800.00–£1310.00 (Hospital only)
  - **Alimta** (Eli Lilly and Company Ltd)
  - Pemetrexed (as Pemetrexed disodium) 100 mg: Alimta 100mg powder for concentrate for solution for infusion vials | 1 vial | £600.00 (Hospital only)
  - Pemetrexed (as Pemetrexed disodium) 500 mg: Alimta 500mg powder for concentrate for solution for infusion vials | 1 vial | £800.00 (Hospital only)

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**Tegafur with gimeracil and oteracil**

06-Feb-2019

- **DRUG ACTION** Tegafur is a prodrug of fluorouracil. Gimeracil inhibits the degradation of fluorouracil and oteracil decreases the activity of fluorouracil in normal gastrointestinal mucosa.

- **INDICATIONS AND DOSE**
  - Treatment of advanced gastric cancer when used in combination with cisplatin
  - **BY MOUTH**
    - Adult: (consult local protocol)

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**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CONTRA-INDICATIONS**
  - Dihydropyrimidine dehydrogenase deficiency
- **INTERACTIONS**
  - Appendix 1: tegafur
- **SIDE-EFFECTS**
  - Common or very common: Anemia, appetite abnormal, asthenia, constipation, cough, decreased leucocytes, dehydration, diarrhoea, dizziness, dry mouth, dysphagia, dyspnoea, electrolyte imbalance, embolism and thrombosis, eye disorders, eye inflammation, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, headache, hearing impairment, hiccups, hyperbilirubinaemia, hypotension, hypoproteinaemia, hypotension, insomnia, nausea, nerve disorders, neutropenia, oral disorders, taste altered, thrombocytopenia, vision disorders, vomiting
  - Uncommon: Aerophobia, allergic rhinitis, alopecia, angina pectoris, anxiety, aphasia, arrhythmias, ascites, breast abnormalities, burping, cerebrovascular insufficiency, chills, coagulation disorders, confusion, depression, drowsiness, dysphoria, ear discomfort, encephalopathy, eosinophilia, fever, gout, hallucination, heart failure, hemiparesis, hyperaemia, hyperglobulinaemia, hyperglycaemia, hyperlipidaemia, hypertrichosis, hypovolaemic shock, increased leucocytes, increased risk of infection, joint disorders, limb discomfort, loss of consciousness, memory loss, movement disorders, mucositis, muscle complaints, muscle weakness, myocardial infarction, nail disorders, nasal complaints, neoplasm complications, nephrotoxicity, oedema, oesophageal spasm, pain, palpitations, pancytopenia, pericardial effusion, personality disorder, renal impairment, seizure, sensation abnormal, sepsis, sexual dysfunction, skin reactions, smell altered, sweat changes, syncope, throat complaints, thrombocytosis, tremor, urinary frequency increased, vasodilatation, vertigo, weight changes

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**Tegafur with gimeracil and oteracil**

06-Feb-2019

- **DRUG ACTION** Tegafur is a prodrug of fluorouracil. Gimeracil inhibits the degradation of fluorouracil and oteracil decreases the activity of fluorouracil in normal gastrointestinal mucosa.

- **INDICATIONS AND DOSE**
  - Treatment of advanced gastric cancer when used in combination with cisplatin
  - **BY MOUTH**
    - Adult: (consult local protocol)

---

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CONTRA-INDICATIONS**
  - Dihydropyrimidine dehydrogenase deficiency
- **INTERACTIONS**
  - Appendix 1: tegafur
- **SIDE-EFFECTS**
  - Common or very common: Anemia, appetite abnormal, asthenia, constipation, cough, decreased leucocytes, dehydration, diarrhoea, dizziness, dry mouth, dysphagia, dyspnoea, electrolyte imbalance, embolism and thrombosis, eye disorders, eye inflammation, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, headache, hearing impairment, hiccups, hyperbilirubinaemia, hypotension, hypoproteinaemia, hypotension, insomnia, nausea, nerve disorders, neutropenia, oral disorders, taste altered, thrombocytopenia, vision disorders, vomiting
  - Uncommon: Aerophobia, allergic rhinitis, alopecia, angina pectoris, anxiety, aphasia, arrhythmias, ascites, breast abnormalities, burping, cerebrovascular insufficiency, chills, coagulation disorders, confusion, depression, drowsiness, dysphoria, ear discomfort, encephalopathy, eosinophilia, fever, gout, hallucination, heart failure, hemiparesis, hyperaemia, hyperglobulinaemia, hyperglycaemia, hyperlipidaemia, hypertrichosis, hypovolaemic shock, increased leucocytes, increased risk of infection, joint disorders, limb discomfort, loss of consciousness, memory loss, movement disorders, mucositis, muscle complaints, muscle weakness, myocardial infarction, nail disorders, nasal complaints, neoplasm complications, nephrotoxicity, oedema, oesophageal spasm, pain, palpitations, pancytopenia, pericardial effusion, personality disorder, renal impairment, seizure, sensation abnormal, sepsis, sexual dysfunction, skin reactions, smell altered, sweat changes, syncope, throat complaints, thrombocytosis, tremor, urinary frequency increased, vasodilatation, vertigo, weight changes

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**Tioguanine**

*(Thioguanine)*

- **INDICATIONS AND DOSE**
  - Acute leukaemia | Chronic myeloid leukaemia
  - **BY MOUTH**
    - Adult: 100–200 mg/m² daily, can be given at various stages of treatment in short-term cycles

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**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CONTRA-INDICATIONS**
  - Absent thiopurine methyltransferase activity
- **CAUTIONS**
  - Thiopurine methyltransferase activity
  - The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.
  - Long-term therapy: Long-term therapy is no longer recommended because of the high risk of liver toxicity.
- **INTERACTIONS**
  - Appendix 1: tioguanine

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**www.getintopharma.com**
Cytotoxic responsive malignancy

SIDE-EFFECTS

- **Common or very common** Bone marrow failure - gastrointestinal disorders - hepatic disorders - hyperbilirubinaemia - hyperuricaemia - hyperuricosuria - nodular regenerative hyperplasia - osseopagal varices - sinusoidal obstruction syndrome - splenomegaly - stomatitis - thrombocytopenia - uric acid nephropathy - weight increased
- **Frequency not known** Photosensitivity reaction

CONCEPTION AND CONTRACEPTION

Ensure effective contraception during treatment in men or women.

PREGNANCY

Avoid (teratogenicity reported when men receiving tioguanine have fathered children). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

RENAL IMPAIRMENT

Dose adjustments Reduce dose.

PRE-TREATMENT SCREENING

Consider measuring thiopurine methyltransferase (TPMT) activity before starting tioguanine therapy.

MONITORING REQUIREMENTS

Monitor liver function weekly—discontinue if liver toxicity develops.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

**BY MOUTH**

Tioguanine (Non-proprietary)

<table>
<thead>
<tr>
<th>Tioguanine 40 mg</th>
<th>25 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>£109.57</td>
<td></td>
</tr>
</tbody>
</table>

Trifluridine with tipiracil

06-Feb-2019

DRUG ACTION

Trifluridine is an antimetabolite that interferes with cancer cell DNA synthesis and inhibits cell proliferation; tipiracil is a TPase inhibitor that boosts trifluridine concentrations.

INDICATIONS AND DOSE

Metastatic colorectal cancer, in patients previously treated with (or unsuitable for treatment with) available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, or anti-vascular endothelial growth factor (VEGF) agents, or anti-epidermal growth factor receptor (EGFR) agents (specialist use only)

- **BY MOUTH**
  - Adult: Initially 35 mg/m² twice daily (max. per dose 80 mg), given on days 1 to 5 and days 8 to 12 of each 28-day cycle, consult product literature for further information on dose adjustment

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Trifluridine with tipiracil for previously treated metastatic colorectal cancer (August 2016) NICE TA405

Scottish Medicines Consortium (SMC) decisions

SMC No. 1221/17

The Scottish Medicines Consortium has advised (February 2017) that trifluridine with tipiracil (Lonsurf®) is recommended, within its marketing authorisation, as an option for treating metastatic colorectal cancer in adults, only when provided by the manufacturer with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

SMC No. 1221/17

The Scottish Medicines Consortium has advised (February 2017) that trifluridine with tipiracil (Lonsurf®) is accepted for use within NHS Scotland for the treatment of adults with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents, and anti-epidermal growth factor receptor agents.

This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

SIDE-EFFECTS

- **Common or very common** Alopecia - anaemia - appetite decreased - asthenia - constipation - cough - decreased leucocytes - diarrhoea - dizziness - dyspnoea - fever - flushing - gastrointestinal discomfort - headache - hyperbilirubinaemia - hypoaalbuminaemia - increased leucocytes - increased risk of infection - insomnia - malaise - mucositis - nausea - neutropenia - oedema - oral disorders - peripheral neuropathy - skin reactions - taste altered - thrombocytopenia - urine abnormalities - vomiting - weight decreased
**Cytotoxic responsive malignancy**

- **Mitomycin**
  - **INDICATIONS AND DOSE**
    - Recurrent superficial bladder tumours (bladder instillation)
      - By intravesical instillation
      - Adult: consult product literature or local protocols
    - Upper gastro-intestinal cancers | Breast cancers
      - By intravenous injection
      - Adult: consult product literature or local protocols
  - **CAUTIONS**
    - Caution in handling—irritant to tissues
  - **INTERACTIONS**
    - Appendix 1: mitomycin
  - **SIDE-EFFECTS**
    - General side-effects
      - Common or very common | Skin reactions
    - Specific side-effects
      - Frequency not known
      - With intravenous use | Neoplasms
        - Bone marrow depression | Haemolysis
        - Bone marrow depression | Heart failure
        - Haemolysis | Hepatic disorders
        - Heart failure | Pulmonary hypertension
        - Hepatic disorders | Sepsis
        - Pulmonary hypertension | Sinusoidal obstruction syndrome
        - Sepsis | Bladder disorders | Urinary tract stenosis
        - Sinusoidal obstruction syndrome | Bladder disorders | Urinary tract stenosis
        - Bladder disorders | Urinary tract stenosis
        - Urinary tract stenosis | Frequency not known
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Tablet**
      - Lonsurf (Seriver Laboratories Ltd)
        - Tipiracil (as Tipiracil hydrochloride) 6.14 mg, Trifluridine 20 mg, Lonsurf 10 mg, Lonsurf 20 mg/8.11 mg tablets | 20 tablet | £66.67
        - Tipiracil (as Tipiracil hydrochloride) 8.19 mg, Trifluridine 20 mg, Lonsurf 10 mg, Lonsurf 20 mg/8.11 mg tablets | 20 tablet | £100.00
  - **Powder for solution for injection**
    - Bleomycin (as Bleomycin sulfate) 15000 unit, Bleomycin 15,000 unit powder for solution for injection vials | 10 vial | £190.60
  - **Bleo-Kyowa**
    - Bleomycin (as Bleomycin sulfate) 15000 unit, Bleo-Kyowa 15,000 unit powder for solution for injection vials | 10 vial | £190.60

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**Antineoplastic drugs > Cytotoxic anti-biotics and related substances**

**Bleomycin**

- **Indications and dose**
  - Squamous cell carcinoma | Metastatic germ cell cancer | Non-Hodgkin’s lymphoma
    - By intramuscular injection, or by intravenous injection, or by intravenous infusion, or by intrarterial infusion, or by local infiltration
    - Adult: consult product literature or local protocols

- **Cautions**
  - Caution in handling—irritant to tissues

- **Interactions**
  - Appendix 1: bleomycin

- **Side-effects**
  - Common or very common: Alopecia, angular stomatitis, appetite decreased, chills, fever (after administration), haemorrhage, headache, interstitial pneumonia, leucopenia, malaise, nail discoloration, nail disorder, nausea, pain, pulmonary fibrosis, dose-related, scleroderma, skin reactions, stomatitis, vomiting, weight decreased
  - Uncommon: Diarrhoea, dizziness, hepatocellular injury, oliguria, shock, urinary disorders, venin wall hypertrophy, venous stenosis

**Side-effects, Further information**

- Progressive pulmonary fibrosis: Progressive pulmonary fibrosis is dose-related, and may occur at lower doses in the elderly. Suspicious chest X-ray changes are an indication to stop therapy with this drug.
- Pulmonary toxicity: Patients who have received bleomycin may be at risk of developing pulmonary toxicity if exposed to high inspired oxygen concentrations, for example peri-operatively, or during lung function testing.

- **Conception and contraception**
  - Contraceptive advice required, see *Pregnancy and reproductive function* in Cytotoxic drugs p. 888

- **Pregnancy**
  - Avoid (teratogenic in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888

- **Breastfeeding**
  - Discontinue breast feeding.

- **Renal impairment**
  - Dose adjustments: Reduce dose by half if serum creatinine 177–354 micromol/litre; reduce dose further if serum creatinine greater than 354 micromol/litre.

- **Prescribing and dispensing information**
  - To conform to the European Pharmacopoeia vials previously labelled as containing ‘15 units’ of bleomycin are now labelled as containing 15,000 units. The amount of bleomycin in the vial has not changed.

- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for injection**
    - Bleomycin (Non-proprietary)
      - Bleomycin (as Bleomycin sulfate) 15000 unit, Bleomycin 15,000 unit powder for solution for injection vials | 10 vial | £170.00
    - Bleomycin (as Bleomycin sulfate) 15000 unit, Bleomycin (Kyowa Kirin Ltd) 15,000 unit powder for solution for injection vials | 10 vial | £190.60
Pentostatin

**INDICATIONS AND DOSE**

**Hairy cell leukaemia (initiated in specialist centres)**
- Adult: To be given on alternate weeks (consult product literature)

**INTERACTIONS** → Appendix 1: pentostatin

**SIDE-EFFECTS**
- **Common or very common**
  - Agranulocytosis, alopecia, amnorrhea, anaemia, angina pectoris, anxiety, appetite decreased, arrhythmias, arthrosis, asthenia, asthma, atrioventricular block, blood disorder, bone disorder, bone marrow disorders, breast mass, cardiac arrest, chest pain, chill, confusion, constipation, cough, deafness, death, depersonalisation, depression, diarrhoea, dizziness, drowsiness, dry eye, dry mouth, dysarthria, dysphagia, dyspnoea, ear pain, electrolyte imbalance, embolism and thrombosis, emotional lability, eosinophilia, eye disorders, eye inflammation, eye pain, febrile neutropenia, fever, fluid imbalance, flushing, gastrointestinal discomfort, gastrointestinal disorders, gout, graft versus host disease, haemorrhage, hallucination, hangover, headache, heart failure, hostility, hyperbilirubinaemia, hyperglycaemia, hyperhidrosis, hypersensitivity, hyperventilation, hypertension, increased risk of infection, influenza like illness, jaundice, joint disorders, leucopenia, lymphadenopathy, malaise, memory loss, meningism, movement disorders, muscle complaints, nausea, neoplasms, nephrolithiasis, nephropathy, nerve disorders, neurotoxicity (withhold or discontinue), oedema, oral disorders, pain, paralysis, pericardial effusion, photosensitivity reaction, pulmonary oedema, rash (withhold if severe), renal impairment, respiratory disorders, retinopathy, seborrhoea, seizures, sensation abnormal, sepsis, sexual dysfunction, skin reactions, sleep disorders, splenomegaly, syncope, taste altered, thinking abnormal, thrombocytopenia, tinnitus, tremor, urinary disorders, urogenital disorder, vasculitis, vertigo, vision disorders, vomiting, weight changes
- **Uncommon**
  - Angioedema, antibiotic associated colitis, capillary leak syndrome, cardiomyopathy, cystitis, haemolytic anaemia, mucositis, multi organ failure, myocardial infarction, pure red cell aplasia, transplant failure, tumour lysis syndrome
- **Rare or very rare**
  - Dementia, pericarditis, shock, Stevens-Johnson syndrome, systemic inflammatory response syndrome

**SIDE-EFFECTS, FURTHER INFORMATION** Pentostatin can cause myelosuppression, immunosuppression, and a number of other side-effects that may be severe. Treatment should be withheld in patients who develop a severe rash, and withheld or discontinued in patients showing signs of neurotoxicity.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises that men should not father children during and for 3 months after treatment.

**PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution (limited information available).

**RENAL IMPAIRMENT** Avoid if creatinine clearance less than 60 mL/minute.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Nipent (Pfizer Ltd)
  - Pentostatin 10 mg

**ANTINEOPLASTIC DRUGS > PLANT ALKALOIDS**

Trabectedin

**INDICATIONS AND DOSE**

**Treatment of advanced soft-tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or is contra-indicated**
- Treatment of relapsed platinum-sensitive ovarian cancer (in combination with pegylated liposomal doxorubicin)

**INTERACTIONS** → Appendix 1: trabectedin

**SIDE-EFFECTS**
- **Common or very common**
  - Alopecia, anaemia, appetite decreased, arthralgia, asthenia, back pain, constipation, cough, dehydration, diarrhoea, dizziness, dyspnoea, fever, flushing, gastrointestinal discomfort, headache, hyperbilirubinaemia, hypereosinophilia, hyperventilation, hypertension, infection, insomnia, leucopenia, mucositis, myalgia, nausea, neutropenia, oedema, paraesthesia, peripheral neuropathy, skin reactions, stomatitis, taste altered, thrombocytopenia, vomiting, weight decreased
- **Uncommon**
  - Capillary leak syndrome, septic shock
- **Rare or very rare**
  - Hepatic failure
- **Frequency not known**
  - Extravasation necrosis
  - Rhabdomyolysis

**SIDE-EFFECTS, FURTHER INFORMATION** A corticosteroid, such as dexamethasone by intravenous infusion, must be given 30 minutes before therapy for its antiemetic and hepatoprotective effects (consult product literature).

**CONCEPTION AND CONTRACEPTION** Effective contraception recommended during and for at least 3 months after treatment in women and during and for at least 5 months after treatment in men.

**PREGNANCY** See Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Manufacturer advises avoid breast-feeding during and for 3 months after treatment.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution (risk of increased exposure).
- **Dose adjustments** Manufacturer advises consider dose reduction.

**RENAL IMPAIRMENT** Avoid monotherapy if creatinine clearance less than 30 mL/minute. Avoid combination regimens if creatinine clearance less than 60 mL/minute.

**MONITORING REQUIREMENTS**
- Specific haematological, renal and hepatic parameters must be monitored and within certain ranges prior to starting treatment and repeated weekly during the first 2 cycles and at least once between treatments in subsequent cycles—consult product literature for full details.
- Monitor for signs and symptoms of rhabdomyolysis (including myelotoxicity, severe liver function disorder, renal failure, muscle weakness or pain)–monitor creatine phosphokinase closely and discontinue treatment (consult product literature).
Cytotoxic responsive malignancy

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Trabectedin for the treatment of advanced soft tissue sarcoma (February 2010) NICE TA185

Trabectedin (Yondelis®) is an option for advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed, is inappropriate or is not tolerated. The cost of trabectedin for treatment after the fifth cycle is met by the manufacturer. www.nice.org.uk/guidance/ta185

- Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA399

Trabectedin (Yondelis®) in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) is not recommended for treating the first recurrence of platinum-sensitive ovarian cancer. Patients currently receiving trabectedin in combination with PLDH should have the option to continue their treatment until they or their NHS clinician consider it appropriate to stop. www.nice.org.uk/guidance/ta399

MEDITICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion

- Yondelis (Pharma Mar, S.A.)

Trabectedin 250 microgram Yondelis 0.25mg powder for concentrate for solution for infusion vials | 1 vial (£363.00 (Hospital only))

Trabectedin 1 mg Yondelis 1mg powder for concentrate for solution for infusion vials | 1 vial (£1,366.00 (Hospital only))

ANTINEOPLASTIC DRUGS > PLATINUM COMPOUNDS

Carboplatin

10-Jun-2016

INDICATIONS AND DOSE

Treatment of advanced ovarian cancer and lung cancer (particularly the small cell type)

BY INTRAVENOUS INFUSION

Adult: The dose of carboplatin is determined according to renal function rather than body surface area (consult product literature)

INTERACTIONS

Appendix 1: platinum compounds

SIDE-EFFECTS

- Common or very common Alopecia, anaemia, asthenia, cardiovascular disorder, constipation, diarrhoea, gastrointestinal discomfort, haemorrhage, hypersensitivity, increased risk of infection, leucopenia, mucosal abnormalities, musculoskeletal disorder, nausea, neutropenia, ototoxicity, peripheral neuropathy, reflexes decreased, respiratory disorders, sensation abnormal, skin reactions, taste altered, thrombocytopenia, urogenital disorder, vision disorders, vomiting

- Rare or very rare Cardiac discomfort, dyspnoea

- Frequency not known Appetite decreased, bone marrow failure, chills, dehydration, embolism,encephalopathy, extravasation necrosis, fever, haemolytic uraemic syndrome, heart failure, hypertension, hypopanaesthesia, hypotension, injection site necrosis, malaise, pancreatitis, stomatitis, stroke, treatment related secondary malignancy

CONCEPTION AND CONCEPTION

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

PREGNANCY

Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

RENAL IMPAIRMENT

Avoid if creatinine clearance less than 20 mL/minute.

Dose adjustments

Reduce dose.

Monitoring

Monitor haematological parameters in renal impairment.

Monitor renal function in renal impairment.

PRESCRIBING AND DISPENSING INFORMATION

Carboplatin can be given in an outpatient setting.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013) NICE TA284

Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).

www.nice.org.uk/TA284

- Bevacizumab in combination with gemcitabine and carboplatin for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (May 2013) NICE TA285

Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) that has not been previously treated with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

www.nice.org.uk/TA285

MEDITICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

- Carboplatin (Non-proprietary)

Carboplatin 10 mg per 1 ml Carboplatin 50mg/5ml concentrate for solution for infusion vials | 1 vial (£20.67–£22.04 (Hospital only))

Carboplatin 150mg/15ml concentrate for solution for infusion vials | 1 vial (£153.39–£156.92 (Hospital only)) | 1 vial (£60.59)

Carboplatin 600mg/60ml concentrate for solution for infusion vials | 1 vial (£243.89–£264.53 (Hospital only)) | 1 vial (£232.64)

Carboplatin 600mg/60ml solution for infusion vials | 1 vial (£260.00 (Hospital only)) | 1 vial (£260.00)

Carboplatin 450mg/45ml concentrate for solution for infusion vials | 1 vial (£158.40–£168.85 (Hospital only)) | 1 vial (£181.77)

Carboplatin 450mg/45ml solution for infusion vials | 1 vial (£197.48 (Hospital only)) | 1 vial (£197.48)

Carboplatin 150mg/15ml solution for infusion vials | 1 vial (£65.83 (Hospital only)) | 1 vial (£65.83)

Carboplatin 50mg/5ml solution for infusion vials | 1 vial (£22.86 (Hospital only)) | 1 vial (£22.86)

Cisplatin

INDICATIONS AND DOSE

Treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer (alone or in combination)

BY INTRAVENOUS INFUSION

Adult: (consult product literature)

CAUTIONS

FURTHER INFORMATION

Hydration Cisplatin requires intensive intravenous hydration and treatment may be complicated by severe nausea and vomiting.

INTERACTIONS

Appendix 1: platinum compounds

SIDE-EFFECTS

- Common or very common Anaemia, arrhythmias, bone marrow failure, electrolyte imbalance, extravasation
necrosis - fever - leucopenia - nephrotoxicity (dose-related and potentially cumulative) - sepsis - thombocytopenia
- Uncommon Anaphylactoid reaction - ototoxicity (dose-related and potentially cumulative) - spermatogenesis abnormal
- Rare or very rare Acute leukaemia - cardiac arrest - encephalopathy - myocardial infarction - nerve disorders - seizure - stomatitis
- CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.
- PREGNANCY Avoid (teratogenic and toxic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- BREAST FEEDING Discontinue breast-feeding.
- RENAL IMPAIRMENT Avoid if possible—nephotoxic.
- MONITORING REQUIREMENTS
  - Monitor full blood count.
  - Monitor audiometry.
  - Monitor plasma electrolytes.
  - Nephrotoxicity Monitoring of renal function is essential.
- DIRECTIONS FOR ADMINISTRATION Cisplatin is increasingly given in a day care setting.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
  - Solution for infusion
    - Cisplatin (Non-proprietary)
      - Cisplatin 1 mg per 1 ml Cisplatin 50mg/50ml concentrate for solution for infusion vials | 1 vial (£8.25–£10.00) £25.11–£28.11 DT = £26.51 (Hospital only)
        Cisplatin 100mg/100ml solution for infusion vials | 1 vial (£8.25–£10.00) £50.22 DT = £50.88 (Hospital only)
        Cisplatin 10mg/10ml solution for infusion vials | 1 vial (£8.25–£10.00) £5.90 (Hospital only) | 1 vial (£5.90) £5.90
        Cisplatin 50mg/50ml solution for infusion vials | 1 vial (£8.25–£10.00) £25.37–£28.11 DT = £26.51 | 1 vial (£8.25–£10.00) £25.37 DT = £26.51 (Hospital only)
        Cisplatin 10mg/10ml concentrate for solution for infusion vials | 1 vial (£8.25–£10.00) £5.90 (Hospital only)
        Cisplatin 100mg/100ml concentrate for solution for infusion vials | 1 vial (£8.25–£10.00) £50.22–£55.64 DT = £50.88 (Hospital only)

Oxaliplatin

- INDICATIONS AND DOSE
  - Treatment of metastatic colorectal cancer (in combination with fluorouracil and folinic acid) - Treatment of colon cancer after resection of the primary tumour (adjuvant treatment)
    - By intravenous infusion
    - Adult: (consult product literature)

- CONTRA-INDICATIONS Peripheral neuropathy with functional impairment
- INTERACTIONS ➔ Appendix 1: platinum compounds
- SIDE-EFFECTS
  - Uncommon Metabolic acidosis - nervousness - ototoxicity
  - Rare or very rare Acute kidney injury - acute tubular necrosis - antibiotic associated colitis - deafness - disseminated intravascular coagulation - dysarthria - haemolytic anaemia - hepatic disorders - immune-allergic thombocytopenia - nephritis acute interstitial - nodular regenerative hyperplasia - pancreatitis - posterior reversible encephalopathy syndrome (PRES) (with oxaliplatin combination chemotherapy) - respiratory disorders - sinosoidal obstruction syndrome - vision loss (reversible on discontinuation)
  - Frequency not known Autoimmune pancytopenia - chest discomfort - dysphagia - extravasation necrosis - gait abnormal - hypersensitivity vasculitis - movement disorders - muscle complaints - muscle contractions involuntary - QT interval prolongation - rhematomyolysis - throat complaints

SIDE-EFFECTS, FURTHER INFORMATION Neurotoxicity is dose limiting.

Respiratory symptoms
If unexplained respiratory symptoms occur, oxaliplatin should be discontinued until investigations exclude interstitial lung disease and pulmonary fibrosis.
- CONCEPTION AND CONTRACEPTION Effective contraception required during and for 4 months after treatment in women and 6 months after treatment in men.
- PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- BREAST FEEDING Discontinue breast-feeding.
- RENAL IMPAIRMENT Avoid if creatinine clearance less than 30 ml/minute.
  - Dose adjustments Reduce dose in mild to moderate impairment (consult product literature).
- NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes’ C) colon cancer (April 2006) NICE TA100 Capecitabine alone or oxaliplatin combined with fluorouracil and folinic acid are options for adjuvant treatment following surgery for stage III (Dukes’ C) colon cancer.
  www.nice.org.uk/TA100

- Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93 A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin are options for first-line treatment for advanced colorectal cancer. Irinotecan alone or fluorouracil and folinic acid with oxaliplatin are options for patients who require further treatment subsequently.
  www.nice.org.uk/TA93

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
  - Solution for infusion
    - Oxaliplatin (Non-proprietary)
      - Oxaliplatin 5 mg per 1 ml Oxaliplatin 50mg/10ml concentrate for solution for infusion vials | 1 vial (£8.25–£10.00) £15.58–£15.83 (Hospital only) | 1 vial (£8.25–£10.00) £14.72–£15.00
      - Oxaliplatin 100mg/20ml concentrate for solution for infusion vials | 1 vial (£8.25–£10.00) £33.37–£33.50 (Hospital only) | 1 vial (£8.25–£10.00) £295.63–£330.00

www.getintopharma.com
Cytotoxic responsive malignancy 923

ANTINEOPLASTIC DRUGS > PODOPHYLLOTOXIN DERIVATIVES

Etoposide

12-Jul-2018

- INDICATIONS AND DOSE
  - Small cell carcinoma of the bronchus, the lymphomas and testicular cancer
    - BY MOUTH
      - Adult: 120–240 mg/m² daily for 5 days
    - BY INTRAVENOUS INFUSION
      - Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

- INTERACTIONS → Appendix 1: etoposide
- SIDE-EFFECTS
  - GENERAL SIDE-EFFECTS
    - Common or very common
      - Abdominal pain - acute
      - leukaemia - alopecia - anaemia - appetite decreased - arthralgia - bleeding tendency - bone marrow depression - constipation - diarrhoea - dizziness - hepatotoxicity - hypertension - leucopenia - malaise - mucositis - myocardial infarction - nausea - neutropenia - skin reactions - thrombocytopenia - vomiting
    - Uncommon
      - Nerve disorders
      - Rare or very rare
        - Dyshagia - neurotoxicity - radiation recall reaction - respiratory disorders - seizure - severe cutaneous adverse reactions (SCARs) - taste altered - vision loss
  - SPECIFIC SIDE-EFFECTS
    - Common or very common
      - With intravenous use Anaphylactic reaction - hypotension - infection
      - With oral use Oesophagitis - stomatitis - transient systolic hypertension
    - Uncommon
      - With intravenous use Haemorrhage
      - Rare or very rare
        - With intravenous use Fever
    - With oral use Drowsiness
    - Frequency not known
      - With intravenous use Angioedema - extravasation necrosis - infertility - tumour lysis syndrome
  - CONCEPTION AND CONTRACEPTION
    - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - PREGNANCY
    - Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - BREAST FEEDING
    - Discontinue breast-feeding.
  - HEPATIC IMPAIRMENT
    - Manufacturer advises caution (increased risk of accumulation).
  - RENAL IMPAIRMENT
    - Dose adjustments: Consider dose reduction—consult local treatment protocol for details.
    - DIRECTIONS FOR ADMINISTRATION
      - Etoposide may be given orally or by slow intravenous infusion, the oral dose being double the intravenous dose. A preparation containing etoposide phosphate can be given by intravenous injection or infusion. Etoposide is usually given daily for 3–5 days and courses should not be repeated more frequently than at intervals of 21 days.

ANTINEOPLASTIC DRUGS > TAXANES

Cabazitaxel

11-Feb-2019

- INDICATIONS AND DOSE
  - Treatment of hormone refractory metastatic prostate cancer in patients who have previously been treated with a docetaxel-containing regimen (in combination with prednisone or prednisolone)
    - BY INTRAVENOUS INFUSION
      - Adult: (consult product literature or local protocols)

- CAUTIONS
  - Avoid in Acute porphyrias p. 1058
  - INTERACTIONS → Appendix 1: taxanes

- SIDE-EFFECTS
  - Common or very common
  - Frequency not known
    - Respiratory disorders
  - CONCEPTION AND CONTRACEPTION
    - Ensure effective contraception during treatment (women) and for up to 6 months after treatment (men).
  - PREGNANCY
    - See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - BREAST FEEDING
    - Discontinue breast-feeding.
  - HEPATIC IMPAIRMENT
    - Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
  - Dose adjustments: Manufacturer advises dose reduction in mild to moderate impairment—consult product literature.
  - RENAL IMPAIRMENT
    - Use with caution if creatinine clearance less than 50 mL/minute.
  - MONITORING REQUIREMENTS
    - Monitor electrolytes—correct dehydration.
**Cytotoxic responsive malignancy**

**DIRECTIONS FOR ADMINISTRATION**
Intravenous infusion incompatible with PVC.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (updated August 2016) NICE TA391
  - Cabazitaxel (Jevtana®) in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients whose disease has progressed during or after docetaxel chemotherapy, only if the following criteria are met:
    - the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
    - the patient has had 225 mg/m² or more of docetaxel
    - treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles
    - the manufacturer provides cabazitaxel with the discount agreed in the patient access scheme
    - NHS trusts purchase cabazitaxel in accordance with the manufacturer provides cabazitaxel with the discount agreed in the patient access scheme

**Scottish Medicines Consortium (SMC) decisions**
SMC No. 735/11
- The Scottish Medicines Consortium has advised (December 2016) that cabazitaxel (Jevtana®) in combination with prednisone or prednisolone is accepted for restricted use within NHS Scotland for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (patients who have received at least 225 mg/m² (three cycles) of docetaxel and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1). This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**EXCIPIENTS:** May contain Ethanol
- Jevtana (Sanofi)
  - Cabazitaxel 40 mg per 1 ml
  - JevTana 60mg/1.5ml concentrate and solvent for solution for infusion vials | 1 vial [R30] £3,696.00
  (Hospital only)

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**Docetaxel**

**INDICATIONS AND DOSE**

Adjuvant treatment of operable node-positive and operable node-negative breast cancer (in combination with doxorubicin and cyclophosphamide) | Initial chemotherapy of locally advanced or metastatic breast cancer (with doxorubicin) | Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline or an alkylating drug has failed (monotherapy) | Locally advanced or metastastic breast cancer where cytotoxic chemotherapy with an anthracycline has failed (with capecitabine) | Initial chemotherapy of metastatic breast cancer which overexpresses human epidermal growth factor-2 (with trastuzumab) | Locally advanced or metastastic non-small cell lung cancer where previous chemotherapy has failed | Initial chemotherapy of unresectable, locally advanced or metastatic non-small cell lung cancer (with cisplatin) | Hormone-resistant metastatic prostate cancer (in combination with prednisone or prednisolone) | Initial treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (with cisplatin and fluorouracil) | Induction treatment of locally advanced squamous cell carcinoma of the head and neck (with cisplatin and fluorouracil)

**BY INTRAVEOUS INFUSION**

- Adult: (consult product literature or local protocols)

**CAUTIONS**
Avoid in Acute porphyrias p. 1058 - consult product literature

**INTERACTIONS**
- Appendix 1: taxanes

**SIDE-EFFECTS**
- Common or very common Abdominal pain · alopecia · anaemia · appetite decreased · arthralgia · asthenia · constipation · diarrhoea · dry mouth · fluid imbalance · haemorrhage · hypersensitivity · hypertension · increased risk of infection · myalgia · nail disorders · nausea · neutropenia · pain · peripheral neuropathy · paresthesia · skin reactions · stomatitis · taste altered · thrombocytopenia · vomiting
- Uncommon Gastrointestinal disorders · heart failure
- Frequency not known Ascites · bone marrow depression · chest tightness · chills · cutaneous lupus erythematosus · disseminated intravascular coagulation · eye disorders · eye inflammation · fever · hearing impairment · hepatitis · hypoaesthesia · loss of consciousness · multi organ failure · myalgia · myocardial infarction · nail discoloration · neurotoxicity · ototoxicity · pericardial effusion · peripheral lymphoedema · peripheral oedema · pulmonary oedema · radiation injuries · renal impairment · respiratory disorders · scleroderma · seizure · sensation abnormal · severe cutaneous adverse reactions (SCARs) · vasodilation · venous thromboembolism · vision disorders · weight increased

**SIDE-EFFECTS, FURTHER INFORMATION**
Pretreatment with dexamethasone by mouth is recommended for reducing fluid retention and hypersensitivity reactions.

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception for men and women during treatment, and for at least 6 months after stopping treatment in men.

**PREGNANCY**
Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in mild to moderate and to avoid in severe impairment.

**Dose adjustments**
Manufacturer advises dose reduction according to liver function tests in mild to moderate impairment — consult product literature.

www.getintopharma.com
Cytotoxic responsive malignancy 925

Paclitaxel 17-Jul-2017

- **DRUG ACTION** Paclitaxel is a member of the taxane group of drugs.

- **INDICATIONS AND DOSE**
  - Treatment of ovarian cancer (advanced or residual disease following laparotomy) in combination with cisplatin (conventional paclitaxel only)
  - Treatment of metastatic ovarian cancer where platinum-containing therapy has failed (conventional paclitaxel only)
  - Treatment of locally advanced or metastatic breast cancer (in combination with other cytotoxics or alone if other cytotoxics have failed or are inappropriate)
    - (conventional paclitaxel only)
    - Adjuvant treatment of node-positive breast cancer following treatment with anthracycline and cyclophosphamide (conventional paclitaxel only)
    - Treatment of non-small cell lung cancer (in combination with cisplatin) when surgery or radiotherapy not appropriate (conventional paclitaxel only)
    - Treatment of advanced AIDS-related Kaposi’s sarcoma where liposomal anthracylene therapy has failed (conventional paclitaxel only)
    - First-line treatment of metastatic adenocarcinoma of the pancreas (in combination with gemcitabine) (conventional paclitaxel only)
    - Monotherapy of metastatic breast cancer when first-line treatment has failed and standard, anthracycline-containing therapy is not indicated (albumin-bound paclitaxel only)
    - In combination with gemcitabine for the first-line treatment of metastatic adenocarcinoma of the pancreas (albumin-bound paclitaxel only)

- **INFORMATION**
  - **BY INTRAVENOUS INFUSION**
    - Adult: consult product literature or local protocols

- **CAUTIONS** Avoid in Acute porphyrias p. 1058 consult product literature patients aged over 75 years with metastatic adenocarcinoma of the pancreas

- **INTERACTIONS** Appendix 1: taxanes

- **SIDE-EFFECTS**
  - Common or very common
  - Uncommon
  - Rare or very rare
    - Atrioventricular block - cardiac arrest - congestive heart failure - left ventricular dysfunction - radiation injuries - severe cutaneous adverse reactions (SCARs)

SIDE-EFFECTS, FURTHER INFORMATION

Manufacturer advises routine premedication with a corticosteroid, an
antihistamine and a histamine H2-receptor antagonist is recommended to prevent severe hypersensitivity reactions; hypersensitivity reactions may occur rarely despite premedication.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during and for at least 6 months after treatment in men or women.

- **PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** (Consult product literature)

- **MONITORING REQUIREMENTS**
  - Cardiac monitoring should be undertaken, particularly if patients have underlying cardiac disease or previous exposure to anthracyclines.
  - Patients should be monitored for signs and symptoms of pneumonitis and sepsis.

- **PRESCRIBING AND DISPENSING INFORMATION** Paclitaxel is available as both conventional and albumin-bound formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Prescribers should specify the brand to be dispensed.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

**EXCIPIENTS:** May contain Polyoxyl castor oils

- **Paclitaxel (Non-proprietary)**
  - Paclitaxel 6 mg per 1 ml Paclitaxel 150mg/25ml concentrate for solution for infusion vials | 1 vial | £504.90–£561.00 (Hospital only) | 1 vial | £300.52
  - Paclitaxel 30mg/5ml concentrate for solution for infusion vials | 1 vial | £112.31–£116.05 (Hospital only) | 1 vial | £66.85
  - Paclitaxel 100mg/16.7ml concentrate for solution for infusion vials | 1 vial | £336.60–£374.00 (Hospital only) | 1 vial | £200.35–£342.59

- **Paclitaxel 300mg/50ml concentrate for solution for infusion vials | 1 vial | £1,009.80–£1,122.00 (Hospital only) | 1 vial | £601.03

### Powder for suspension for infusion

**ELECTROLYTES:** May contain Sodium

- **Abraxane® (Celgene Ltd)**
  - Paclitaxel albumin 100 mg Abraxane 100mg powder for suspension for infusion vials | 1 vial | £246.00 (Hospital only)

### ANTINEOPLASTIC DRUGS > TOPOISOMERASE I INHIBITORS

#### Irinotecan hydrochloride

**DRUG ACTION** Irinotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

**INDICATIONS AND DOSE** Metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed | Treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of chemotherapy that has included irinotecan (in combination with cetuximab) | First-line treatment of metastatic carcinoma of the colon or rectum (in combination with fluorouracil, folinic acid and bevacizumab) | First-line treatment of metastatic colorectal carcinoma (in combination with capcitabine with or without bevacizumab)

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature or local protocols)

### Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (April 2010) that paclitaxel albumin (Abraxane®) is accepted for restricted use within NHS Scotland for treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard anthracycline containing therapy is not indicated; use is restricted to patients who would otherwise receive docetaxel or 3-weekly solvent-based paclitaxel as second-line treatment for metastatic breast cancer.

The Scottish Medicines Consortium has advised (February 2015) that paclitaxel albumin (Abraxane®) is accepted for use within NHS Scotland in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

### NICE decisions

- **Paclitaxel for ovarian cancer (January 2003)**

  Either paclitaxel in combination with a platinum compound (cisplatin or carboplatin) or a platinum compound alone are alternatives for the first-line treatment of ovarian cancer (usually following surgery).

- **Paclitaxel for the adjuvant treatment of early node-positive breast cancer (September 2006)**

  Paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer.

- **Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013)**

  Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).

- **Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016)**

  Paclitaxel, in combination with platinum or as monotherapy, is recommended as an option for treating recurrent ovarian cancer.

- **Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer (September 2017)**

  Paclitaxel as albumin-bound nanoparticles (nab-paclitaxel) with gemcitabine is recommended as an option for untreated metastatic adenocarcinoma of the pancreas in adults, only if:
  - other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy, and
  - the manufacturer provides nab-paclitaxel with the discount agreed in the patient access scheme.

Patients whose treatment with nab-paclitaxel was started before this guidance was published, should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.
Metastatic adenocarcinoma of the pancreas in patients who have progressed following gemcitabine based therapy (in combination with fluorouracil and leucovorin) (specialist use only)

• BY INTRAVENOUS INFUSION USING LIPID FORMULATION

• Adult: (consult product literature or local protocols)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: **Oниvye®** (IRINOTECAN, LIPOSOMAL FORMULATIONS): REPORTS OF SERIOUS AND FATAL THROMBOEMBOLIC EVENTS (MARCH 2019)

Oниvye® has been associated with reports of serious thromboembolic events, such as pulmonary embolism, venous thrombosis, and arterial thromboembolism. Healthcare professionals are advised to obtain a thorough medical history to identify patients with multiple risk factors. Patients should be advised to seek medical advice immediately if signs or symptoms of thromboembolism occur, such as sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing.

**CONTRA-INDICATIONS** Bowel obstruction • chronic inflammatory bowel disease

**CAUTIONS** Raised plasma-bilirubin concentration • risk factors for cardiac disease • risk factors for pulmonary toxicity • underweight patients—increased risk of adverse events

**INTERACTIONS** Appendix 1: irinotecan

**SIDE-EFFECTS**

• Common or very common Alopecia • anaemia (dose-limiting) • appetite decreased • asthma • cholinergic syndrome • constipation • decreased leucocytes • diarrhoea (delayed diarrhoea requires prompt treatment) • dizziness • dysphonia • dyspnoea • electrolyte imbalance • embolism and thrombosis • febrile neutropenia (dose-limiting) • fever • fluid imbalance • gastrointestinal disorders • gastrointestinal syndrome • hypoglycaemia • hypotension • increased risk of infection • infusion related reaction • insomnia • mucusitis • nausea • neutropenia (dose-limiting) • oedema • renal impairment • sepsis • stomatitis • taste altered • thrombocytopenia (dose-limiting) • vomiting • weight decreased

• Uncommon Hypersensitivity • hypoxia • nail discoloration • skin reactions

• Frequency not known Antibiotic associated colitis • circulatory collapse • gastrointestinal haemorrhage • hiccups • hypertension • interstitial lung disease • muscle cramps • paraesthesia • speech disorder • ulcerative colitis

**CONCEPTION AND CONTRACEPTION** For conventional formulations, manufacturer advises effective contraception during treatment and for up to 1 month after treatment in women of child-bearing potential, and up to 3 months after treatment in men. For liposomal formulations, manufacturer advises effective contraception during treatment and for up to 1 month after treatment in women of child-bearing potential, and up to 4 months after treatment in men.

**PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** For conventional formulations, manufacturer advises avoid. For liposomal formulations, manufacturer advises avoid until one month after the last dose—no information available.

**HEPATIC IMPAIRMENT** For conventional formulations, manufacturer advises caution if bilirubin concentration 1.5–3 times the upper limit of normal (risk of decreased clearance)—monitor liver function at baseline and before each cycle; avoid if bilirubin concentration greater than 3 times the upper limit of normal (no information available for combination therapy). For liposomal formulations, manufacturer advises caution; avoid if bilirubin greater than 2 mg/dL, or if transaminases are greater than 2.5 times the upper limit of normal, or greater than 5 times the upper limit of normal if liver metastasis present (limited information available).

**Dose adjustments** For conventional formulations, manufacturer advises dose reduction—consult product literature.

**RENAI IMPAIRMENT** For conventional formulations, manufacturer advises avoid—no information available. For liposomal formulations, manufacturer advises avoid in severe impairment—no information available.

**MONITORING REQUIREMENTS** Manufacturer advises monitor for respiratory symptoms in patients with risk factors for interstitial lung disease before and during treatment; monitor complete blood count weekly during treatment.

**PRESCRIBING AND DISPENSING INFORMATION** Irinotecan is available as both conventional and liposomal formulations. Manufacturers advise that the different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and visual disturbances within 24 hours of administration.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

• Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93

A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin are options for first-line treatment for advanced colorectal cancer. Irinotecan alone or oxaliplatin and folinic acid with oxaliplatin are options for patients who require further treatment subsequently.

www.nice.org.uk/TA93

• Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine (April 2017) NICE TA440

Pegylated liposomal irinotecan, in combination with fluorouracil and leucovorin, is not recommended for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA440

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (March 2017) that liposomal irinotecan (Oниvye®) is not recommended for use within NHS Scotland for the treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil and leucovorin (folinic acid), in patients who have progressed following gemcitabine based therapy as there was insufficient evidence submitted.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

• Irinotecan hydrochloride (Non-proprietary) 500mg/25ml concentrate for solution for infusion vials | 1 vial (Bax) £393.75–£730.82 (Hospital only)
**Topotecan**

**INDICATIONS AND DOSE**
Topotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

**Metastatic ovarian cancer when first-line or subsequent treatment has failed**
- Topotecan (Hycamtin®) is recommended for treating recurrent carcinoma of the cervix, after radiotherapy, and for patients with stage IVB disease (in combination with cisplatin).
- Oral topotecan is recommended as an option for treatment in patients who have not previously received cisplatin treatment.

**Relapsed small-cell lung cancer when retreatment with the first-line regimen is considered inappropriate**
- Oral topotecan is recommended as an option for retreatment with cisplatin for treatment of recurrent carcinoma of the cervix after radiotherapy and for stage IVB disease; it is restricted to patients who have not previously received cisplatin treatment.

**SIDE-EFFECTS**
- **Common or very common**
  - Alopecia
  - Anaemia
  - Appetite decreased
  - Apathy
  - Nausea
  - Vomiting
- **Rare or very rare**
  - Angioedema
  - Interstitial lung disease
- **Frequency not known**
  - Bone marrow depression
  - Neutropenia

**CONCEPTION AND CONCEPTION**
Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
Avoid (teratogenicity and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREASTFEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises avoid in severe impairment (limited information available).

**RENAL IMPAIRMENT**
Avoid infusion if creatinine clearance less than 20 mL/minute. Avoid oral route if creatinine clearance less than 60 mL/minute.

**DOSE ADJUSTMENTS**
Reduce dose.

**INTERACTIONS**
Appendix 1: topotecan

**CAUTIONARY AND ADVISORY LABELS**
See Cytotoxic drugs p. 888.

**IMPORTANT SAFETY INFORMATION**
Risks of incorrect dosing of oral anti-cancer medicines

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- **Topotecan for the treatment of recurrent and stage IVB cervical cancer (October 2009) NICE TA183**
  - Topotecan in combination with cisplatin is recommended as a treatment option for recurrent or stage IVB cervical cancer in patients who have not previously received cisplatin.
  - [www.nice.org.uk/TA183](http://www.nice.org.uk/TA183)
- **Topotecan for the treatment of relapsed small-cell lung cancer (November 2009) NICE TA184**
  - Oral topotecan is recommended as an option for treatment in patients with relapsed small-cell lung cancer only if retreatment with the first-line regimen is not considered appropriate, and the combination of cyclophosphamide, doxorubicin and vincristine is contra-indicated.
  - Intravenous topotecan is not recommended for people with relapsed small-cell lung cancer.
  - [www.nice.org.uk/TA184](http://www.nice.org.uk/TA184)
- **Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (April 2016) NICE TA389**
  - Topotecan is not recommended for treating first recurrence of platinum-sensitive ovarian cancer, recurrent platinum-resistant ovarian cancer, or platinum-refractory ovarian cancer.
  - Patients currently receiving topotecan should have the option to continue their treatment until they or their clinician consider it appropriate to stop.
  - [www.nice.org.uk/TA389](http://www.nice.org.uk/TA389)

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium has advised (November 2007) that topotecan (Hycamtin®) is accepted for restricted use in combination with cisplatin for treatment of recurrent carcinoma of the cervix after radiotherapy and for stage IVB disease; it is restricted to patients who have not previously received cisplatin treatment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- **Topotecan (Non-proprietary)**
  - Topotecan (as Topotecan hydrochloride) 1 mg per 1 ml
  - Topotecan 4 mg/4 ml concentrate for solution for infusion vials | 5 vial | £1,453.10 (Hospital only)

**Powder for solution for infusion**
- **Hycamtin (Novartis Pharmaceuticals UK Ltd)**
  - Topotecan (as Topotecan hydrochloride) 1 mg
  - Topotecan 1 mg powder for concentrate for solution for infusion vials | 1 vial | £97.65

- **Topotecan (as Topotecan hydrochloride) 4 mg**
  - Topotecan 4 mg powder for concentrate for solution for infusion vials | 1 vial | £348.76

- **Potactasol (Actavis UK Ltd)**
  - Topotecan (as Topotecan hydrochloride) 4 mg
  - Potactasol 4 mg powder for concentrate for solution for infusion vials | 1 vial | £290.00 (Hospital only)

**Capsule**
**CAUTIONARY AND ADVISORY LABELS** 25
- **Hycamtin (Novartis Pharmaceuticals UK Ltd)**
  - Topotecan (as Topotecan hydrochloride) 250 microgram
  - Topotecan (as Topotecan hydrochloride) 1 mg
  - Topotecan 1 mg capsules | 10 capsule | £75.00
  - Topotecan 1 mg capsules | 10 capsule | £360.00
**ANTINEOPLASTIC DRUGS** ▶**VINCA ALKALOIDS**

**Vinblastine sulfate**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
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<td>Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)</td>
</tr>
<tr>
<td>Adult: (consult product literature)</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION**

Vinblastine is for **intra**venous administration only. Inadvertent intracranial administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 ml minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

**CONTRA-INDICATIONS**, FURTHER INFORMATION

Intracranial injection contra-indicated.

**CAUTIONS**

Caution in handling—irritant to tissues.

**INTERACTIONS**

▶ Appendix 1: vinca alkaloids

**SIDE-EFFECTS**

▶ Rare or very rare

- Hypersensitivity, rash - SIADH
- Frequency not known

**SIDE-EFFECTS, FURTHER INFORMATION**

**Bronchospasm**

Severe bronchospasm following administration is more common when used in combination with mitomycin-C.

**Neurotoxicity**

Sensory and motor neuropathies are common and are cumulative. Manufacturer advises monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment—requires dose reduction, treatment interruption or discontinuation depending on severity.

Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

**CONCEPTION AND CONTRACEPTION**

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**

Avoid (limited experience suggests fetal harm; teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in significantly impaired hepatic or biliary function.

**DOSE ADJUSTMENTS**

Manufacturer advises consider initial dose reduction in significantly impaired hepatic or biliary function.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

▶ Vinblastine sulfate (Non-proprietary)

| Vinblastine sulfate 1 mg per 1 ml | 5 vial (PN) £85.00 (Hospital only) |

**Vincristine sulfate**

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<td>Adult: (consult local protocol)</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION**

Vincristine injections are for **intra**venous administration only. Inadvertent intracranial administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 ml minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Intrathecal injection contra-indicated.

**CAUTIONS**

Caution in handling—irritant to tissues - neuromuscular disease

**INTERACTIONS**

▶ Appendix 1: vinca alkaloids

**SIDE-EFFECTS**

▶ Rare or very rare

- Hypersensitivity, rash - SIADH
- Frequency not known

**SIDE-EFFECTS, FURTHER INFORMATION**

**Bronchospasm**

Severe bronchospasm following administration is more common when used in combination with mitomycin-C.

**Neurotoxicity**

Sensory and motor neuropathies are common and are cumulative. Manufacturer advises monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment—requires dose reduction, treatment interruption or discontinuation depending on severity.

Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

**CONCEPTION AND CONTRACEPTION**

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**

Avoid (teratogenicity and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution.

**DOSE ADJUSTMENTS**

Manufacturer advises dose reduction.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

▶ Vincristine sulfate (Non-proprietary)

| Vincristine sulfate 1 mg per 1 ml | 1 vial (PN) £11.47 (Hospital only) | 5 vial (PN) £67.35 (Hospital only) | 2mg/2ml solution for injection vials | 1 vial (PN) £26.66 (Hospital only) | 5 vial (PN) £113.30 (Hospital only) | 5mg/5ml solution for injection vials | 5 vial (PN) £329.50 (Hospital only) |

www.getintopharma.com
Vindesine sulfate

**INDICATIONS AND DOSE**

- **Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)**
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

Vindesine injections are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

- **CONTRA-INDICATIONS, FURTHER INFORMATION**
  - Intrathecal injection contra-indicated.
  - **CAUTIONS**
    - Caution in handling—irritant to tissues - neuromuscular disease
  - **INTERACTIONS**
    - Appendix 1: vinca alkaloids
  - **SIDE-EFFECTS**
    - **Common or very common**
      - Alopecia
    - **Frequency not known**

**SIDE-EFFECTS, FURTHER INFORMATION**

Neurotoxicity, usually as peripheral or autonomic neuropathy; it occurs less often with vindesine than with vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes; and otoxicity has been reported. There have been instances in which neurotoxicity has made it necessary to reduce the dosage or temporarily discontinue use of vindesine.

**CONCEPTION AND CONTRACEPTION**

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**

Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

Dose adjustments Dose reduction may be necessary.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for injection**
    - **Eldisine** (Genus Pharmaceuticals Ltd)
      - Vindesine sulfate 5 mg Eldisine 5mg powder for solution for injection vials | 1 vial (P20) £78.30 (Hospital only)

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Vinflunine

**INDICATIONS AND DOSE**

- **Treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen (monotherapy)**
  - Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

Vinflunine injections are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**CONTRA-INDICATIONS**

- **CONTRA-INDICATIONS, FURTHER INFORMATION**
  - Intrathecal injection contra-indicated.
  - **CAUTIONS**
    - Cardiovascular disease - QT-interval prolongation (avoid hypokalaemia)
  - **INTERACTIONS**
    - Appendix 1: vinca alkaloids
  - **SIDE-EFFECTS**
    - **Common or very common**
    - **Uncommon**
      - Acute respiratory distress syndrome (ARDS) - cancer pain - laryngeal pain - myocardial infarction - myocardial ischaemia - neutropenic sepsis - renal failure - SIADH - tinnitus - vertigo - visual impairment
    - **Rare or very rare**
      - Posterior reversible encephalopathy syndrome (PRES)
  - **CONCEPTION AND CONTRACEPTION**
    - Manufacturer advises effective contraception during and for up to 3 months after treatment.
  - **PREGNANCY**
    - Avoid unless essential—teratogenicity and embryotoxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - **BREAST FEEDING**
    - Discontinue breast-feeding.
  - **HEPATIC IMPAIRMENT**
    - Manufacturer advises caution (no information available in severe impairment).
  - **Dose adjustments**
    - Manufacturer advises dose reduction.
  - **RENAL IMPAIRMENT**
    - Dose adjustments Reduce dose if creatinine clearance less than 60 mL/minute—consult product literature.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - **NICE decisions**
      - Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (January 2013) NICE TA272

Vinflunine (Javelon®) is not recommended for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

www.nice.org.uk/guidance/ta272
Vinorelbine is a semi-synthetic vinca alkaloid.

**INDICATIONS AND DOSE**

- **Advanced breast cancer**
  - **By mouth**
    - Adult: 60 mg/m² once weekly for 3 weeks, then increased if tolerated to 80 mg/m² once weekly (max. per dose 160 mg once weekly)
  - **By intravenous injection, or by intravenous infusion**
    - Adult: (consult product literature)

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Bronchospasm**
  - Severe bronchospasm following administration of the vinca alkaloids is more common when used in combination with mitomycin-C.

**Neurotoxicity**

- Neurotoxicity reported in clinical trials, most commonly as constipation, paresthesia, hyperreflexia, and hyporeflexia.

**CONCEPTION AND CONTRACEPTION**

- Manufacturer advises effective contraception during and for at least 3 months after treatment; men must avoid fathering a child during and for at least 3 months after treatment.

**PREGNANCY**

- Avoid unless essential (teratogenicity, and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

- With oral use: Manufacturer advises caution in moderate impairment; avoid in severe impairment (no information available).

- With intravenous use: Manufacturer advises caution in severe impairment.

**Dose adjustments**

- With oral use: Manufacturer advises dose reduction in moderate impairment—consult product literature.

- With intravenous use: Manufacturer advises dose reduction in severe impairment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Javlor** (Pierre Fabre Ltd)
  - Vinflunine (as Vinflunine ditartrate) 25 mg per 1 ml Javlor 250mg/10ml concentrate for solution for infusion vials | 1 vial £1,062.50
  - Javlor 50mg/2ml concentrate for solution for infusion vials | 1 vial £212.50

**Vinorelbine**

- **Capsule** (Pierre Fabre Ltd)
  - Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml
  - Vinorelbine (as Vinorelbine tartrate) 30 mg capsules | 1 capsule £39.96 (Hospital only)
  - Vinorelbine (as Vinorelbine tartrate) 50 mg capsules | 1 capsule £65.98 (Hospital only)

- **Solution for infusion**
  - Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml
    - Vinorelbine 50mg/5ml concentrate for solution for infusion vials | 1 vial £139.00 | 10 vials £1,339.80
    - Vinorelbine 10mg/1ml concentrate for solution for infusion vials | 1 vial £22.00 | 10 vials £220.00
    - Navelbine (Pierre Fabre Ltd)
    - Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml
      - Navelbine 10mg/1ml concentrate for solution for infusion vials | 1 vial £297.45 (Hospital only)
      - Navelbine 50mg/5ml concentrate for solution for infusion vials | 10 vials £1,399.79 (Hospital only)

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 21, 25
  - Navelbine (Pierre Fabre Ltd)
    - Vinorelbine (as Vinorelbine tartrate) 20 mg
      - Navelbine 20mg capsules | 1 capsule £43.96 (Hospital only)
    - Vinorelbine (as Vinorelbine tartrate) 30 mg
      - Navelbine 30mg capsules | 1 capsule £65.98 (Hospital only)
    - Vinorelbine (as Vinorelbine tartrate) 80 mg
      - Navelbine 80mg capsules | 1 capsule £175.92 (Hospital only)
**ANTINEOPLASTIC DRUGS > OTHER**

### Amsacrine

**INDICATIONS AND DOSE**

**Acute leukaemia (refractory to anthracycline chemotherapy used alone or in combination with other chemotherapy agents) (specialist use only)**

- By intravenous infusion
- Adult: (consult local protocol)

**CAUTIONS**

- Hypokalaemia—increased risk of ventricular fibrillation (correct hypokalaemia before initiating treatment)
- INTERACTIONS → Appendix 1: amsacrine
- SIDE-EFFECTS

- Common or very common Abdominal pain - alopecia - arrhythmias - bone marrow disorders - cardiotoxicity - congestive heart failure - diarrhoea - dyspepsia - emotional lability - fever - generalised tonic-clonic seizure - haemorrhage - hepatic disorders - hypokalaemia - hypotension - infection - nausea - necrosis - skin reactions - stomatitis - thrombocytopenia - vomiting
- Rare or very rare Anaemia - cardiomyopathy - confusion - dizziness - granulocytopenia - headache - lethargy - leucopenia - numbness - peripheral neuropathy - proteinuria - renal impairment - visual impairment - weight changes
- Frequency not known Cardiac arrest - hyperuricaemia
- CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for 6 months after treatment in women of child-bearing potential, and during and for 6 months after treatment in men.
- PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT Manufacturer advises caution—increased risk of toxicity.
- RENAL IMPAIRMENT Manufacturer advises consider dose reduction (consult product literature).
- Dose adjustments Manufacturer advises consider dose reduction (consult product literature).
- MONITORING REQUIREMENTS

- Manufacturer advises monitor full blood count, liver function and renal function regularly; electrolytes should be re-evaluated prior to each treatment.
- Manufacturer advises monitor for cardiotoxicity during treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Amsidine** (Eurocept International bv)
  - Amsacrine 50 mg per 1 ml
  - Amsidine 75mg/1.5ml solution for infusion ampoules and diluent
  - 6 ampoule (PFS) £1,200.00 (Hospital only)

### Arsenic trioxide

**INDICATIONS AND DOSE**

**Acute promyelocytic leukaemia in patients who have relapsed or failed to respond to previous treatment with a retinoid and chemotherapy**

- By intravenous infusion
- Adult: (consult local protocol)

**CAUTIONS**

- Hypokalaemia (correct before treatment) - hypomagnesaemia (correct before treatment) - previous treatment with anthracyclines (increased risk of QT interval prolongation)

**INTERACTIONS → Appendix 1: arsenic trioxide

**SIDE-EFFECTS**

- Frequency not known Confusion - decreased leucocytes - fluid imbalance - heart failure - hepatotoxicity - peripheral neuropathy - sepsis

**SIDE-EFFECTS, FURTHER INFORMATION**

Signs and symptoms of differentiation syndrome (leucocyte activation syndrome) include unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, with or without leucocytosis—treat with high dose corticosteroids, consult product literature.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment in men and women.

**PREGNANCY** Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises use with caution—no information available.

**RENAL IMPAIRMENT** Manufacturer advises caution—limited information available.

**MONITORING REQUIREMENTS** ECG required before and during treatment—consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Arsenic trioxide for treating acute promyelocytic leukaemia (June 2018) NICE TA526

Arsenic trioxide is recommended, within its marketing authorisation, as an option for inducing remission and consolidation in acute promyelocytic leukaemia (characterised by the presence of the t(15;17) translocation or the PML/RAR-alpha gene) in adults with:

- untreated, low-to-intermediate risk disease (defined as a white blood cell count of 10x10⁹ per microlitre or less), when given with all-trans-retinoic acid (ATRA)
- relapsed or refractory disease, after a retinoid and chemotherapy.

[www.nice.org.uk/guidance/ta526](http://www.nice.org.uk/guidance/ta526)

**Scottish Medicines Consortium (SMC) decisions**

SMC No. SMC2025

The Scottish Medicines Consortium (SMC) has advised (January 2019) that arsenic trioxide (Trisenox®) is not recommended for use within NHS Scotland in combination with all-trans-retinoic acid (ATRA [tretinoin]) for the induction of remission, and consolidation in adults with newly diagnosed, low-to-intermediate risk acute promyelocytic leukaemia (characterised by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene), as the economic case was not demonstrated.
Cytotoxic responsive malignancy

**Asparaginase**

11-Sep-2018

**DRUG ACTION**
Asparaginase is an enzyme which acts by breaking down L-asparagine to aspartic acid and ammonia, this disrupts proteins synthesis of tumour cells.

**INDICATIONS AND DOSE**

**Acute lymphoblastic leukaemia (in combination with other antineoplastic drugs) (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - Adults: 5000 units/m² every 3 days

**CONTRA-INDICATIONS**
History of pancreatitis related to asparaginase therapy - history of serious haemorrhage related to asparaginase therapy - history of serious thrombosis related to asparaginase therapy - pancreatitis - pre-existing known coagulopathy

**CAUTIONS**
Diabetes (may raise blood glucose) - hypersensitivity reactions - hypertriglyceridaemia (severe)—increased risk of acute pancreatitis

**SIDE-EFFECTS**
- Uncommon Headache - hyperammonaemia - hyperuricaemia
- Rare or very rare Coma - consciousness impaired - diabetic ketoacidosis - hepatic disorders - hyperparathyroidism - hypoparathyroidism - ischaemic stroke - necrotising pancreatitis - pancreatic pseudocyst - posterior reversible encephalopathy syndrome (PRES) - seizures - tremor

**SIDE-EFFECTS, FURTHER INFORMATION**
There have been rare reports of cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome; manufacturer advises interrupt treatment if these symptoms develop.

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception in men and women of childbearing potential during treatment and for at least 3 months after last dose; asparaginase may reduce effectiveness of oral contraceptives—additional precautions (e.g. barrier method) are required, see also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**HEPATIC FEEDING**
Manufacturer advises avoid in severe impairment—no information available.

**MONITORING REQUIREMENTS**
Manufacturer advises monitor trough serum asparaginase levels 3 days after administration; consider switching to a different asparaginase preparation if target levels not reached—seek expert advice.

**HANDLING AND STORAGE**
Manufacturer advises store in a refrigerator (2-8°C)—consult product literature for storage conditions after reconstitution and dilution.

**PATIENT AND CARER ADVICE**
Driving and skilled tasks Manufacturer advises asparaginase has moderate influence on driving and performance of skilled tasks—increased risk of dizziness and somnolence.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) decisions
SMC No. 1319/18
The Scottish Medicines Consortium has advised (April 2018) that asparaginase (Spectria) is accepted for use within NHS Scotland when used as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia in paediatric patients from birth to 18 years and adults.

**CRISANTASPASE**

16-Mar-2017

**DRUG ACTION**
Crisantaspase is the enzyme asparaginase produced by Erwinia chrysanthemi.

**INDICATIONS AND DOSE**

**Acute lymphoblastic leukaemia**

- **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INJECTION**
  - Adult: consult product literature

**CONTRA-INDICATIONS**
History of pancreatitis related to asparaginase therapy

**CAUTIONS**
Diabetes (may raise blood glucose)

**INTERACTIONS**
Appendix 1: crisantaspase

**SIDE-EFFECTS**
- Common or very common Chill s - coagulation disorders - confusion - diarrhoea - dizziness - drowsiness - dyspnoea - face oedema - fever - headache - hepatic disorders - hypersensitivity - limb swelling - lip swelling - neurotoxicity - pain - pallor - pancreatitis - seizures - skin reactions - thrombosis
- Uncommon Hyperglycaemia - hyperlipidaemia - hypoxia - increased risk of infection - respiratory disorders
- Rare or very rare Arthritis reactive - coma - diabetic ketoacidosis - dysphagia - dysphasia - encephalopathy - haemorrhage - level of consciousness decreased - myalgia -
myocardial infarction, necrotising pancreatitis, neutropenia, paresis, sepsis, thrombocytopenia

- Frequency not known: Abdominal pain, flushing, hyperammonaemia, hypertension, hypotension, nausea, pseudocyst, vomiting

- Conception and contraception: Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- Pregnancy: Avoid. See also, Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- Breast feeding: Discontinue breast-feeding.

- Dose adjustments: Manufacturer advises dose reduction—consult product literature.

- Renal impairment: Dose adjustments—Consider dose reduction if creatinine clearance less than 40 mL/minute.

- Monitoring requirements: Monitor for signs of peripheral neuropathy—severe peripheral neurotoxicity requires treatment delay or dose reduction (consult product literature).

- ECG monitoring recommended in patients prescribed concomitant use of drugs that prolong the QT-interval or who are susceptible to QT-interval prolongation.

- Monitor electrolytes periodically.

- National funding/access decisions

- NICE decisions:
  - Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (December 2016) NICE TA423
  - Eribulin (Halaven®) is recommended for the treatment of locally advanced or metastatic breast cancer, only if:
    - the condition has progressed after at least 2 chemotherapy regimens (which may include an anthracycline and a taxane, and capetitabine), and
    - the manufacturer provides eribulin with the discount agreed in the patient access scheme.

- Scottish Medicines Consortium (SMC) decisions

  - SMC No. 1065/15
  - The Scottish Medicines Consortium has advised (March 2016) that eribulin (Halaven®) is accepted for restricted use within NHS Scotland for the treatment of patients with locally advanced or metastatic breast cancer that has progressed after at least two prior chemotherapy regimens for advanced disease, which includes capecitabine if indicated. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

- Medicinal forms: There can be variation in the licensing of different medicines containing the same drug.

- Powder for solution for injection:
  - Eribulin (Jazz Pharmaceuticals UK)
    - Crisantaspase 10000 unit
    - Erwinase 10,000 unit powder for solution for injection vials | 5 vials £3,065.00

- Eribulin

  - 08-Feb-2019

- Indications and dose:

  - Treatment of locally advanced or metastatic breast cancer when the disease has progressed after treatment with at least 1 chemotherapy regimen for advanced disease
    - By intravenous injection
    - Adult: Give on day 1 and day 8 of a 21-day cycle, previous therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless the patient is unsuitable for these treatments (consult local protocol)

- Contra-indications: Congenital long QT syndrome

- Caution: Bradyarrhythmias (increased susceptibility to QT-interval prolongation), congestive heart failure (increased susceptibility to QT-interval prolongation), electrolyte disturbances (increased susceptibility to QT-interval prolongation), susceptibility to QT-interval prolongation

- Interactions: Appendix 1: eribulin

- Side-effects:
  - Common or very common: Alopecia, anaemia, appetite decreased, arthralgia, asthenia, chest pain, chills, conjunctivitis, constipation, cough, decreased leucocytes, dehydration, depression, diarrhoea, dizziness, dry mouth, dyspnoea, dysuria, electrolyte imbalance, embolism and thrombosis, excessive tearing, fever, gastrointestinal discomfort, gastroesophageal reflux disease, haemorrhage, headache, hot flush, hyperbilirubinaemia, hypoglycaemia, increased risk of infection, influenza like illness, insomnia, lethargy, mucositis, muscle complaints, muscle weakness, nail disorder, nausia, nerve disorders, neurotoxicity, neutropenia, oral disorders, oropharyngeal pain, pain, peripheral oedema, rhinorrhoea, sensation abnormal, skin reactions, sweat changes, tachycardia, taste altered, thrombocytopenia, tinnitus, vertigo, vomiting, weight decreased

  - Uncommon: Angioedema, hepatotoxicity, interstitial lung disease, pancreatitis, proteinuria, renal failure, sepsis

  - Rare or very rare: Disseminated intravascular coagulation

  - Frequency not known: QT interval prolongation, severe cutaneous adverse reactions (SCARs)

  - Conception and contraception: Ensure effective contraception during and for up to 3 months after treatment in men or women.

  - Pregnancy: Avoid unless essential (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

  - Breast feeding: Discontinue breast-feeding.

  - Hepatic impairment: Manufacturer advises caution (increased risk of neutropenia).

  - Dose adjustments: Manufacturer advises dose reduction—consult product literature.

  - Renal impairment: Dose adjustments: Consider dose reduction if creatinine clearance less than 40 mL/minute.

  - Monitoring requirements: Monitor for signs of peripheral neuropathy—severe peripheral neurotoxicity requires treatment delay or dose reduction (consult product literature).

  - ECG monitoring recommended in patients prescribed concomitant use of drugs that prolong the QT-interval or who are susceptible to QT-interval prolongation.

  - Monitor electrolytes periodically.

  - National funding/access decisions

  - NICE decisions:
    - Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (December 2016) NICE TA423
    - Eribulin (Halaven®) is recommended for the treatment of locally advanced or metastatic breast cancer, only if:
      - the condition has progressed after at least 2 chemotherapy regimens (which may include an anthracycline and a taxane, and capetitabine), and
      - the manufacturer provides eribulin with the discount agreed in the patient access scheme.

  - Scottish Medicines Consortium (SMC) decisions

    - SMC No. 1065/15
    - The Scottish Medicines Consortium has advised (March 2016) that eribulin (Halaven®) is accepted for restricted use within NHS Scotland for the treatment of patients with locally advanced or metastatic breast cancer that has progressed after at least two prior chemotherapy regimens for advanced disease, which includes capecitabine if indicated. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

  - Medicinal forms: There can be variation in the licensing of different medicines containing the same drug.

  - Powder for solution for injection:
    - Eribulin (Jazz Pharmaceuticals UK)
      - Crisantaspase 10000 unit
      - Erwinase 10,000 unit powder for solution for injection vials | 5 vials £3,065.00

  - Eribulin 44 mg per 1 ml Halaven 0.88mg/2ml solution for injection vials | 1 vial £36.10 (Hospital only)
Hydroxycarbamide (Hydroxyurea)

INDICATIONS AND DOSE

Polycthæmia vera (specialist use only)

- BY MOUTH
  - Adult: Initially 15–20 mg/kg daily, adjusted according to response, for information on dose adjustment based on haematocrit and platelet count—consult product literature; usual dose 500–1000 mg daily, dosage should be based on actual or ideal body weight, whichever is less

Essential thrombocythaemia (specialist use only)

- BY MOUTH
  - Adult: Initially 15 mg/kg daily, adjusted according to response, for information on dose adjustment based on platelet count and white cell count—consult product literature, dosage should be based on actual or ideal body weight, whichever is less

Chronic myeloid leukaemia (specialist use only)

- BY MOUTH
  - Adult: Initially 40 mg/kg daily, then reduced to 20 mg/kg daily, adjusted according to response, for information on dose adjustment based on platelet count and white cell count—consult product literature, dosage should be based on actual or ideal body weight, whichever is less

Chronic myeloid leukaemia (specialist use only) Cancer of the cervix (specialist use only)

- BY MOUTH
  - Adult: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days, for information on dose adjustment based on platelet count, white cell count and actual or ideal body weight—consult product literature

Sickle-cell disease [prevention of recurrent vaso-occlusive crises] (initiated by a specialist)

- BY MOUTH
  - Adult: Initially 15 mg/kg daily, increased in steps of 2.5–5 mg/kg daily, dose to be increased every 12 weeks according to response; usual dose 15–30 mg/kg daily; maximum 35 mg/kg per day

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

- CAUTIONS Leg ulcers (review treatment if cutaneous vasculitic ulcers develop)
- INTERACTIONS → Appendix 1: hydroxycarbamide
- SIDE-EFFECTS
  - Rare or very rare Gangrene
- CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception before and during treatment.
- PREGNANCY Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

Mitotane

- DRUG ACTION Mitotane selectively inhibits the activity of the adrenal cortex, necessitating corticosteroid replacement therapy.

INDICATIONS AND DOSE

Symptomatic treatment of advanced or inoperable adrenocortical carcinoma

- BY MOUTH
  - Adult: Initially 2–3 g daily in 2–3 divided doses adjusted according to plasma-concentration monitoring, in severe illness initial dose can be increased up to 6 g daily, reduce dose or interrupt treatment if signs of toxicity, discontinue if inadequate response after 3 months

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

- CAUTIONS Avoid in Acute porphyrias p. 1058 - risk of accumulation in overweight patients
- INTERACTIONS → Appendix 1: mitotane
- SIDE-EFFECTS
  - Common or very common Adrenal insufficiency - anaemia - appetite decreased - asthenia - cognitive impairment - confusion - diarrhoea - dizziness - drowsiness - dyslipidaemia - gastrointestinal discomfort -
Panobinostat

**DRUG ACTION** Panobinostat is a histone deacetylase inhibitor, which promotes cell-cycle arrest and apoptosis of tumour cells via multiple pathways.

**INDICATIONS AND DOSE** Treatment of relapsed or refractory multiple myeloma (in combination with bortezomib and dexamethasone), in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent

- **BY MOUTH**
  - Adult 18-74 years: 20 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks), for doses of dexamethasone and bortezomib, or dose adjustment due to side-effects—consult product literature

- Adult 75 years and over: 15 mg once daily, on days 1, 3, 5, 8, 10 and 12 of a 21-day cycle for 8 cycles. Patients with clinical benefit should continue treatment for 8 additional cycles; total duration 16 cycles (48 weeks), for doses of dexamethasone and bortezomib, or dose adjustment due to side-effects—consult product literature

**SIDE-EFFECTS**

- **Common or very common** Anaemia; antimicrobial associated colitis; appetite decreased; arthralgia; arthritis; asthenia; chemicalitis; chills; cough; decreased leucocytes; diarrhoea; dizziness; dry mouth; dysphagia; electrolyte imbalance; fever; fluid imbalance; gastrointestinal discomfort; gastrointestinal disorders; haemorrhage; headache; hepatocellular injury; hyperbilirubinaemia; hyperglycaemia; hypertension; hyperuricaemia; hypocalcaemia; hypotension; hypothyroidism; increased risk of infection; insomnia; intracranial haemorrhage; joint swelling; malaise; nausea; neutropenia; palpitations; pancreatitis; peripheral oedema; QT interval prolongation; renal failure; respiratory disorders; sepsis; skin reactions; syncope; taste altered; thrombocytopenia; tremor; urinary incontinence; vomiting; weight decreased
- **Uncommon** Haemorrhagic shock; myocardial infarction

**SIDE-EFFECTS, FURTHER INFORMATION** Side-effects are reported when used in combination with bortezomib and dexamethasone.

**Gastro-intestinal disorders** Manufacturer advises that patients are treated with anti-diarrhoeals, or any additional treatment, in accordance with local treatment guidelines at the first sign of abdominal cramping or onset of diarrhoea.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before starting treatment in women of child-bearing potential, and ensure highly effective contraception used during treatment and for 3 months after last dose. Women using hormonal contraceptives should also use a barrier method of contraception. Highly effective contraception also required for men and their partners.
female partners during treatment and for 6 months after last dose.

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises frequent monitoring of hepatic function in mild and moderate impairment, particularly during the dose escalation phase; avoid in severe impairment—no information available.

**Dose adjustments** Manufacturer advises reduce initial dose to 15 mg during the first treatment cycle in mild impairment—dose may be increased to 20 mg based on patient tolerability; reduce initial dose to 10 mg during the first treatment cycle in moderate impairment—dose may be increased to 15 mg based on patient tolerability.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor full blood count before treatment, then frequently during treatment; reduce dose or interrupt treatment if thrombocytopenia or neutropenia occur—consult product literature.
  - Manufacturer advises monitor ECG before treatment and repeat periodically before each treatment cycle; QTcF should be <480 milliseconds before treatment initiation—consult product literature.
  - Manufacturer advises monitor electrolytes before treatment and periodically as clinically indicated, especially in patients with diarrhoea; monitor thyroid and pituitary function (free T4 and TSH) as clinically indicated; monitor hepatic function before treatment and regularly during treatment as clinically indicated.
  - Manufacturer advises monitor patients over 65 years more frequently, especially for thrombocytopenia and gastrointestinal toxicity.

- **PATIENT AND CARER ADVICE** Manufacturer advises that patients and their carers should be told to seek medical advice if severe gastro-intestinal toxicity occurs.

- **Missed doses** Manufacturer advises if a dose is missed, it can be taken up to 12 hours after the specified dose time.

- **Driving and skilled tasks** Dizziness may affect performance of skilled tasks (e.g. driving).

- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Panobinostat for treating multiple myeloma at least 2 previous treatments (January 2016) NICE TA380 Panobinostat, in combination with bortezomib and dexamethasone, is recommended as an option for treating relapsed or refractory multiple myeloma in patients who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent when the manufacturer provides panobinostat with the discount agreed in the patient access scheme. www.nice.org.uk/TA380

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS** 25
  - Farydak (Novartis Pharmaceuticals UK Ltd) ▼ Panobinostat (as Panobinostat lactate anhydrous) 10 mg: Farydak 10 mg capsules | 6 capsule [PD] £3,492.00 Panobinostat (as Panobinostat lactate anhydrous) 15 mg: Farydak 15 mg capsules | 6 capsule [PD] £3,492.00
  - Panobinostat (as Panobinostat lactate anhydrous) 20 mg: Farydak 20 mg capsules | 6 capsule [PD] £4,056.00

**Pegaspargase**

- **DRUG ACTION** Pegaspargase breaks down the amino acid L-asparagine, thereby interfering with the growth of malignant cells, which are unable to synthesise L-asparagine.

- **INDICATIONS AND DOSE**
  - Acute lymphoblastic leukaemia (in combination with other antineoplastic drugs) (specialist use only)
    - By intramuscular injection, or by intravenous infusion
      - Adult 18-21 years: 2500 units/m² every 14 days
      - Adult 22 years and over: 2000 units/m² every 14 days

- **CONTRA-INDICATIONS** History of pancreatitis - history of serious haemorrhagic event with previous L-asparaginase therapy - history of serious thrombosis with previous L-asparaginase therapy

- **CAUTIONS** Concomitant use of other hepatotoxic drugs (particularly in pre-existing hepatic impairment)—monitor hepatic function. Diabetes (may raise blood glucose) - hypersensitivity reactions - marked decrease of leukocyte count at start of treatment is possible—may be associated with significant rise in serum uric acid and development of uric acid nephropathy

- **CAUTIONS, FURTHER INFORMATION**
  - Hypersensitivity reactions Serious hypersensitivity reactions, including life-threatening anaphylaxis, can occur—pegaspargase should only be administered when appropriately trained staff and resuscitation facilities are immediately available; manufacturer advises patients should be closely monitored for signs of hypersensitivity during treatment and for an hour after administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

- **INTERACTIONS** → Appendix 1: pegaspargase

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain - bone marrow depression - diarrhoea - hyperglycaemia - hypersensitivity - hypoxia - pain in extremity - pancreatitis (discontinue if suspected and do not restart if confirmed) - peripheral neuropathy - rash - seizure - stomatitis - syncope - thrombosis (discontinue) - vomiting
  - Rare or very rare Acute kidney injury - posterior reversible encephalopathy syndrome (PRES) - tremor

- **Frequency not known** Confusion - diabetic ketoacidosis - drowsiness - hepatobiliary disorder - hyperammonaemia (monitor if symptoms present) - toxic epidermal necrolysis

- **SIDE-EFFECTS, FURTHER INFORMATION** There have been rare reports of cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome in patients receiving pegaspargase.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception in men and women of child-bearing potential during treatment and for at least 6 months after discontinuing treatment; pegaspargase may reduce effectiveness of oral contraceptives—additional precautions (e.g. barrier method) are required, see also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY** Manufacturer advises avoid unless essential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises trough serum asparaginase activity levels may be measured before the next administration of
Pegaspargase for treating acute lymphoblastic leukaemia

- **SIDE-EFFECTS**
  - Common or very common: Appetite decreased
  - Frequency not known: Azosperma, hepatic disorders, infection, lethargy, leucopenia, nausea, neutropenia, ovarian failure, pneumonitis, skin reactions, thrombocytopenia, vomiting

- **CONCEPTION AND CONTRACEPTION**
  - Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Avoid (teratogenic in animal studies and isolated reports in humans). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Manufacture advises caution in mild to moderate impairment; avoid in severe impairment.

- **RENAL IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  
  **Capsule**
  
  **CAUTIONARY AND ADVISORY LABELS**
  
  **4**
  
  **Procarbazine (Non-proprietary)**
  
  Procarbazine (as Procarbazine hydrochloride)
  
  - 50 mg
  - Procarbazine 50mg capsules (50 capsule £411.35–£452.48 OT + £431.92

**Raltitrexed**

- **DRUG ACTION**
  - Raltitrexed is a thymidylate synthase inhibitor.

- **INDICATIONS AND DOSE**
  - Palliation of advanced colorectal cancer when fluorouracil and folic acid cannot be used
    - **BY INTRAVENOUS INFUSION**
    - Adult: (consult local protocol)

**Procarbazine**

- **DRUG ACTION**
  - Procarbazine is a mild monoamine-oxidase inhibitor.

- **INDICATIONS AND DOSE**
  - Hodgkin's lymphoma
    - **BY MOUTH**
    - Adult: (consult local protocol)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CONTRA-INDICATIONS**
  - Pre-existing severe leucopenia, pre-existing severe thrombocytopenia

- **CAUTIONS**
  - Cardiovascular disease, cerebrovascular disease, epilepsy, phaeochromocytoma; procarbazine is a mild monoamineoxidase inhibitor (dietary restriction is rarely considered necessary).

- **INTERACTIONS**
  - Appendix 1: procarbazine
Cytotoxic responsive malignancy

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93
      Raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use should be confined to clinical studies. [www.nice.org.uk/TA93](http://www.nice.org.uk/TA93)

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Powder for solution for infusion**
    - **Tomudex** (Pfizer Ltd)
      - Raltitrexed 2 mg Tomudex 2mg powder for solution for infusion vials
        - 1 vial (£44.75) 1148.75 (Hospital only)

**RETINOID AND RELATED DRUGS**

**Bexarotene**

- **DRUG ACTION** Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. Bexarotene can cause regression of cutaneous T-cell lymphoma.

- **INDICATIONS AND DOSE**
  - **Skin manifestations of cutaneous T-cell lymphoma refractory to previous systemic treatment**
    - **BY MOUTH**
    - **Adult:** Initially 300 mg/m² once daily, adjusted according to response, to be taken with a meal

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CONTRA-INDICATIONS** History of pancreatitis · hypervitaminosis A · uncontrolled hyperlipidaemia · uncontrolled hypothyroidism
- **CAUTIONS** Avoid in Acute porphyrias p. 1058 · hyperlipidaemia · hypothyroidism
- **INTERACTIONS** → Appendix 1: retinoids
- **SIDE-EFFECTS**
  - **Common or very common** Alopecia · anaemia · appetite decreased · arthralgia · asthenia · chills · constipation · deafness · diarrhoea · dizziness · dry eye · dry mouth · dyslipidaemia · eye disorders · gastrointestinal discomfort · gastrointestinal disorders · headaches · hyperhidrosis · hypersensitivity · hypoproteinaemia · hypothyroidism · increased risk of infection · insomnia · leucopenia · lymphadenopathy · muscle complaints · nausea · oedema · oral disorders · pain · pseudolymphoma · sensation abnormal · skin nodule · skin reactions · skin ulcer · thyroid disorder · vomiting · weight changes
  - **Uncommon** Albuminuria · anxiety · arrhythmias · ataxia · blood disorder · cataract · coagulation disorder · depression · ear disorder · eosinophilia · eye inflammation · fever · gout · haemorrhage · hair disorder · hepatic failure · hyperbilirubinemia · hypertension · hyperthyroidism · increased leucocytes · mucous membrane disorder · muscle weakness · nail disorder · neoplasms · nerve disorders · pancreatitis · renal impairment · serous drainage · thrombocytopenia · thrombocytosis · varicose veins · vasodilation · vertigo · vision disorders
  - **Frequency not known** Burping · chest pain · confusion · cough aggravated · dehydration · drowsiness · dysphagia · dyspnoea · emotional lability · hypercalcaemia · hyperuricaemia · libido decreased · muscle tone increased · pelvic pain · peripheral vascular disease · red blood cell abnormality · taste altered · thirst · tinnitus · white blood cell abnormalities

**ALLERGY AND CROSS-SENSITIVITY** Caution—hypersensitivity to retinoids.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for at least 1 month after treatment in men and women.

**PREGNANCY** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in hepatic insufficiency.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 14/02

The Scottish Medicines Consortium has advised (November 2002) that bexarotene (Targretin®) is recommended for restricted use as a second-line treatment for patients with advanced (stages IIb or III) cutaneous T-cell lymphoma who have proved refractory both to local skin directed therapy and to at least one systemic therapy.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - **Targretin** (Eisai Ltd)
      - Bexarotene 75 mg Targretin 75mg capsules 100 capsule (£937.50)

**Tretinoin**

- **INDICATIONS AND DOSE**
  - **Induction of remission in acute promyelocytic leukaemia** (used in previously untreated patients as well as in those who have relapsed after standard chemotherapy or who are refractory to it)
    - **BY MOUTH**
    - **Adult:** 45 mg/m² daily in 2 divided doses maximum duration of treatment is 90 days, consult product literature for details of concomitant chemotherapy

**CAUTIONS** Increased risk of thromboembolism during first month of treatment

**INTERACTIONS** → Appendix 1: retinoids

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · alopecia · anxiety · appetite decreased · arrhythmia · asthma · bone pain · chest pain · chills · confusion · constipation · depression · diarrhoea · dizziness · dry mouth · flushing · headache · hearing impairment · hyperhidrosis · insomnia · intracranial pressure increased · malaise · nasal dryness · nausea · pancreatitis · paraesthesia · respiratory disorders · skin reactions · visual impairment · vomiting
- **Frequency not known** Embolism and thrombosis · erythema nodosum · genital ulceration · hepatotoxicity · hypercalcaemia · increased leucocytes · myocardial infarction · myositis · necrotising fasciitis · QT interval prolongation · stroke · thrombocytosis · vasculitis

**SIDE-EFFECTS, FURTHER INFORMATION**

Retinoic acid syndrome

Fever · dyspnoea · acute respiratory distress · pulmonary infiltrates · pleural effusion · hyperleucocytosis · hypotension · oedema · weight gain · hepatic · renal and multi-organ failure requires immediate treatment—consult product literature.

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives not considered effective).

**PREGNANCY** Teratogenic. See Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Avoid (discontinue breast-feeding).
Cytotoxic responsive malignancy

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HEPATIC IMPAIRMENT  Manufacturer advises caution.
Dose adjustments  Manufacturer advises dose reduction to 25 mg/m².

RENAL IMPAIRMENT  Manufacturer advises caution.
Dose adjustments  Reduce dose to 25 mg/m².

MONITORING REQUIREMENTS  Monitor haematological and coagulation profile, liver function, serum calcium and plasma lipids before and during treatment.

DESCRIBING AND DISPENSING INFORMATION  Tretinoin is the acid form of vitamin A.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.
Capsule

CAUTIONARY AND ADVISORY LABELS  21, 25
- Tretinoin (Non-proprietary)
  - Tretinoin 10 mg  Tretinoin 10mg capsules  1 100 capsule  

3.1 Cytotoxic drug-induced side effects

ANTIDOTES AND CHELATORS  IRON CHELATORS

Dexrazoxane

- INDICATIONS AND DOSE

CARDIOXANE  
Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin treatment in advanced or metastatic breast cancer patients who have received a prior cumulative dose of 500 mg/m² of doxorubicin or a prior cumulative dose of 540 mg/m² of epirubicin when further anthracycline treatment is required
  - BY INTRAVENOUS INFUSION
    - Adult: Administer 10 times the doxorubicin-equivalent dose or 10 times the epirubicin-equivalent dose, dose to be given 30 minutes before anthracycline administration

SAVENE  
Anthracycline extravasation
  - BY INTRAVENOUS INFUSION
    - Adult: Initially 1 g/m² daily (max. per dose 2 g) for 2 days, then 500 mg/m² for 1 day, first dose to be given as soon as possible and within 6 hours after injury

CONTRA-INDICATIONS  Children

CAUTIONS  Myelosuppression (effects may be additive to those of chemotherapy)

CARDIOXANE  Manufacturer advises caution in patients with heart failure—no information available - manufacturer advises caution in patients with myocardial infarction in previous 12 months—no information available - manufacturer advises caution in patients with symptomatic valvular heart disease—no information available - manufacturer advises caution in patients with uncontrolled angina—no information available

INTERACTIONS  Appendix 1: iron chelators

SIDE-EFFECTS
  - Common or very common  Alopecia - anaemia - appetite decreased - asthenia - constipation - cough - diarrhea - dizziness - dry mouth - diplopia - embolism and thrombosis - fever - gastrointestinal discomfort - headache - increased risk of infection - leucopenia - myalgia - nail disorder - nausea - neutropaenia - peripheral neuropathy - peripheral oedema - post procedural infection - sensation abnormal - skin reactions - stomatitis - syncope - tachycardia - thrombocytopenia - tremor - vaginal haemorrhage - vomiting - weight decreased - wound complications
  - Uncommon  Acute myeloid leukaemia - lymphoedema - sepsis - thirst - vertigo
  - Frequency not known  Anaphylactic reaction

CONCEPTION AND CONTRACEPTION  Ensure effective contraception during and for at least 3 months after treatment in men and women.

PREGNANCY  Avoid unless essential (toxicity in animal studies).

BREAST FEEDING  Discontinue breast-feeding.

HEPATIC IMPAIRMENT

CARDIOXANE  Manufacturer advises caution (no information available).
Dose adjustments  Manufacturer advises if anthracycline dose is reduced, reduce the Cardioxane® dose by a similar ratio.

SAVENE  Manufacturer advises avoid (no information available).

RENAL IMPAIRMENT

CARDIOXANE  DOSE ADJUSTMENTS  Manufacturer advises reduce dose by 50% if creatinine clearance less than 40 mL/minute.

SAVENE  Manufacturer advises avoid—risk of accumulation.

MONITORING REQUIREMENTS
  - Monitor full blood count.
  - Monitor for cardiac toxicity.
  - Monitor liver function.

DIRECTIONS FOR ADMINISTRATION  Local coolants such as ice packs should be removed at least 15 minutes before administration.

CARDIOXANE  For intravenous infusion, give intermittently in Compound sodium lactate; reconstitute each vial with 25 mL water for injections and dilute each vial with 25–100 mL infusion fluid; give requisite dose over 15 minutes.

SAVENE  For intravenous infusion, give intermittently in diluent; reconstitute each 500-mg vial with 25 mL of diluent; dilute requisite dose further in remaining diluent and give over 1–2 hours into a large vein in an area other than the one affected.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
- Cardoxane (Clinigen Healthcare Ltd)
  - Dexrazoxane 500 mg  Cardoxane 500mg powder for solution for infusion vials  1 1 vial  (£57.51)

Powder and solvent for solution for infusion
- ELECTROLYTES: May contain Potassium, sodium
  - Savene (Clinigen Healthcare Ltd)
    - Dexrazoxane 500 mg  Savene 500mg powder for concentrate and solvent for solution for infusion vials  1 10 vial  (£30.00)

DETOXIFYING DRUGS  UROPROTECTIVE DRUGS

Mesna

- INDICATIONS AND DOSE

Cytotoxic induced urothelial toxicity
  - BY MOUTH, OR BY INTRAVENOUS INJECTION
    - Adult: Dose to be calculated according to oxazaphosphorine (cyclophosphamide or ifosfamide) treatment (consult product literature)

SIDE-EFFECTS
  - Common or very common  Appetite decreased - arthralgia - asthenia - chest pain - chills - concentration impaired -
Cytotoxic drug-induced side effects

- **CAUTIONS** Avoid simultaneous administration of methotrexate • not indicated for pernicious anaemia or other megaloblastic anaemias caused by vitamin B12 deficiency
- **INTERACTIONS**  ➔ Appendix 1: folates
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - **Uncommon** Fever
    - **Rare or very rare** Agitation (with high doses) • depression (with high doses) • epilepsy exacerbated • gastrointestinal disorder (with high doses) • insomnia (with high doses)
- **SPECIFIC SIDE-EFFECTS**
  - **Common or very common**
    - With intravenous use Bone marrow failure • dehydration • diarrhoea (with high doses) • mucositis • nausea • oral disorders • skin reactions • vomiting
  - **Rare or very rare**
    - With intramuscular use Urticaria
    - With intravenous use Sensitisation
  - **Frequency not known**
    - With intravenous use Hyperammonaemia
  - **PREGNANCY** Not known to be harmful; benefit outweighs risk
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capcitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212
      - Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capcitabine is not recommended for the treatment of metastatic colorectal cancer.

  - **www.nice.org.uk/guidance/ta212**
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

### Folates

**Folinic acid**

12-Apr-2019

- **INDICATIONS AND DOSE**
  - **Prevention of methotrexate-induced adverse effects**
    - **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** Initial dose equal to or exceeding dose of methotrexate, to be given at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management
  - **Suspected methotrexate overdosage**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** (consult product literature)
  - **Adjunct to fluorouracil in colorectal cancer**
    - **BY SLOW INTRAVENOUS INJECTION**
    - **Adult:** (consult product literature)
  - **SODIOFOLIN**
    - As an antidote to methotrexate
      - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - **Adult:** (consult product literature)
  - **Adjunct to fluorouracil in colorectal cancer**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** (consult product literature)

- **CONTRA-INDICATIONS** Intrathecal injection

**Cystic fibrosis**

- **CONTRA-INDICATIONS** Intrathecal injection

**VITAMINS AND TRACE ELEMENTS**

**Folinic acid**

**Prevention of methotrexate-induced adverse effects**

- **BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - **Adult:** Initial dose equal to or exceeding dose of methotrexate, to be given at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management
  - **Suspected methotrexate overdosage**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** (consult product literature)
  - **Adjunct to fluorouracil in colorectal cancer**
    - **BY SLOW INTRAVENOUS INJECTION**
    - **Adult:** (consult product literature)
  - **SODIOFOLIN**
    - As an antidote to methotrexate
      - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
      - **Adult:** (consult product literature)
  - **Adjunct to fluorouracil in colorectal cancer**
    - **BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
    - **Adult:** (consult product literature)

**CONTRA-INDICATIONS** Intrathecal injection
Levofolinic acid

**DRUG ACTION** Levofolinic acid is an isomer of folic acid.

**INDICATIONS AND DOSE**

- Prevention of methotrexate-induced adverse effects
  - By intramuscular injection, or by intravenous injection, or by intravenous infusion
  - Adult: Usual dose: 7.5 mg every 6 hours for 10 doses, usually started 12–24 hours after beginning of methotrexate infusion

- Suspected methotrexate overdose
  - By intravenous infusion, or by intravenous injection
  - Adult: Initial dose at least 50% of the dose of methotrexate, intravenous infusion to be administered at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management

**Adjunct to fluorouracil in colorectal cancer**

- Prevention of methotrexate-induced adverse effects
  - By slow intravenous injection
  - Adult: (consult product literature)

**CONTRA-INDICATIONS** Intrathecal injection

**CAUTIONS** Avoid simultaneous administration of methotrexate - not indicated for pernicious anaemia or other megaloblastic anaemias caused by vitamin B12 deficiency

**INTERACTIONS** → Appendix 1: folates

**SIDE-EFFECTS**

- Common or very common
  - Dehydration - diarrhoea - mucosal toxicity - nausea - vomiting

- Uncommon
  - Fever

- Rare or very rare
  - Agitation (with high doses) - depression (with high doses) - epilepsy exacerbated - gastrointestinal disorder - insomnia (with high doses) - urticaria

**PREGNANCY** Not known to be harmful; benefit outweighs risk.

**BREAST FEEDING** Presence in milk unknown but benefit outweighs risk.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Levofolinic acid (Non-proprietary)
  - Levofolinic acid (as Disodium levofolate) 50 mg per 1 ml Levofolinic acid 50mg/1ml solution for injection vials | 1 vial (£2.47) £4.70 (Hospital only)
  - Levofolinic acid 200mg/4ml solution for injection vials | 1 vial (£0.80) £0.79 (Hospital only)
  - Isoverin (Pfizer Ltd)
  - Levofolinic acid (as Calcium levofolate) 10 mg per 1 ml Isoverin 175mg/17.5ml solution for injection vials | 1 vial (£1.01) £1.33 (Hospital only)
  - Isoverin 25mg/2.5ml solution for injection vials | 1 vial (£1.11) £1.62 (Hospital only)

3.1a Hyperuricaemia associated with cytotoxic drugs

**Other drugs used for Hyperuricaemia associated with cytotoxic drugs**

- Allopurinol, p. 1121 - Febuxostat, p. 1121

DETOXIFYING DRUGS > URATE OXIDASES

Rasburicase

**INDICATIONS AND DOSE**

- Prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and high tumour burden at risk of rapid lysis
  - By intravenous infusion
  - Adult: 200 micrograms/kg once daily for up to 7 days according to plasma-uric acid concentration

**CONTRA-INDICATIONS** G6PD deficiency

**CAUTIONS** Atopic allergies

**SIDE-EFFECTS**

- Common
  - Diarrhoea - fever - headache - nausea - skin reactions - vomiting

- Uncommon
  - Bronchospasm - haemolysis - haemolytic anaemia - hypersensitivity - hypotension - methaemoglobinemia - seizure

- Rare or very rare
  - Rhinitis

- Frequency not known
  - Muscle contractions involuntary

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**MONITORING REQUIREMENTS** Monitor closely for hypersensitivity.

**EFFECT ON LABORATORY TESTS** May interfere with test for uric acid—consult product literature.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Fasturtec®), give intermittently in Sodium chloride 0.9%; reconstitute with solvent provided; gently swirl vial without shaking to dissolve; dilute requisite dose to 50 mL with infusion fluid and give over 30 minutes.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for infusion**

- Fasturtec (Sanofi)
  - Rasburicase 1.5 mg: Fasturtec 1.5mg powder and solvent for solution for infusion vials | 3 vial (£20.83) £60.39 (Hospital only)
  - Rasburicase 7.5 mg: Fasturtec 7.5mg powder and solvent for solution for infusion vials | 1 vial (£34.72) £104.17 (Hospital only)

4 Hormone responsive malignancy

Breast cancer

**Description of condition**

Breast cancer is the most common form of malignancy in women, especially in those aged over 50 years. Established risk factors include age, early onset of menstruation, late menopause, older age at first completed pregnancy, and a family history of breast cancer. The use of oral contraceptives or hormone replacement therapy (HRT) is also associated with an increased risk of breast cancer.

Breast cancer in men is rare. Although risk factors are not fully understood, it may be associated with abnormalities of sex hormone metabolism, including those caused by liver disease or testicular trauma, genetic predisposition, and environmental risk factors such as industrial exposure to chronic heat.

Additional risk factors include obesity and alcohol consumption.
Physical activity and breast-feeding protect against breast cancer. Non-invasive breast cancer, also known as ductal carcinoma in situ, is when the cancer remains localised in the ducts. However, in most cases, the cancer is invasive at the time of diagnosis, which means that malignant cells are liable to spread beyond the immediate area of the tumour. Invasive breast cancer, where malignant cells spread beyond the ducts, can be defined as early breast cancer (stage I/II), locally advanced disease (stage III) and advanced disease (stage IV).

**Aims of treatment**

Reducing mortality, increasing progression-free and disease-free survival and improving quality of life are the main aims of treatment, and are dependent on the stage of the disease.

Surgery and radiotherapy aim to remove the tumour mass, whilst adjuvant drug therapy (drug treatment following surgery) aims to reduce the risk of disease recurrence and the risk of developing invasive disease. Neoadjuvant drug therapy (drug treatment before surgery) aims to reduce the size of the tumour to allow breast-conserving surgery to be possible and to reduce axillary lymph node involvement.

Advanced breast cancer is not curable, and treatment aims to prolong survival, relieve symptoms and improve quality of life.

**Overview**

The management of patients with breast cancer involves surgery, radiotherapy, drug therapy, or a combination of these. The course of the disease and the therapeutic approach vary depending on the characteristics of the cancer. Factors such as patient age, menopausal status, tumour size and grade, involvement of axillary lymph nodes or skin, and the presence of hormone receptors within the tumour, may inform the extent and aggressiveness of the disease. The risks and benefits of each therapy should be discussed with the patient before being started.

**Early and locally advanced breast cancer**

For operable breast cancer, treatment involves surgery to the breast (breast-conserving surgery or mastectomy) and to the axillary lymph nodes, with or without radiotherapy to reduce local recurrence rates. This is often followed by adjuvant drug therapy to eradicate the micro-metastases that cause relapses. In women with invasive breast cancer, radiotherapy is recommended after breast-conserving surgery with clear margins (no cancer cells are found at the edges of the removed tissue), as it reduces local recurrence rates. However, the use of radiotherapy may be omitted if risk of local recurrence is very low and the woman is willing to take adjuvant endocrine therapy for a minimum of 5 years. Radiotherapy is also recommended after mastectomy in patients with node-positive invasive breast cancer or involved resection margins (cancer cells are found at the edges of the removed tissue). It should also be considered in patients with node-negative T3 or T4 invasive breast cancer.

**Adjuvant drug therapy**

Adjuvant drug therapy may include the use of chemotherapy, endocrine therapy, biological therapy, or bisphosphonate therapy. The decision to use adjuvant drug therapy should be based on the risks and benefits of treatment, disease prognosis and predictive factors such as oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor 2 (HER2) status of the primary tumour.

In women with invasive breast cancer in only one breast who have not received treatment, including the use of neoadjuvant chemotherapy, NICE clinical guideline 101 recommends the use of the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy (www.predict.nhs.uk).

**Chemotherapy**

Adjuvant anthracycline–taxane combination chemotherapy is recommended in patients with invasive breast cancer who are at sufficient risk of disease recurrence to require chemotherapy. The choice of chemotherapy regimen is usually guided by local policy, Cancer Alliances, and the National Cancer Drugs Fund list.

**Biological therapy**

Trastuzumab p. 885 should be offered to patients with tumour size T1c and above HER2-positive invasive breast cancer, in combination with surgery, chemotherapy, or radiotherapy. It should also be considered in patients with a smaller tumour size (T1a or T1b) depending on their comorbidities, prognosis, and possible toxicity with concomitant chemotherapy. Cardiac function should be regularly assessed in patients receiving trastuzumab p. 885, and particular caution should be taken in patients with underlying cardiac disease (consult product literature for further details).

**Endocrine therapy**

Tamoxifen p. 953 should be used as initial adjuvant endocrine therapy in men and premenopausal women with oestrogen-receptor–positive invasive breast cancer. In addition, ovarian function suppression with a gonadotropin-releasing hormone (GnRH) should be considered in premenopausal women, taking into account the risk of temporary or permanent menopause. Ovarian function suppression aims to stop the production of circulating oestrogen, which can stimulate breast cancer progression. It may be most beneficial in women who are at sufficient risk of disease recurrence to have been offered chemotherapy.

In postmenopausal women with oestrogen-receptor positive invasive breast cancer who are at medium or high-risk of disease recurrence, an aromatase inhibitor should be given as first-line therapy. Alternatively, tamoxifen should be given if an aromatase inhibitor is not tolerated or is contra-indicated, or if the risk of disease recurrence is low.

**Extended endocrine therapy**

Extended endocrine therapy (total duration longer than 5 years) with an aromatase inhibitor [unlicensed indication] should be offered to postmenopausal women with oestrogen-receptor–positive invasive breast cancer at medium or high-risk of disease recurrence who have been taking tamoxifen for 2 to 5 years. Extended therapy should also be considered in postmenopausal women at low risk of disease recurrence.

Extended tamoxifen therapy for longer than 5 years can also be considered in both premenopausal and postmenopausal women with oestrogen-receptor–positive invasive breast cancer.

**Endocrine therapy for ductal carcinoma in situ**

Following breast-conserving surgery, endocrine therapy should be offered to women with oestrogen-positive ductal carcinoma in situ, if radiotherapy is recommended but not given. If radiotherapy is not recommended, the use of endocrine therapy should also be considered.

**Bisphosphonate therapy**

Zoledronic acid p. 732 and sodium clodronate p. 731 have been shown to improve disease-free survival and overall survival in postmenopausal women with node-positive invasive breast cancer. However, there is insufficient evidence to recommend their use in premenopausal women.

Intravenous zoledronic acid [unlicensed indication] or oral sodium clodronate [unlicensed indication] should be offered to postmenopausal women with lymph-node-positive invasive breast cancer. Treatment should be considered in those with lymph-node-negative invasive breast cancer who are at high-risk of recurrence.
Bisphosphonate therapy is also recommended in women at high-risk of osteoporosis due to the use of aromatase inhibitors in postmenopausal women, or in women with treatment-induced premature menopause. For further information, see Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group, 2008.

**Neoadjuvant drug therapy**

Neoadjuvant drug therapy may involve the use of chemotherapy or endocrine therapy.

**Chemotherapy**

Neoadjuvant chemotherapy should be offered to reduce tumour size in patients with oestrogen-receptor-negative invasive breast cancer. In patients with oestrogen-receptor-positive invasive breast cancer, chemotherapy should be considered. In patients with HER2-positive invasive breast cancer, neoadjuvant chemotherapy should be offered in combination with trastuzumab p. 885 and pertuzumab p. 880.

A chemotherapy regimen containing both a platinum [unlicensed indication] and an anthracycline should be considered in patients with triple-negative invasive breast cancer (oestrogen-receptor-negative, progesterone-receptor negative and HER2-negative).

**Endocrine therapy**

If chemotherapy is not indicated, neoadjuvant endocrine therapy should be considered as an alternative in postmenopausal women with oestrogen-receptor-positive invasive breast cancer. Chemotherapy and endocrine therapy are equally effective in postmenopausal women in terms of breast-conservation and shrinking of the tumour. Although chemotherapy is more effective than endocrine therapy at shrinking the tumour in premenopausal women, some tumours may respond to endocrine treatment.

**Advanced breast cancer**

Treatment of advanced breast cancer depends on the patient’s treatment history, disease severity, and oestrogen receptor and HER2 status.

**Endocrine therapy**

For the majority of patients with oestrogen-receptor-positive advanced breast cancer, endocrine therapy is recommended as first-line treatment. Aromatase inhibitors should be offered to postmenopausal women with no previous history of endocrine treatment, or to those previously treated with tamoxifen p. 953.

Tamoxifen in combination with ovarian function suppression should be offered as first-line treatment to pre- and perimenopausal women with oestrogen-receptor-positive advanced breast cancer not previously treated with tamoxifen.

Ovarian function suppression should be offered to pre- and perimenopausal women who have had disease progression despite treatment with tamoxifen.

Tamoxifen should be offered as first-line treatment to men with oestrogen-receptor-positive advanced breast cancer.

**Chemotherapy**

Chemotherapy should be offered as first-line treatment in patients with oestrogen-receptor-positive advanced breast cancer that is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement. Once chemotherapy treatment is completed, endocrine therapy should be offered. The choice of chemotherapy regimen is usually guided by local policy, Cancer Alliances, and the National Cancer Drugs Fund list.

**Biological therapy**

Trastuzumab is recommended for the treatment of HER2-positive advanced breast cancer. It is used in combination with paclitaxel p. 925 in those who have not received chemotherapy for metastatic breast cancer, and as monotherapy for patients who have received at least two chemotherapy regimens for metastatic breast cancer (see trastuzumab National funding/access decisions).

**Bisphosphonate therapy**

The use of bisphosphonates should be considered in patients with metastatic breast cancer to reduce pain and prevent skeletal complications of bone metastases.

**Familial breast cancer**

Chemoprevention should be offered to all women who have been identified as being at high-risk of developing breast cancer. Chemoprevention should also be considered in women at moderate-risk. Other strategies to reduce breast cancer risk should also be considered, for example bilateral mastectomy or bilateral oophorectomy. Women who were at high-risk of breast cancer and have undergone a bilateral mastectomy should not receive chemoprevention.

**Treatment options for chemoprevention**

Chemoprevention should only be continued for 5 years. Tamoxifen [unlicensed indication] is recommended for premenopausal women who do not have a history of, or increased risk of thromboembolic disease or endometrial cancer.

Anastrozole p. 954 [unlicensed indication] is recommended in postmenopausal women who do not have severe osteoporosis, see Osteoporosis p. 725. In women who have severe osteoporosis, or who do not wish to take anastrozole, treatment with tamoxifen can be given, provided there is no history, or increased risk of thromboembolic disease or endometrial cancer. Alternatively, raloxifene hydrochloride p. 754 is an option [unlicensed indication] in postmenopausal women with a uterus who do not wish to take tamoxifen, unless there is a history or increased risk of thromboembolic disease.

**Treatment of menopausal symptoms**

Some treatments used in the management of breast cancer, such as tamoxifen or ovarian function suppression may lead to menopausal symptoms or early menopause, and women should be counselled about these side-effects prior to starting any of these treatments.

Women diagnosed with breast cancer should discontinue their hormone replacement therapy (HRT) because of possible tumour stimulation and interference with adjuvant endocrine therapy. HRT should not be offered routinely to women with menopausal symptoms if they have a history of breast cancer; however, in exceptional circumstances, HRT can be offered to women with severe menopausal symptoms once the associated risks have been discussed.

Selective serotonin re-uptake inhibitor (SSRIs) antidepressants may be offered to relieve menopausal symptoms such as hot flushes in women with breast cancer who are not taking tamoxifen. Clonidine hydrochloride p. 145, venlafaxine p. 368 [unlicensed indication] and gabapentin p. 315 [unlicensed indication] are sometimes used for the treatment of hot flushes in women with breast cancer after discussion with the patient and information given about side effects.

**Useful Resources**


www.nice.org.uk/guidance/ng101


www.nice.org.uk/guidance/cg81

Prostate Cancer

31 May 2016

Description of condition
Prostate cancer is the most common form of cancer affecting men. The main risk factors are age (most cases being diagnosed in men over 65 years of age), ethnicity (more common in black African–Caribbean men), and a familial component. Prostate cancer is usually slow-growing and asymptomatic at diagnosis, however, the presenting symptoms of advanced disease are usually urinary outflow obstruction, or, pelvic or back pain due to bone metastases. Treatment decisions are guided by baseline prostate specific antigen (PSA) levels, tumour grade (Gleason score), the stage of the tumour, the patient’s life expectancy (based on age and comorbid conditions), treatment morbidity, and patient preference.

Aims of treatment
In early or locally advanced prostate cancer, radical treatment aims to eliminate the malignancy. In metastatic disease, drug therapy is aimed at prolonging survival and reducing symptoms.

Drug treatment
Treatment options for patients with prostate cancer include active monitoring, radical prostatectomy, external beam radiotherapy, and brachytherapy. Hormone therapy (androgen deprivation or anti-androgens) is the primary treatment for metastatic prostate cancer, but is also increasingly being used for patients with locally advanced, non-metastatic disease.

In patients with localised prostate cancer, the choice of treatment is guided by whether the disease is considered low, intermediate, or high risk according to the Gleason score, the serum PSA level, and the tumour stage.

Localised or locally advanced prostate cancer
In patients with low-risk localised prostate cancer, and those at intermediate risk who decline radical treatments (prostatectomy or radiotherapy), active monitoring is a suitable option. This involves close monitoring to avoid unnecessary treatment until disease progression occurs (or until the patient requests treatment).

In patients with intermediate-risk or high-risk localised prostate cancer (when there is a realistic prospect of long-term disease control) and in those with locally advanced disease, radical prostatectomy or radical radiotherapy should be offered. Other treatment options include a combination of radical radiotherapy and androgen deprivation therapy, consisting of 6 months of androgen deprivation therapy before, during or after radiotherapy. Pelvic radiotherapy should be considered in those with locally advanced prostate cancer who have a higher than 15% risk of pelvic lymph node involvement and are to receive neoadjuvant hormonal therapy.

Androgen deprivation therapy involves the use of a luteinising hormone-releasing hormone (LHRH) agonist (buserelin p. 738, goserelin p. 739, leuprorelin acetate p. 740, or triptorelin p. 741), or bilateral orchidectomy, which removes the supply of endogenous hormone. Androgen deprivation therapy may be continued for up to 3 years in patients with high-risk localised prostate cancer.

Patients should be informed about the side-effects of treatment, particularly urinary and sexual dysfunction, loss of fertility, radiation-induced enteropathy, and hot flushes. Although there is limited evidence, intermittent therapy may be considered for patients who are having long-term androgen deprivation therapy, to reduce drug toxicity. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment with androgen deprivation therapy and prophylactic anti-androgen therapy (such as cyproterone acetate p. 770) may be added.

Medroxyprogesterone acetate p. 810 [unlicensed indication] can be used, initially for up to 10 weeks, to manage troublesome hot flushes caused by long-term androgen suppression; cyproterone acetate is an alternative if medroxyprogesterone acetate is not effective or not tolerated.

Patients who experience a reduction in libido and loss of sexual function should have access to specialist erectile dysfunction services and be considered for treatment with a phosphodiesterase type-5 inhibitor.

Osteoporosis and fatigue may also be a problem with androgen deprivation therapy. A bisphosphonate can be offered to men who have osteoporosis; denosumab p. 734 is an alternative if bisphosphonates are not appropriate. Gynaecomastia can occur with long-term (longer than 6 months) bicalutamide p. 947 treatment. Prophylactic radiotherapy (within the first month of treatment), or weekly tamoxifen p. 953 [unlicensed indication], if radiotherapy is unsuccessful, can be considered.

Metastatic prostate cancer
Bilateral orchidectomy should be offered to all patients with metastatic prostate cancer as an alternative to continuous LHRH agonist treatment. Anti-androgen monotherapy with bicalutamide [unlicensed indication] can be offered to those who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function. However, if satisfactory sexual function is not maintained, stop bicalutamide and start androgen deprivation therapy.

Ablative therapy p. 946 (in combination with prednisone or prednisolone p. 678) and enzalutamide p. 947 are both recommended as options for the treatment of castration-resistant metastatic prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel p. 924-containing chemotherapy regimen.

In patients who develop hormone-relapsed metastatic tumour, chemotherapy with docetaxel can be used. It is recommended to stop the treatment with docetaxel after 10 cycles, or if severe adverse events occurred, or if there is evidence of disease progression.

Ablative therapy p. 946 (in combination with prednisone or prednisolone) is also recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated.

In patients with hormone-relapsed prostate cancer, a corticosteroid, such as dexamethasone p. 675, can be offered as third line therapy, after androgen deprivation therapy and anti-androgen therapy. A

Useful Resources

www.nice.org.uk/guidance/cg175

Other drugs used for Hormone responsive malignancy
Ethinyloxadiol, p. 759 - Norethisterone, p. 764
Abiraterone acetate

**INDICATIONS AND DOSE**

Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel-containing chemotherapy regimen (in combination with prednisone or prednisolone) or Metastatic castration-resistant prostate cancer in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (in combination with prednisone or prednisolone)

- **BY MOUTH**

  - Adult: 1 g once daily, for dose of concurrent prednisone or prednisolone—consult product literature

**CAUTIONS**

Diabetes (increased risk of hyperglycaemia—monitor blood sugar frequently) | history of cardiovascular disease

**CAUTIONS, FURTHER INFORMATION**

- Cardiovascular disease: Correct hypertension and hypokalaemia before treatment (if significant risk of congestive heart failure, such as history of cardiac failure, uncontrolled hypertension or cardiac events, consult product literature for management and increased monitoring).

**INTERACTIONS**

→ Appendix 1: abiraterone

**SIDE-EFFECTS**

- Common or very common: Angina pectoris, arrhythmias, bone fracture, diarrhoea, dyspepsia, haematuria, heart failure, hepatic disorders, hypertension, hypertriglyceridaemia, hypokalaemia, left ventricular dysfunction, osteoporosis, peripheral oedema, rash, sepsis, urinary tract infection

- Uncommon: Adrenal insufficiency, myopathy

- Rare or very rare: Alveolitis allergic

- Frequency not known: Myocardial infarction, QT interval prolongation

**CONCEPTION AND CONTRACEPTION**

Men should use condoms if their partner is pregnant, and use condoms in combination with another effective contraceptive method to avoid in severe impairment.

**HEPATIC IMPAIRMENT**

Manufacturer advises use with caution in moderate impairment and only if benefit clearly outweighs risk; avoid in severe impairment.

**RENAL IMPAIRMENT**

Use with caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor blood pressure, serum potassium concentration, and fluid balance before treatment, and at least monthly during treatment—consult product literature for management of hypertension, hypokalaemia and oedema.

- Monitor liver function before treatment, then every 2 weeks for the first 3 months of treatment, then monthly thereafter—interrupt treatment if serum alanine aminotransferase or aspartate aminotransferase greater than 5 times the upper limit (consult product literature for details of restarting treatment at a lower dose) and discontinue permanently if 20 times the upper limit.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (updated July 2016) NICE TA259

  - Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer only if:

  - their disease has progressed on or after one docetaxel-containing chemotherapy regimen, and

  - the manufacturer provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

  Patients currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet the first criteria should be able to continue therapy until they and their clinician consider it appropriate to stop.

  - www.nice.org.uk/guidance/ta259

- Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (updated July 2016) NICE TA387

  - Abiraterone, in combination with prednisone or prednisolone, is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

    - in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated

    - only when the manufacturer provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

  - www.nice.org.uk/guidance/ta387

**Scottish Medicines Consortium (SMC) decisions**

**SMC No. 764/12**

The **Scottish Medicines Consortium** has advised (August 2012) that abiraterone acetate (Zytiga®), in combination with prednisone or prednisolone, is accepted for restricted use within NHS Scotland for the treatment of metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with docetaxel-containing chemotherapy regimen, and have received only one prior chemotherapy regimen. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

**SMC No. 873/13**

The **Scottish Medicines Consortium** has advised (October 2015) that abiraterone acetate (Zytiga®) in combination with prednisone or prednisolone, is accepted for use within NHS Scotland for the treatment of metastatic castration-resistant prostate cancer in patients who are asymptomatic or mildly symptomatic, after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 23**

  - Zytiga (Janssen-Cilag Ltd)

  - Abiraterone acetate 500 mg Zytiga 500mg tablets 1 56 tablet pack £2,735.00

Apalutamide

**DRUG ACTION**

Apalutamide is an androgen receptor inhibitor that decreases tumour cell proliferation and increases apoptosis.

**INDICATIONS AND DOSE**

Prostate cancer (specialist use only)

- **BY MOUTH**

  - Adult: 240 mg once daily, for dose adjustments due to side-effects—consult product literature

**CONTRA-INDICATIONS**

History or risk of seizures
**Bicalutamide**  07-Jun-2018

- **INDICATIONS AND DOSE**
  Locally advanced prostate cancer at high risk of disease progression either alone or as adjuvant treatment to prostatectomy or radiotherapy / Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate
  - BY MOUTH
    - Adult: 150 mg once daily
  Advanced prostate cancer, in combination with gonadorelin analogue or surgical castration
  - BY MOUTH
    - Adult: 50 mg once daily, to be started at the same time as surgical castration or at least 3 days before gonadorelin therapy

- **PROSTATE CANCER (METASTATIC) WITH THE AIM OF RETAINING SEXUAL FUNCTION.**
  - BY MOUTH
    - Adult: 150 mg once daily

- **UNLICENSED USE**
  Bicalutamide is used in prostate cancer (metastatic) with the aim of retaining sexual function, but it is not licensed for this indication.

- **CAUTIONS**
  Risk of photosensitivity—avoid excessive exposure to UV light and sunlight

- **INTERACTIONS**
  Appendix 1: bicalutamide

- **SIDE-EFFECTS**
  - Common or very common
    - Alopecia
    - Anaemia
    - Appetite decreased
    - Asthenia
    - Breast tenderness
    - Chest pain
    - Constipation
    - Depression
    - Dizziness
    - Drowsiness
    - Flatulence
    - Gastrointestinal discomfort
    - Gynaecomastia
    - Haematuria
    - Hair changes
    - Hepatic disorders
    - Hot flush
    - Hypertension
    - Memory loss
    - Muscle weakness
    - Nasal congestion
    - Oedema
    - Skin reactions
    - Weight increased
  - Uncommon
    - Angioedema
    - Interstitial lung disease

- **MONITORING REQUIREMENTS**
  Consider periodic liver function tests.

- **PATIENT AND CARER ADVICE**
  Risk of photosensitivity. Patients should be advised to consider the use of sunscreen.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- **Erleada** (Janssen-Cilag Ltd)
  - **Aplutamide 60 mg** Erleada 60mg tablets | 122 tablet
  - £2,735.00

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**Enzalutamide**  14-Jul-2018

- **INDICATIONS AND DOSE**
  Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after docetaxel therapy
  - BY MOUTH
    - Adult: 160 mg once daily, for dose adjustments due to side-effects, consult product literature

- **DOSE ADJUSTMENTS DUE TO INTERACTIONS**
  - Manufacturer advises if concurrent use of potent inhibitors of CYP2C8 is unavoidable, reduce dose to 80 mg daily.

- **CAUTIONS**
  Alcoholism
  Bradycardia
  Brain injury
  Brain metastases
  Brain tumours
  History of QT-interval prolongation
  History or risk of seizure
  Recent cardiovascular disease
  Risk factors for QT-interval prolongation
  Stroke
  Uncontrolled hypertension

- **INTERACTIONS**
  Appendix 1: enzalutamide

- **SIDE-EFFECTS**
  - Common or very common
    - Anxiety
    - Asthenia
    - Bone fracture
    - Concentration impaired
    - Fall
    - Gynaecomastia
    - Headache
    - Hot flush
    - Hypertension
    - Memory loss
    - Muscle weakness
    - Nasal congestion
    - Oral disorders
    - Posterior reversible encephalopathy syndrome
    - QT interval prolongation
    - Throat oedema
    - Thrombocytopenia
    - Vomiting
  - Uncommon
    - Cognitive disorder
    - Leucopenia
    - Neutropenia
    - Seizure
    - Visual hallucinations
  - Frequency not known
    - Back pain
    - Diarrhoea
    - Muscle complaints
    - Muscle weakness
    - Nausea
    - Oral disorders
    - Posterior reversible encephalopathy syndrome
    - Scrotal swelling
  - Hypersensitivity
    - Photosensitivity reaction

- **CONCEPTION AND CONTRACEPTION**
  Men should use condoms during treatment and for 3 months after stopping treatment if their partner is of child-bearing potential—risk of fetal toxicity in animal studies.

- **RENAL IMPAIRMENT**
  Caution in severe impairment—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (January 2016) NICE TA377

Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer in patients who have mild or no symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated,
and only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. www.nice.org.uk/TA377

**HEPATIC IMPAIRMENT**

Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer in adults only if, their disease has progressed during or after docetaxel-containing chemotherapy, and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. This guidance does not cover the use of enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with abiraterone.

www.nice.org.uk/TA316

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

| CAUTIONARY AND ADVISORY LABELS | 25 |
| Xtandi (Astellas Pharma Ltd) | Enzalutamide 40 mg | 112 capsule | PTX |
| £2,734.67 DT = £2,734.67 |

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**Flutamide** 28-Mar-2017

**INDICATIONS AND DOSE**

Advanced prostate cancer | Metastatic prostate cancer refractory to gonadorelin analogue therapy (monotherapy)

**CAUTIONS** Avoid excessive alcohol consumption - avoid in Acute porphyrias p. 1058 • cardiac disease (oedema reported).

**SIDE-EFFECTS**

- Common or very common Appetite abnormal • asthma • breast abnormalities • diarrhoea • drowsiness • galactorrhoea • gynaecomastia • hepatic function abnormal (sometimes fatal) • hepatitis (sometimes fatal) • insomnia • nausea • vomiting
- Rare or very rare Alopecia • anxiety • breast neoplasm • cardiovascular disorder • chest pain • constipation • cough • depression • dizziness • dyspepsia • gastrointestinal discomfort • gastrointestinal disorders • hair growth abnormal • headache • herpes zoster • hot flush • hypertension • interstitial pneumonitis • libido decreased • lupus-like syndrome • lymphoedema • malaise • muscle cramps • oedema • photosensitivity reaction • skin reactions • thirst • vision blurred
- Frequency not known QT interval prolongation
- HEPATIC IMPAIRMENT Manufacturer advises caution.

**MONITORING REQUIREMENTS** Liver function tests, monthly for first 4 months, periodically thereafter and at the first sign or symptom of liver disorder (e.g. pruritus, dark urine, persistent anorexia, jaundice, abdominal pain, unexplained influenza-like symptoms).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Flutamide (Non-proprietary) |
| Flutamide 250 mg | Flutamide 250mg tablets | 84 tablet | POM |
| £106.24 DT = £106.24 |

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**Diethylstilbestrol** (Stilboestrol) 06-Aug-2018

**INDICATIONS AND DOSE**

**Breast cancer in postmenopausal women**

- **BY MOUTH**
  - Adult: 10–20 mg daily

**Prostate cancer**

- **BY MOUTH**
  - Adult: 1–3 mg daily

**CAUTIONS** Cardiovascular disease

**SIDE-EFFECTS** Bone pain (in breast cancer) • breast abnormalities • cervical mucus increased • cholelithiasis • contact lens intolerance • depression • erectile dysfunction • erythema nodosum • feminisation • fluid retention • gynaecomastia • headaches • hypercalcaemia (in breast cancer) • hypertension • increased risk of thrombosis • jaundice cholestatic • mood altered • nausea • neoplasms • skin reactions • sodium retention • testicular atrophy • uterine disorders • vomiting • weight changes • withdrawal bleed

**PREGNANCY** In first trimester, high doses associated with vaginal carcinoma, urogenital abnormalities, and reduced fertility in female offspring. Increased risk of hypospadias in male offspring.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe or active impairment.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Diethylstilbestrol (Non-proprietary) |
| Diethylstilbestrol 1 mg | Diethylstilbestrol 1mg tablets | 28 tablet | POM |
| £117.85 DT = £117.61 |
| Diethylstilbestrol 5 mg | Diethylstilbestrol 5mg tablets | 28 tablet | POM |
| £185.00–£208.00 DT = £208.00 |

**PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES** ANTI-GONADOTROPHIN-RELEASING HORMONES

**Degarelix** 08-Feb-2019

**INDICATIONS AND DOSE**

Advanced hormone-dependent prostate cancer

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 240 mg, to be administered as 2 injections of 120 mg, then 80 mg every 28 days, dose to be administered into the abdominal region

**CAUTIONS** Diabetes • susceptibility to QT-interval prolongation

**SIDE-EFFECTS**

- Common or very common Anaemia • chills • diarrhoea • dizziness • fatigue • fever • gynaecomastia • headache • hot flush • influenza like illness • insomnia • musculoskeletal discomfort • musculoskeletal pain • nausea • sexual dysfunction • skin reactions • sweat changes • testicular disorders • weight changes
- Uncommon Alopecia • appetite decreased • arrhythmias • bone disorders • breast pain • cognitive impairment • constipation • depression • diabetes mellitus • dry mouth • dyspepsia • gastrointestinal discomfort • genitai discomfort • hyperglycaemia • hypertension • hypotension • joint disorders • malaise • muscle spasms • muscle weakness • numbness • palpitations • pelvic pain • peripheral oedema

www.getintopharma.com
Hormone responsive malignancy 949

Somatostatin analogues, malignant disease

Overview
Lanreotide, octreotide, and pasireotide are somatostatin analogues used for the treatment of hormone-responsive malignancies. They are indicated for the relief of symptoms associated with neuroendocrine tumours. Octreotide and lanreotide are indicated for the treatment of hormone-responsive malignancies, and pasireotide is indicated for the treatment of acromegaly. They work by inhibiting the release of hormones from tumours.

Indications and dose

Somatuline Autogel®

Acromegaly (if somatostatin analogue not given previously)

- By deep subcutaneous injection
  - Adult: Initially 60 mg every 28 days, adjusted according to response (consult product literature), for patients previously treated with somatostatin analogue, consult product literature for initial dose, dose to be given in the gluteal region.

Neuroendocrine (particularly carcinoid) tumours

- By deep subcutaneous injection
  - Adult: Initially 60–120 mg every 28 days, adjusted according to response, dose to be given in the gluteal region.

Unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded

- By deep subcutaneous injection
  - Adult: 120 mg every 28 days.

Somatuline LA®

Acromegaly and neuroendocrine (particularly carcinoid) tumours

- By intramuscular injection
  - Adult: Initially 30 mg every 14 days, increased to 30 mg every 7–10 days, adjusted according to response.

Thyroid tumours

- By intramuscular injection
  - Adult: Initially 30 mg every 14 days, increased to 30 mg every 10 days, adjusted according to response.

Cautions

- Cardiac disorders (including bradycardia), patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment.

Interactions

- Appendix 1: lanreotide

Side effects

- Common or very common: Biliary dilatation, lethargy, muscularkeletal pain, weight decreased.
- Uncommon: Hot flush, insomnia.
- Rare or very rare: Pancreatitis.

Pregnancy

Manufacturer advises use only if potential benefit outweighs risk.

Medicinal forms

- There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

- Firmagon® (Ferring Pharmaceuticals Ltd)
  - Degarelix (as Degarelix acetate) 80 mg: Firmagon 80mg powder and solvent for solution for injection vials 1 vial [Pack] £129.37 DT + £129.37.
  - Degarelix (as Degarelix acetate) 120 mg: Firmagon 120mg powder and solvent for solution for injection vials 2 vial [Pack] £260.00 DT + £260.00.

Pituitary and hypothalamic hormones and analogues

Somatostatin analogues

- CAUTIONS: Diabetes mellitus (antidiabetic requirements may be reduced) - insulinoma (increased depth and duration of hypoglycaemia may occur—observe patients and monitor blood glucose levels when initiating treatment and changing doses) - may cause growth hormone-secreting pituitary tumour expansion during treatment (causing serious complications).

- SIDE-EFFECTS
  - Common or very common: Alopecia - appetite decreased - asthenia - cholecytosis - cholestasis (following long term use) - cholestasis - constipation - diabetes mellitus - diarrhoea - dizziness - gastrointestinal discomfort - gastrointestinal disorders - glucose tolerance impaired (following long term use) - headache - hyperglycaemia (long term use) - hypoglycaemia - myalgia - nausea - pruritus - sinus bradycardia - vomiting.

- CAUTIONS
  - Cardiac disorders (including bradycardia) - patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment.

- INTERACTIONS
  - Appendix 1: lanreotide.

- SIDE-EFFECTS
  - Common or very common: Biliary dilatation, lethargy, muscularkeletal pain, weight decreased.
  - Uncommon: Hot flush, insomnia.
  - Frequency not known: Pancreatitis.

- PREGNANCY
  - Manufacturer advises use only if potential benefit outweighs risk.

www.getintopharma.com
**BREAST FEEDING**  Manufacturer advises caution—no information available.

**MONITORING REQUIREMENTS**  Monitor for hypothyroidism when clinically indicated.

**NATIONAL FUNDING/ACCESS DECISIONS**

All Wales Medicines Strategy Group (AWMSG) decisions

AWMSG No. 1988

The All Wales Medicines Strategy Group has advised (September 2018) that lanreotide (Somatuline® Autogel®) is recommended as an option for use within NHS Wales for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adults with unresectable locally advanced or metastatic disease.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Somatuline Autogel (Ipsen Ltd)
- Lanreotide (as Lanreotide acetate) 120 mg per 1 ml Somatuline Autogel 60mg/0.5ml solution for injection pre-filled syringes
- Lanreotide (as Lanreotide acetate) 180 mg per 1 ml Somatuline Autogel 90mg/0.5ml solution for injection pre-filled syringes
- Lanreotide (as Lanreotide acetate) 240 mg per 1 ml Somatuline Autogel 120mg/0.5ml solution for injection pre-filled syringes
- Lanreotide (as Lanreotide acetate) 30 mg Somatuline LA 30mg powder and solvent for suspension for injection vials

**Powder and solvent for suspension for injection**

- Somatuline LA (Ipsen Ltd)
- Lanreotide (as Lanreotide acetate) 30 mg Somatuline LA 30mg powder and solvent for suspension for injection vials

**INTERACTIONS**

- Common or very common Arrhythmias, biliary sludge, dyspepsia, hyperbilirubinemia, hypothyroidism, skin reactions, thyroid disorder
- Uncommon Dehydration
- Frequency not known Hepatic disorders, pancreatitis acute (after administration), thrombocytopenia

**SIDE-EFFECTS**

- Effective contraception required during treatment.
- Possible effect on fetal growth; manufacturer advises use only if potential benefit outweighs risk.
- Manufacturer advises caution (risk of increased half-life in cirrhosis).
- Manufacturer advises avoid—present in milk in animal studies.
- Manufacturer advises caution (risk of increased half-life in cirrhosis).
- Manufacturer advises consider dose reduction—consult product literature.
- Monitor thyroid function on long-term therapy.
- Monitor liver function.
- With intravenous use ECG monitoring and after dilution.

**Octreotide**

**INDICATIONS AND DOSE**

Symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, glucagonomas

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 micrograms 1–2 times a day, adjusted according to response; increments to 200 micrograms 3 times a day, higher doses may be required exceptionally; maintenance doses are variable; in carcinoid tumours, discontinue after 1 week if no effect, if rapid response required, initial dose may be given by intravenous injection (with ECG monitoring and after dilution)

**Acromegaly**

Short-term treatment before pituitary surgery or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 100–200 micrograms 3 times a day, discontinue if no improvement within 3 months

**Prevention of complications following pancreatic surgery**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: (consult product literature)

**Test dose before use of depot preparation**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Test dose 50–100 micrograms for 1 dose, test dose should be given if subcutaneous octreotide not previously given

**Acromegaly**

Neuroendocrine (particularly carcinoid) tumour adequately controlled by subcutaneous octreotide

- **BY DEEP INTRAMUSCULAR INJECTION USING DEPOT INJECTION**
  - Adult: Initially 20 mg every 4 weeks for 3 months then adjusted according to response, increased if necessary up to 30 mg every 4 weeks, to be administered into the gluteal muscle, for acromegaly, start depot 1 day after the last dose of subcutaneous octreotide, for neuroendocrine tumours, continue subcutaneous octreotide for 2 weeks after first dose of depot octreotide

**Advanced neuroendocrine tumours of the midgut, or tumours of unknown primary origin where non-midgut sites of origin have been excluded**

- **BY DEEP INTRAMUSCULAR INJECTION USING DEPOT INJECTION**
  - Adult: 30 mg every 4 weeks

**Reduce intestinal secretions in palliative care**

- Reduce vomiting due to bowel obstruction in palliative care

- **BY CONTINUOUS SUBCUTANEOUS INFUSION**
  - Adult: 0.25–0.5 mg/24 hours (max. per dose 0.75 mg/24 hours), occasionally doses higher than the maximum are sometimes required
Acromegaly [when surgery has failed or is inappropriate, and control with another somatostatin analogue is inadequate]

- By deep intramuscular injection
  - Adult: Initially 40 mg every 4 weeks, increased if necessary up to 60 mg every 4 weeks, dose may be increased if levels of growth hormone and/or insulin-like growth factor-1 are not fully controlled after 3 months of initial dosing, for dose adjustment due to side-effects—consult product literature

CAUTIONS

Cardiac disorders (including bradycardia)—susceptibility to QT-interval prolongation (including electrolyte disturbances)

INTERACTIONS

- Appendix 1: pasireotide

SIDE-EFFECTS

- Common or very common Adrenal insufficiency - arthralgia - hypotension - QT interval prolongation
- Uncommon Anaemia

PREGNANCY

Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution in moderate impairment (risk of increased exposure); avoid in severe impairment.

Dose adjustments

- With subcutaneous use for Cushing's disease Manufacturer advises reduce initial dose to 300 micrograms twice daily (max. dose 600 micrograms twice daily) in moderate impairment.
- With intramuscular use for Cushing's disease Manufacturer advises max. dose 20 mg every four weeks in moderate impairment.
- When used for Acromegaly Manufacturer advises reduce initial dose to 20 mg every four weeks (max. dose 40 mg every four weeks) in moderate impairment.

RENAL IMPAIRMENT

Manufacturer advises caution in severe impairment—increased plasma-pasireotide exposure.

MONITORING REQUIREMENTS

- Manufacturer advises consider monitoring pituitary function before treatment initiation and periodically thereafter.
- With subcutaneous use Manufacturer advises monitor liver function before treatment initiation, after 1, 2, 4, 8, and 12 weeks of treatment, and thereafter as clinically indicated. Manufacturer advises assess glycaemic status before treatment initiation, weekly for the first 2–3 months of treatment, over the first 2–4 weeks after any dose increase, periodically thereafter, and 3 months after treatment is complete—if glycaemic control is poor, diabetes management and monitoring should be intensified before and during treatment. Manufacturer advises monitor ECG and electrolytes before treatment initiation, after one week of treatment, and periodically thereafter.
- With intramuscular use Manufacturer advises monitor liver function before treatment initiation, after the first 2–3 weeks of treatment, then monthly for 3 months, and thereafter as clinically indicated. Manufacturer advises assess glycaemic status before treatment initiation, weekly for the first 3 months of treatment, over the first 4–6 weeks after any dose increase, periodically thereafter, and 3 months after treatment is complete—if glycaemic control is poor, diabetes management and monitoring should be intensified before and during treatment. Manufacturer advises monitor ECG and electrolytes before treatment initiation, after 3 weeks of treatment, and periodically thereafter.

Pasireotide

INDICATIONS AND DOSE

Cushing's disease [when surgery has failed or is inappropriate]

- By subcutaneous injection
  - Adult: Initially 600 micrograms twice daily for 2 months, then increased if necessary to 900 micrograms twice daily, consider discontinuation if no response after 2 months of treatment, for dose adjustment due to side-effects—consult product literature

- By deep intramuscular injection
  - Adult: Initially 10 mg every 4 weeks, increased if necessary up to 40 mg every 4 weeks, dose may be titrated every 2–4 months based on response and tolerability, consider discontinuation if no clinical benefit observed, for dose adjustment due to side-effects—consult product literature
PROGESTOGENS

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Signifor (Novartis Pharmaceuticals UK Ltd)
  - Pasireotide (as Pasireotide diaspargate) 300 microgram per 1 ml Signifor 0.3mg/1ml solution for injection ampoules | 60 ampoule (PO) £2,800.00
  - Pasireotide (as Pasireotide diaspargate) 600 microgram per 1 ml Signifor 0.6mg/1ml solution for injection ampoules | 60 ampoule (PO) £3,240.00
  - Pasireotide (as Pasireotide diaspargate) 900 microgram per 1 ml Signifor 0.9mg/1ml solution for injection ampoules | 60 ampoule (PO) £3,240.00

Powder and solvent for suspension for injection
- Signifor (Novartis Pharmaceuticals UK Ltd)
  - Pasireotide (as Pasireotide pamoate) 10 mg Signifor 10mg powder and solvent for suspension for injection vials | 1 vial (PO) £2,300.00
  - Pasireotide (as Pasireotide pamoate) 20 mg Signifor 20mg powder and solvent for suspension for injection vials | 1 vial (PO) £2,300.00
  - Pasireotide (as Pasireotide pamoate) 30 mg Signifor 30mg powder and solvent for suspension for injection vials | 1 vial (PO) £2,300.00
  - Pasireotide (as Pasireotide pamoate) 40 mg Signifor 40mg powder and solvent for suspension for injection vials | 1 vial (PO) £2,300.00
  - Pasireotide (as Pasireotide pamoate) 60 mg Signifor 60mg powder and solvent for suspension for injection vials | 1 vial (PO) £2,300.00

Hormone responsive breast cancer

Antineoplastic Drugs > Anti-oestrogens

Fulvestrant 14-Jul-2018

INDICATIONS AND DOSE
Oestrogen-receptor-positive breast cancer
- By deep intramuscular injection
- Adult: 500 mg every 2 weeks for the first 3 doses, then 500 mg every month, to be administered into the buttock

INTERACTIONS
- Appendix 1: fulvestrant

SIDE-EFFECTS
- Uncommon Hepatic disorders - vaginal discharge
- Frequency not known Myalgia

PREGNANCY
- Manufacturer advises avoid—increased incidence of fetal abnormalities and death in animal studies.

 BREAST FEEDING
- Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
- Manufacturer advises caution in mild to moderate impairment—risk of increased exposure; avoid in severe impairment—no information available.

RENAL IMPAIRMENT
- Manufacturer advises caution if creatinine clearance less than 30 ml/minute—no information available.

DIRECTIONS FOR ADMINISTRATION
- 500 mg dose should be administered as one 250-mg injection (slowly over 1–2 minutes) into each buttock.
Tamoxifen

**DRUG ACTION** An anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used as an adjunct in the treatment of female infertility.

**INDICATIONS AND DOSE**

- **Pre- and perimenopausal women with oestrogen-receptor-positive breast cancer not previously treated with tamoxifen**
  - BY MOUTH
    - Adult: 20 mg daily
  - **Anovulatory infertility**
    - BY MOUTH
      - Adult: Initially 20 mg daily on days 2, 3, 4 and 5 of cycle, if necessary the daily dose may be increased to 40 mg then 80 mg for subsequent courses; if cycles irregular, start initial course on any day, with subsequent course starting 45 days later or on day 2 of cycle if menstruation occurs

**Gynaecomastia** (prevention in men undergoing long-term bicalutamide treatment, if radiotherapy unsuccessful)

- BY MOUTH
  - Adult: 20 mg once weekly

**Breast cancer** (chemoprevention in women at moderate-to-high risk)

- BY MOUTH
  - Adult: 20 mg daily for 5 years

**UNLICENSED USE** Tamoxifen may be used as detailed below, although these situations are considered outside the scope of its licence:

- **CONTRA-INDICATIONS** Treatment of infertility contra-indicated if personal or family history of idiopathic venous thromboembolism or genetic predisposition to thromboembolism

**CAUTIONS**

- Acute porphyrias p. 1058

**INTERACTIONS**

- **Common or very common**
  - Alopecia, anaemia, cataract, cerebral ischaemia, constipation, diarrhoea, dizziness, embolism and thrombosis, fatigue, fluid retention -

**SIDE-EFFECTS**

- Headache, hepatic disorders, hot flush, hypersensitivity, hypertriglyceridaemia, muscle complaints, nausea, neoplasms, retinopathy, sensation abnormal, skin reactions, taste altered, uterine disorders, vaginal haemorrhage, vomiting, vulvovaginal disorders

- **Uncommon**
  - Hypercalcaemia, interstitial pneumonitis, leucopenia, pancreatitis, thromboembolism, vision disorders

- **Rare or very rare**
  - Agranulocytosis, angioedema, corneal changes, cutaneous lupus erythematosus, cutaneous vasculitis, cystic ovarian swelling, nerve disorders, neutropenia, radiation recall reaction, Stevens-Johnson syndrome, tumour flare

**FURTHER INFORMATION**

- **SIDE-EFFECTS**
  - Increased endometrial changes, including hyperplasia, polyps, cancer, and uterine sarcoma reported; prompt investigation required if abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure in those receiving (or who have received) tamoxifen.

- **Risk of thromboembolism** Tamoxifen can increase the risk of thromboembolism particularly during and immediately after major surgery or periods of immobility (consider interrupting treatment and initiating anticoagulant measures).

**CONCEPTION AND CONTRACEPTION** Unless being used in the treatment of female infertility, effective contraception must be used during treatment and for 2 months after stopping. Patients being treated for infertility should be warned that there is a risk of multiple pregnancy (rarely more than twins).

**PREGNANCY** Avoid—possible effects on fetal development.

**BREAST FEEDING** Suppresses lactation. Avoid unless potential benefit outweighs risk.

**PATIENT AND CARER ADVICE**

- Endometrial changes Patients should be informed of the risk of endometrial cancer and told to report relevant symptoms promptly.

- Thromboembolism Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness and any pain in the calf of one leg.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

<table>
<thead>
<tr>
<th>Oral solution</th>
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<tbody>
<tr>
<td>Tamoxifen (Non-proprietary)</td>
</tr>
<tr>
<td>Tamoxifen (as Tamoxifen citrate) 2 mg per 1 ml Tamoxifen 10mg/5ml oral solution sugar-free sugar-free</td>
</tr>
<tr>
<td>Tablet</td>
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<tr>
<td>Tamoxifen (Non-proprietary)</td>
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<tr>
<td>Tamoxifen (as Tamoxifen citrate) 10 mg Tamoxifen 10mg tablets</td>
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<tr>
<td>Tamoxifen (as Tamoxifen citrate) 20 mg Tamoxifen 20mg tablets</td>
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<tr>
<td>Tamoxifen (as Tamoxifen citrate) 40 mg Tamoxifen 40mg tablets</td>
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**Toremifene**

**INDICATIONS AND DOSE**

- Hormone-dependent metastatic breast cancer in postmenopausal women
  - BY MOUTH
    - Adult: 60 mg daily

**CONTRA-INDICATIONS** Bradycardia, electrolyte disturbances (particularly uncorrected hypokalaemia), endometrial hyperplasia, heart failure with reduced left-
HORMONE ANTAGONISTS AND RELATED AGENTS

Anastrozole

28-May-2018

INDICATIONS AND DOSE
Adjuvant treatment of oestrogen-receptor-positive early invasive breast cancer in postmenopausal women
Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy
Advanced breast cancer in postmenopausal women which is oestrogen-receptor-positive or responsive to tamoxifen

SIDE-EFFECTS
Frequency not known

CONTRA-INDICATIONS
Not for postmenopausal women

CAUTIONS
Susceptibility to osteoporosis

LICENSED USE
Anastrozole is used for chemoprevention of breast cancer, but it is not licensed for this indication.

CONTRA-INDICATIONS
Not indicated for premenopausal women

CAUTIONS
Avoid in Acute porphyrias p. 1058.

INTERACTIONS
Appendix 1: toremifene

SCOTTISH MEDICINES CONSORTIUM (SMC) decisions
The Scottish Medicines Consortium (SMC) has advised (August 2005 and October 2006) that anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland, within the licensed indications, for early breast cancer and early invasive breast cancer.

NATIONAL FUNDING/ACCESS DECISIONS

ARIMIDEX®

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (August 2005 and October 2006) that anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland, within the licensed indications, for early breast cancer and early invasive breast cancer.

NATIONAL FUNDING/ACCESS DECISIONS

Exemestane

12-Jul-2018

INDICATIONS AND DOSE
Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy
Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed

SIDE-EFFECTS
Common or very common

CONTRA-INDICATIONS
Not indicated for premenopausal women

INTERACTIONS
Appendix 1: exemestane

CAUTIONS
Avoid in Acute porphyrias p. 1058.

LICENSED USE
Exemestane is used for chemoprevention of breast cancer, but it is not licensed for this indication.

CONTRA-INDICATIONS
Not for postmenopausal women

CAUTIONS
Susceptibility to osteoporosis

SIDE-EFFECTS
Frequency not known

SCOTTISH MEDICINES CONSORTIUM (SMC) decisions
The Scottish Medicines Consortium has advised (October 2005) that exemestane (Aromasin®) is accepted for restricted use within NHS Scotland as an adjuvant treatment in postmenopausal women with oestrogen-receptor-positive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

NATIONAL FUNDING/ACCESS DECISIONS
Immunotherapy responsive malignancy

ANTINEOPLASTIC DRUGS

Talimogene laherparepvec

- **DRUG ACTION** Talimogene laherparepvec is an oncolytic immunotherapy derived from herpes simplex virus type-1 which causes tumour lysis and the release of tumour-derived antigens.

- **INDICATIONS AND DOSE**
  - Unresectable metastatic melanoma with no bone, brain, or visceral disease
  - By intraleisional injection
  - Adult: consult product literature

- **CONTRA-INDICATIONS**
  - Severely immunocompromised patients

- **CONTRA-INDICATIONS, FURTHER INFORMATION**
  - Manufacturer advises caution in patients who are severely immunocompromised, for example, those with severe congenital or acquired cellular and/or humoral immune deficiency—may be at increased risk of disseminated herpetic infection.

- **CAUTIONS**
  - Administration of antivirals (may interfere with effectiveness of Imlygic®) - autoimmune disease - immunocompromised patients - multiple myeloma (risk of plasmacytoma at injection site)

- **CAUTIONS, FURTHER INFORMATION**
  - Immunocompromised patients
  - Manufacturer advises caution in patients who are immunocompromised, for example, those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency, or in those who require chronic high-dose steroids or other immunosuppressive agents—risk of disseminated herpetic infection.

- **SIDE-EFFECTS**
  - Common or very common - anaemia, anxiety, arthralgia, chill, confusion, constipation, cough, deep vein thrombosis, dehydration, depression, diarrhoea, dizziness, dyspnoea exertional, ear pain, fatigue, fever, flushing, gastrointestinal discomfort, headache, hypertension, immune-mediated events, increased risk of infection, influenza like illness, insomnia, malaise, myalgia, nausea, neoplasm complications, oropharyngeal pain, pain, peripheral oedema, post procedural infection, respiratory disorders, vasculitis

  - Uncommon - Glomerulonephritis - injection site plasmacytoma - post procedural infection - respiratory disorders - vasculitis

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Necrosis or ulceration of tumour tissue may occur, and impaired healing at the injection site has been reported.
  - Manufacturer advises careful wound care and infection precautions; if persistent infection or delayed healing develops, the risks and benefits of continuing treatment should be considered.
Imlygic
Talimogene laherparepvec is recommended as an option for treating unresectable metastatic melanoma (September 2016)

Talimogene laherparepvec is recommended as an option for treating unresectable, regionally or distantly metastatic (Stage IIIb, IIIc or IV Melanoma) melanoma that has not spread to bone, brain or other internal organs, only if:

- treatment with systemically administered immunotherapies is not suitable and,
- the manufacturer provides talimogene laherparepvec with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA410

- CONCEPTION AND CONTRACEPTION Manufacturer advises use of latex condoms.
- PREGNANCY Manufacturer advises avoid—no information available.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- DIRECTIONS FOR ADMINISTRATION Consult product literature for information on injection technique.
- HANDLING AND STORAGE Manufacturer advises caution in handling—risk of accidental exposure; avoid preparation or administration if immunocompromised or pregnant. For further information, see the Physician’s Brochure provided by the manufacturer. Store and transport frozen at -90°C to -70°C—consult product literature for further information on thawing and storage after thawing.
- PATIENT AND CARER ADVICE Manufacturer advises that patients and carers should be informed about the risks of treatment, advised to avoid touching or scratching injection sites, and to keep these sites covered with occlusive dressings. Close contacts should avoid direct contact with injected lesions or body fluids of treated patients during treatment and for up to 30 days after last treatment—if exposed, clean the affected area and seek medical attention if symptoms of herpetic infection develop; close contacts who are immunocompromised or pregnant should not be exposed to potentially contaminated materials. For further information, see the Information for Patients and Close Contacts provided by the manufacturer.

Provide patient alert card—record batch number for each administration of Imlygic®.

Driving and skilled tasks Manufacturer advises that patients and their carers should be counselled on the effects on driving and performance of skilled tasks—risk of dizziness and confusion.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Talimogene laherparepvec for treating unresectable metastatic melanoma (September 2016)

Talimogene laherparepvec is recommended as an option for treating unresectable, regionally or distantly metastatic (Stage IIIb, IIIc or IV Melanoma) melanoma that has not spread to bone, brain or other internal organs, only if:

- treatment with systemically administered immunotherapies is not suitable and,
- the manufacturer provides talimogene laherparepvec with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA410

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for injection EXCipients: May contain Sorbitol ELECTROLYTES: May contain Sodium

Imlygic (Amgen Ltd.)

Talimogene laherparepvec 1 million plaque forming units per 1 ml Imlygic 1 million plaque forming units/1ml solution for injection vials | 1 vial £1,670.00

Talimogene laherparepvec 100 million plaque forming units per 1 ml Imlygic 100 million plaque forming units/1ml solution for injection vials | 1 vial £1,670.00

IMMUNOSTIMULANTS > INTERFERONS

Interferon alfa

- DRUG ACTION Interferon alfa has shown some antitumour effect in certain lymphomas and solid tumours.

- INDICATIONS AND DOSE

INTRA® PEN

Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine) | Hairy cell leukaemia | Follicular lymphoma | Lymphoid or liver metastases of carcinoid tumour | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | Maintenance of remission in multiple myeloma

- BY SUBCUTANEOUS INJECTION
  - Adult: (consult local protocol)

INTRA® VIALS

Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine) | Hairy cell leukaemia | Follicular lymphoma | Lymphoid or liver metastases of carcinoid tumour | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | Maintenance of remission in multiple myeloma

- BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INFUSION
  - Adult: (consult local protocol)

ROFERON-A®

Chronic myelogenous leukaemia | Hairy cell leukaemia | Chronic hepatitis B | Chronic hepatitis C | Adjunct to surgery in malignant melanoma | AIDS-related Kaposi’s sarcoma | Advanced renal cell carcinoma | Progressive cutaneous T-cell lymphoma | Follicular non-Hodgkin’s lymphoma

- BY SUBCUTANEOUS INJECTION
  - Adult: (consult local protocol)

- CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION For contra-indications consult product literature and local treatment protocol.

- CAUTIONS

CAUTIONS, FURTHER INFORMATION For cautions consult product literature and local treatment protocol.

- INTERACTIONS → Appendix 1: interferons

- SIDE-EFFECTS

  - Common or very common Alopecia | anaemia | anxiety | appetite abnormal | arrhythmias | arthritis | asthma | atioventricular block | breast pain | chest pain | chills | concentration impaired | confusion | constipation | cough | cyanosis | decreased leucocytes | dehydration | depression | diarrhoea | dizziness | drowsiness | dry mouth | dyspnoea | electrolyte imbalance | eye disorders | eye inflammation | eye pain | fever | flushing | gastrointestinal discomfort | haemorrhage | headaches | hepatic disorders | hyperhidrosis | hypertension | hyperthyroidism | hyperuricaemia | hypothyroidism | increased risk of infection | influenza like illness | lymphadenopathy | malaise | menstrual cycle irregularities | mood altered | muscle complaints | nasal complaints | nausea | oedema | oral disorders | pain | palpitations | respiratory disorders | sensation abnormal | sexual dysfunction | skin reactions | sleep disorders | taste altered | thirst | thrombocytopenia | tinnitus | tremor | urinary frequency increased | vaginal disorder | vertigo | vision disorders | vomiting | weight decreased

  - Uncommon Behaviour abnormal | hypotension | memory loss | nerve disorders | pericarditis | proteinuria | psychiatric disorders

  - Rare or very rare Agranulocytosis | angioedema | aplastic anaemia | autoimmune disorder | cardiac arrest |
cardiomyopathy - central nervous system haemorrhage - cerebrovascular insufficiency - coma (more common with high doses in the elderly) - congestive heart failure - consciousness impaired - diabetes mellitus - embolism and thrombosis - encephalopathy - gastrointestinal disorders - haemolytic anaemia - hallucination - hearing impairment - hyperglycaemia - hyperlipidaemia - hypertriglyceridaemia (sometimes severe) - injection site necrosis - mucosal dryness - myocardial infarction - myocardial ischaemia - myopathy - nph reticulocyte syndrome - pancreatitis - peripheral ischaemia - psychosis - pulmonary oedema - renal impairment - retinopathy - sarcoidosis - seizure (more common at high doses) - sepsis - severe cutaneous adverse reactions (SCARs) - suicidal tendencies - systemic lupus erythematosus (SLE) - thyroid disorder - ulcerative colitis - vasculitis

- Frequency not known: Hepatitis B reactivation - neutropenia - pericardial effusion - pulmonary arterial hypertension - pure red cell aplasia - tongue discoloration - transplant rejection

- CONCEPTION AND CONTRACEPTION: Effective contraception required during treatment—consult product literature.

- PREGNANCY: Avoid unless potential benefit outweighs risk (toxicity in animal studies).

- BREAST FEEDING: Unlikely to be harmful.

- HEPATIC IMPAIRMENT: Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment. Monitoring Close monitoring required in mild to moderate hepatic impairment.

- RENAL IMPAIRMENT: Avoid in severe renal impairment. Monitoring Close monitoring required in mild to moderate renal impairment.

- MONITORING REQUIREMENTS: Monitoring of lipid concentration is recommended.

- DIRECTIONS FOR ADMINISTRATION
  - INTRONA A® VIALS: IntronaA® injection vials for subcutaneous injection or intravenous infusion.

- NATIONAL FUNDING/ACCESS DECISIONS
  - NICE decisions
    - Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200
    - Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa. www.nice.org.uk/Ta200

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

- Introna (Merck Sharp & Dohme Ltd)
  - Interferon alfa-2b 10 mega u per 1 ml Introna 10million units/1ml solution for injection vials | 1 vial (POD) £113.94
  - Introna 20million units/0.5ml solution for injection multidose vials | 1 vial (POD) £103.94
  - Interferon alfa-2b 15 mega u per 1 ml Introna 1Bmillion units/1.2ml solution for injection multidose pens | 1 pre-filled disposable injection (POD) £74.83
  - Interferon alfa-2b 25 mega u per 1 ml Introna 30million units/1.2ml solution for injection multidose pens | 1 pre-filled disposable injection (POD) £124.72
  - Interferon alfa-2b 50 mega u per 1 ml Introna 60million units/1.2ml solution for injection multidose pens | 1 pre-filled disposable injection (POD) £243.45

- Roferon-A (Roche Products Ltd)
  - Interferon alfa-2a 6 mega u per 1 ml Roferon-A 3million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (POD) £14.20 DT = £14.20
  - Interferon alfa-2a 9 mega u per 1 ml Roferon-A 4.5million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (POD) £21.29 DT = £21.29
  - Interferon alfa-2a 12 mega u per 1 ml Roferon-A 6million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (POD) £28.37 DT = £28.37

- CONTRA-INDICATIONS: Simultaneous administration of foreign proteins including immunological products (such as vaccines)—risk of exaggerated immune response

- CAUTIONS: Arrhythmias - cardiac disease - congestive heart failure - ischaemia - seizure disorders (including seizures associated with fever)

- SIDE-EFFECTS
  - Common or very common: Abdominal pain - arthralgia - back pain - chills - depression - diarrhoea - fatigue - fever - headache - nausea - rash - vomiting

- CONCEPTION AND CONTRACEPTION: Effective contraception required during treatment—consult product literature.

- PREGNANCY: Manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in animal studies).

- BREAST FEEDING: Manufacturers advise avoid—no information available.

- HEPATIC IMPAIRMENT: Manufacturer advises caution in severe impairment (increased risk of accumulation).

- RENAL IMPAIRMENT: Manufacturer advises caution in severe impairment—risk of accumulation.

- MONITORING REQUIREMENTS: Monitor before and during treatment: haematological tests (including full blood count, differential white cell count, and platelet count), blood chemistry tests (including renal and liver function tests) and urinalysis.

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- ImmuKin (Horizon Pharma Ireland Ltd)
  - Interferon gamma-1b (recombinant human) 200 microgram per 1 ml Immukin 100micrograms/0.5ml solution for injection vials | 6 vial (POD) £450.00
IMMUNOSTIMULANTS > INTERLEUKINS

Aldesleukin

- **Drug Action** Aldesleukin produces tumour shrinkage in a small proportion of patients, but it has not been shown to increase survival.

- **Indications and Dose**
  - Metastatic renal cell carcinoma (specialist use only)
  - By subcutaneous injection, or by intravenous infusion
  - Adult: (consult product literature)

- **Unlicensed Use** Aldesleukin is not licensed for use in patients in whom all three of the following prognostic factors are present: performance status of Eastern Cooperative Oncology Group of 1 or greater, more than one organ with metastatic disease sites, and a period of less than 24 months between initial diagnosis of primary tumour and date of evaluation of treatment.

- **Contra-Indications** Consult product literature for information about aldesleukin contra-indications.

- **Cautions** Consult product literature for information about aldesleukin cautions.

- **Side-effects**
  - Common or very common
    - Acidity
    - Alopea
    - Anaemia
    - Anxiety
    - Appetite decreased
    - Arrhythmias
    - Arthralgia
    - Ascites
    - Asthenia
    - Cardiovascular disorders
    - Chest pain
    - Chills
    - Coagulation disorders
    - Confusion
    - Conjunctivitis
    - Constipation
    - Cough
    - Cyanosis
    - Dehydration
    - Depression
    - Diarrhoea
    - Dizziness
    - Drowsiness
    - Dyspepsia
    - Dysphagia
    - Dyspnoea
    - Electrolyte imbalance
    - Eosinophilia
    - Fever
    - Gastrointestinal disorders
    - Haemorrhage
    - Hallucination
    - Headache
    - Heart failure
    - Hepatic disorders
    - Hyperbilirubinaemia
    - Hyperglycaemia
    - Hyperhidrosis
    - Hypertension
    - Hyperthermia
    - Hypotension
    - Hypothermia
    - Hypothyroidism
    - Hypoxia
    - Increased risk of infection
    - Insomnia
    - Irritability
    - Ischaemic heart disease
    - Leucopenia
    - Malaise
    - Myalgia
    - Nasal congestion
    - Nausea
    - Nerve disorders
    - Oedema
    - Oral disorders
    - Pain
    - Palpitations
    - Paraesthesia
    - Pulmonary oedema
    - Renal impairment
    - Respiratory disorders
    - Sepsis
    - Skin reactions
    - Speech disorder
    - Syncope
    - Taste loss
    - Thrombocytopenia
    - Vomiting
    - Weight changes
  - Uncommon
    - Angioedema
    - Cardiac arrest
    - Cardiac inflammation
    - Cardiomyopathy
    - Coma
    - Embolism and thrombosis
    - Hypoglycaemia
    - Muscle weakness
    - Myopathy
    - Neutropenia
    - Pancreatitis
    - Paralysis
    - Pericardial disorders
    - Seizure
  - Rare or very rare
    - Agranulocytosis
    - Aplastic anaemia
    - Cholecystitis
    - Crohn’s disease aggravated
    - Diabetes mellitus
    - Haemolytic anaemia
    - Infection site necrosis
    - Stevens-Johnson syndrome
    - Ventricular dysfunction
  - Frequency not known
    - Capillary leak syndrome
    - Immune complex RPGN
    - Inflammatory arthritis
    - Intracranial haemorrhage
    - Leukenoencephalopathy
    - Myocardial infarction
    - Oculo-bulbar myasthenia gravis
    - Psychiatric disorders
    - Stroke
    - Thyroiditis
    - Vasculitis

- **Conception and Contraception** Ensure effective contraception during treatment in men and women.

- **Pregnancy** Use only if potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **Breast feeding** Discontinue breast-feeding.

- **Directions for Administration** Aldesleukin is now rarely given by intravenous infusion because of an increased risk of capillary leak syndrome, which can cause pulmonary oedema and hypotension.

- **Medicinal Forms** There can be variation in the licensing of different medicines containing the same drug.
  - Powder for solution for injection
    - Proleukin (Novartis Pharmaceuticals UK Ltd)
    - Aldesleukin 18 mega u Proleukin 18 million unit powder for solution for injection vials | 1 vial | £12.00 | 10 vial | £1,036.00

IMMUNOSTIMULANTS > OTHER

Bacillus Calmette-Guérin

- **Drug Action** Bacillus Calmette-Guérin is a live attenuated strain derived from Mycobacterium bovis.

- **Indications and Dose**
  - Bladder instillation for the treatment of primary or recurrent bladder carcinoma and for the prevention of recurrence following transurethral resection
  - By Intravesical instillation
  - Adult: (consult product literature)

- **Contra-Indications** Fever of unknown origin - HIV infection - impaired immune response - severe haematuria - tuberculosis - urinary-tract infection

- **Cautions** Bladder injury (delay administration until mucosal damage healed) - traumatic catheterisation (delay administration until mucosal damage healed) - urethral injury (delay administration until mucosal damage healed)

- **Side-effects**
  - Common or very common
    - Appetite decreased
    - Arthritis
    - Bladder cramps
    - Bladder disorders
    - Cardiovascular event
    - Chills
    - Cystitis
    - Diarrhoea
    - Fatigue
    - Fever
    - Haematuria
    - Hepatic disorders
    - Increased risk of infection
    - Joint disorders
    - Malaise
    - Myalgia
    - Nausea
    - Pain
    - Skin reactions
    - Urinary disorders
    - Vomiting
  - Uncommon
    - Abdominal pain
    - Anaemia
    - Coagulation disorder
    - Constipation
    - Dizziness
    - Genital pain
    - Headache
    - Leucopenia
    - Mucositis
    - Nephrotoxicity
    - Stomatitis
    - Thrombocytopenia
    - Tissue in urine
    - Urinary obstruction
  - Frequency not known
    - Erythema nodosum
    - Eye disorders
    - Eye inflammation
    - Gleromerulonephritis
    - Influenza like illness
    - Interstitial lung disease
    - Nephritis
    - Renal abscess
    - Renal failure

- **Pregnancy** Avoid.

- **Breast Feeding** Avoid.

- **Pre-Treatment Screening** Screen for active tuberculosis (contra-indicated if tuberculosis confirmed).

- **Medicinal Forms** There can be variation in the licensing of different medicines containing the same drug.
  - Powder for reconstitution for instillation
    - OncoTICE (Merck Sharp & Dohme Ltd)
    - TICE strain Bacillus of Calmette-Guérin 12.5 mg OncoTICE 12.5mg powder for reconstitution for instillation vials | 1 vial | £71.61 (Hospital only)

Mifamurtide

- **Indications and Dose**
  - Treatment of high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection (in combination with chemotherapy)
  - By Intravenous infusion
  - Adult: Infusion to be given over 1 hour (consult product literature or local protocols)

- **Unlicensed Use** Not licensed for use in patients over 30 years of age at initial diagnosis.

- **Cautions** Asthma—consider prophylactic bronchodilator therapy - chronic obstructive pulmonary disease—consider
prophylactic bronchodilator therapy · history of autoimmune disease · history of collagen disease · history of inflammatory disease

- **INTERACTIONS** → Appendix 1: mifamurtide
- **SIDE-EFFECTS**
  - **Common or very common**
    - Alopecia · anaemia · anxiety · appetite decreased · arthralgia · asthenia · cancer pain · chest discomfort · chills · confusion · constipation · cough · cyanosis · dehydration · depression · diarrhoea · dizziness · drowsiness · dysmenorrhoea · dyspnoea · feeling cold · fever · flushing · gastrointestinal discomfort · haemorrhage · headache · hearing loss · hepatic pain · hyperhidrosis · hypertension · hypokalaemia · hypotension · hypothermia · increased risk of infection · insomnia · laryngeal pain · leucopenia · malaise · mucositis · muscle complaints · musculoskeletal stiffness · nasal congestion · nausea · neutropenia · oedema · pain · pallor · palpitations · respiratory disorders · sensation abnormal · sepsis · skin reactions · tachycardia · thrombocytopenia · tinnitus · tremor · urinary disorders · vertigo · vision blurred · vomiting · weight decreased
- **CONCEPTION AND CONTRACEPTION**
  - Effective contraception required.
- **PREGNANCY**
  - Avoid.
- **BREAST FEEDING**
  - Avoid—no information available.
- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in moderate impairment (risk of increased half-life and exposure); avoid in severe impairment (no information available).
- **RENAL IMPAIRMENT**
  - Use with caution—no information available.
- **MONITORING REQUIREMENTS**
  - Monitor renal function, hepatic function and clotting parameters.
  - Monitor patients with history of venous thrombosis, vasculitis, or unstable cardiovascular disorders for persistent or worsening symptoms during administration—consult product literature.
- **NATIONAL FUNDING/ACCESS DECISIONS**

### Mifamurtide decisions

- **Mifamurtide for the treatment of osteosarcoma (October 2011) NICE TA235**
  - Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended (within its licensed indication), as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme.
  - [www.nice.org.uk/TA235](http://www.nice.org.uk/TA235)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

#### Powder for suspension for infusion

- **Mifamurtide 4 mg**
  - Mepact 4mg powder for suspension for infusion vials | 1 vial | £2.375.00

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### Immunotherapy responsive malignancy

#### IMMUNOSUPPRESSANTS

- **THALIDOMIDE AND RELATED ANALOGUES**

### Lenalidomide

- **DRUG ACTION**
  - Lenalidomide is an immunomodulating drug with anti-neoplastic, anti-angiogenic, and pro-erythropoietic properties.

#### INDICATIONS AND DOSE

- **Multiple myeloma (newly diagnosed) in patients not eligible for transplant, given in combination with dexamethasone until disease progression**
  - **BY MOUTH**
    - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature.

- **Multiple myeloma (newly diagnosed) in patients not eligible for transplant, given in combination with melphalan and prednisone followed by maintenance monotherapy**
  - **BY MOUTH**
    - Adult: 10 mg once daily for 21 consecutive days of repeated 28-day cycles for up to 9 cycles, for doses of melphalan and prednisone, and dose adjustments due to side-effects, consult product literature.

- **Multiple myeloma in patients who have received at least one prior therapy, given in combination with dexamethasone**
  - **BY MOUTH**
    - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature.

- **Treatment of transfusion-dependent anaemia due to low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other treatment options are insufficient or inadequate**
  - **BY MOUTH**
    - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature.

#### CAUTIONS

- **High tumour burden—risk of tumour lysis syndrome · patients with risk factors for myocardial infarction**

#### CAUTIONS, FURTHER INFORMATION

- **Thromboembolism**
  - Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised and thromboprophylaxis should be considered in patients with multiple risk factors.
- **Second primary malignancy**
  - Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

- **INTERACTIONS** → Appendix 1: lenalidomide
- **SIDE-EFFECTS**
  - **Common or very common**
    - Anaemia · appetite decreased · arthralgia · asthenia · atrial fibrillation · chills · constipation · cough · decreased leucocytes · dehydration · diarrhoea · dizziness · dry mouth · dyspnoea · electrolyte imbalance · embolism and thrombosis · fall · fever · gastrointestinal discomfort · haemorrhage · headache · heart failure · hyperglycaemia · hypertension · hyperthyroidism · hypotension · hypothyroidism · increased risk of infection · influenza like illness · insomnia · iron overload · lethargy · mood altered · muscle complaints · muscle weakness · myocardial infarction ·
nauae - neoplasms - neutropenia - night sweats - pain - pancytopenia - paraesthesia - peripheral neuropathy - peripheral oedema - renal failure - rhinorrhoea - sepsis - skin reactions - taste altered - thrombocytopenia - toothache - tumour flare - vertigo - vomiting - weight decreased
▶ Uncommon Angioedema
▶ Rare or very rare Severe cutaneous adverse reactions (SCARs) - tumour lysis syndrome
▶ Frequency not known Acquired haemophilia - gastrointestinal disorders - hepatic disorders - hypersensitivity - hypersensitivity vasculitis - interstitial pneumonitis - pancreatitis - reactivation of infections

SIDE-EFFECTS, FURTHER INFORMATION
If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation.
Discontinue permanently if angioedema, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected.

CONCEPTION AND CONTRACEPTION
For women of childbearing potential, pregnancy must be excluded before starting treatment with lenalidomide (perform pregnancy test on initiation or within 3 days prior to initiation). Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

PREGNANCY
Important: teratogenic risk. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis.

BREAST FEEDING
Discontinue breast-feeding—no information available.

RENAL IMPAIRMENT
Dose adjustments Reduce dose in moderate to severe impairment—consult product literature.

MONITORING REQUIREMENTS
Monitor full blood count (including differential white cell count, platelet count, haemoglobin, and haematocrit) and liver function before treatment, then every week for the first 8 weeks, then monthly thereafter (reduce dose or interrupt treatment if neutropenia, thrombocytopenia or impaired liver function develop—consult product literature).
Monitor for arterial or venous thromboembolism (if thromboembolic event occurs, discontinue lenalidomide and treat with standard anticoagulation therapy; lenalidomide may be restarted with continued anticoagulation therapy once thromboembolic event resolved—consult product literature).
Monitor thyroid function.
Monitor for signs and symptoms of peripheral neuropathy.
Monitor visual acuity regularly (risk of cataract).

PATIENT AND CARER ADVICE
Thromboembolism Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.
Neutropenia and thrombocytopenia Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop.

Conception and contraception Patient counselling is advised for lenalidomide capsules (pregnancy and contraception).

NATIONAL FUNDING/ACCESS DECISIONS
NICE decisions
▶ Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (September 2014) NICE TA322
Lenalidomide is recommended as an option, within its marketing authorisation, for treating transfusion-dependent myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, with the following condition:
• the drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the company.
www.nice.org.uk/guidance/ta322
▶ Lenalidomide for the treatment of multiple myeloma (updated April 2014) NICE TA171
Lenalidomide in combination with dexamethasone is an option for the treatment of multiple myeloma in patients who have received two or more prior therapies. The drug cost of lenalidomide will be met by the manufacturer for patients who remain on treatment for more than 26 cycles.
www.nice.org.uk/guidance/ta171
▶ Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (February 2018) NICE TA505
Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if:
• they have already had 2 or 3 lines of therapy, and
• the conditions in the managed access agreement for ixazomib are followed.
Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
www.nice.org.uk/guidance/ta505

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (May 2010) that lenalidomide, in combination with dexamethasone, is accepted for restricted use within NHS Scotland for patients with multiple myeloma who have received at least two prior therapies.
The Scottish Medicines Consortium has advised (April 2014) that lenalidomide, in combination with dexamethasone, is accepted for restricted use within NHS Scotland for treatment of multiple myeloma in adults to use at first relapse in those who have received prior therapy with bortezomib and for whom thalidomide has not been tolerated or is contra-indicated.
The Scottish Medicines Consortium has advised (December 2015) that lenalidomide is accepted for restricted use within NHS Scotland for patients with previously untreated multiple myeloma who are not eligible for transplant and when thalidomide-containing regimens are unsuitable.

www.getintopharma.com
INTERACTIONS
Second primary malignancy

DRUG ACTION
Pomalidomide is structurally related to thalidomide and has immunomodulatory properties and direct anti-melanoma tumoricidal activity.

INDICATIONS AND DOSE
Treatment of relapsed and refractory multiple myeloma in patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and who have had disease progression during the last treatment (in combination with dexamethasone)

DRUG COMBINATION
- Adult: 4 mg once daily for 21 consecutive days of repeated 28–day cycles, for doses of dexamethasone and dose adjustment due to side effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS
- Manufacturer advises halve dose with concurrent use of potent inhibitors of CYP1A2 and ciprofloxacin.

IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B REACTIVATION
An EU wide review has concluded that pomalidomide can cause hepatitis B reactivation; the MHRA recommends to establish hepatitis B virus status in all patients before initiation of treatment.

CAUSATIONS
- Cardiac disease - cardiac risk factors - hepatitis B infection - high tumour burden - risk of tumour lysis syndrome - interstitial lung disease — discontinue if suspected - peripheral neuropathy

CAUTIONS, FURTHER INFORMATION
- Thromboembolism: Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised. Thromboprophylaxis should be considered, particularly in patients with additional risk factors.
- Second primary malignancy: Patients should be carefully evaluated before and during treatment with pomalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.
- Hepatitis B infection: The MHRA advises that those with a history of hepatitis B infection should be closely monitored for signs and symptoms of active infection throughout treatment; expert advice should be sought for patients who test positive for active infection.

INTERACTIONS
- Appendix 1: pomalidomide

SIDE-EFFECTS
- Uncommon: Hepatitis - hyperbilirubinaemia - neoplasms - stroke - tumour lysis syndrome
- Frequency not known: Hepatitis B reactivation

CONCEPTION AND CONTRACEPTION
For women of childbearing potential, pregnancy must be excluded before starting treatment with pomalidomide (perform pregnancy test on initiation or within 3 days prior to initiation). Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

PREGNANCY
- Important: teratogenic risk.
- Breast feeding: Avoid—present in milk in animal studies.
- Hepatic impairment: Manufacturer advises caution (risk of increased exposure).
- Renal impairment: Manufacturer advises caution—no information available.

MONITORING REQUIREMENTS
- Manufacturer advises monitor full blood count before treatment, then every week for the first 8 weeks, then monthly thereafter (reduce dose or interrupt treatment if neutropenia or thrombocytopenia develop—consult product literature).
- Manufacturer advises monitor for arterial or venous thromboembolism.
- Manufacturer advises monitoring for signs and symptoms of cardiac failure.
- Manufacturer advises monitor for acute onset or unexplained worsening of respiratory symptoms.
- Manufacturer advises monitor liver function for 6 months after initiation, then as clinically indicated.

PRESCRIBING AND DISPENSING INFORMATION
- Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form.

PATIENT AND CARER ADVICE
- Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.
- Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop.

Conception and contraception: Patient counselling is advised for pomalidomide capsules (pregnancy and contraception).

www.getintopharma.com
Thalidomide

07-Feb-2009

Thalidomide has immunomodulatory and anti-inflammatory activity.

**INDICATIONS AND DOSE**
First-line treatment for untreated multiple myeloma, in patients aged 65 years and over, or for those not eligible for high-dose chemotherapy (for example, patients with significant co-morbidity such as cardiac risk factors) in combination with melphalan and prednisolone.

**CAUTIONS**
High tumour burden—risk of tumour lysis syndrome - patients aged 76 years and over—increased risk of serious side-effects

**CONCEPTION AND CONTRACEPTION**
Women of child-bearing potential, pregnancy must be excluded prior to starting treatment with thalidomide (perform pregnancy test on initiation or within 3 days prior to initiation).

**PREGNANCY**
Important: teratogenic risk.

**BREAST FEEDING**
Avoid present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment (no information available).

**RENAL IMPAIRMENT**
Caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**
Monitor white blood cell count (including differential count) and platelet count (reduce dose or interrupt treatment if neutropenia or thrombocytopenia develop—consult product literature).

**PREScribing AND DISPensing INFORMATION**
Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a complete Prescription Authorisation Form.

**PATIENT AND CARER ADVICE**
Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, increased risk of infection, malaise, movement disorders—neutropenia—peripheral neuropathy—peripheral oedema—respiratory disorders—sensation abnormal—skin reactions—thrombocytopenia—tremor, vomiting—frequency not known—atrioventricular block—gastrointestinal disorders—gastrointestinal haemorrhage—hearing impairment—hypothyroidism—liver disorder—menstrual cycle irregularities—myocardial infarction—neoplasms—pancreatitis—pancytopenia—posterior reversible encephalopathy syndrome (PRES)—pulmonary hypertension—reactivation of infections—renal failure—seizure—sexual dysfunction—toxic epidermal necrolysis—tumour lysis syndrome—SIDE-EFFECTS, FURTHER INFORMATION:

**Rash** If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation.

**Peripheral neuropathy** If symptoms suggestive of peripheral neuropathy develop (such as paraesthesia, abnormal coordination, or weakness) dose reduction, dose interruption, or treatment discontinuation may be necessary—consult product literature.

**EFFECTS, FURTHER INFORMATION**

**PATIENTS AND CARERS**

**IMMUNOTHERAPY RESPONSIVE MALIGNANCY**

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (January 2017) NICE TA427
- Pomalidomide (Imnovid®), in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse (that is, after three previous treatments including both lenalidomide and bortezomib), only when the manufacturer provides pomalidomide with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta427

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

| CAUTIONARY AND ADVISORY LABELS | 3, 25 |
| EXPERTISES: May contain Propylene glycol |  |
| Pomalidomide |  |
| Pomalidomide 1 mg | Innovid 1mg capsules | 21 capsule | £884.00 |
| Pomalidomide 2 mg | Innovid 2mg capsules | 21 capsule | £884.00 |
| Pomalidomide 3 mg | Innovid 3mg capsules | 21 capsule | £884.00 |
| Pomalidomide 4 mg | Innovid 4mg capsules | 21 capsule | £884.00 |

**PATIENT AND CARER ADVICE**

- Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
- patients aged 76 years and over—this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
- patients aged 76 years and over, or for those not eligible for high-dose chemotherapy (for example, patients with significant co-morbidity such as cardiac risk factors) in combination with melphalan and prednisolone.
- Adult 18–75 years: 200 mg once daily for 6–week cycle for a maximum of 6 cycles, dose to be taken at bedtime
- Adult 76 years and over: 100 mg once daily for 6–week cycle for a maximum of 12 cycles, dose to be taken at bedtime

**INTERACTIONS**

- Appendix 1: thalidomide

**SIDE-EFFECTS**

- Common or very common Anaemia - arrhythmias - asthenia - confusion - constipation - decreased leucocytes - depression - dizziness - dryness - dry mouth - dyspnoea - embolism and thrombosis - fever - heart failure - increased risk of infection - malaise - movement disorders—neutropenia—peripheral neuropathy—peripheral oedema—respiratory disorders—sensation abnormal—skin reactions—thrombocytopenia—tremor—vomiting
- Frequency not known—atrioventricular block—gastrointestinal disorders—gastrointestinal haemorrhage—hearing impairment—hypothyroidism—liver disorder—menstrual cycle irregularities—myocardial infarction—neoplasms—pancreatitis—pancytopenia—posterior reversible encephalopathy syndrome (PRES)—pulmonary hypertension—reactivation of infections—renal failure—seizure—sexual dysfunction—toxic epidermal necrolysis—tumour lysis syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**

**Rash** If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation.

**Peripheral neuropathy** If symptoms suggestive of peripheral neuropathy develop (such as paraesthesia, abnormal coordination, or weakness) dose reduction, dose interruption, or treatment discontinuation may be necessary—consult product literature.

**CONCEPTION AND CONTRACEPTION**
For women of child-bearing potential, pregnancy must be excluded before starting treatment with thalidomide (perform pregnancy test on initiation or within 3 days prior to initiation).

Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

**PREGNANCY**
Important: teratogenic risk.

**BREAST FEEDING**
Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment (no information available).

**RENAL IMPAIRMENT**
Caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**
Monitor white blood cell count (including differential count) and platelet count (reduce dose or interrupt treatment if neutropenia or thrombocytopenia develop—consult product literature).

**Monitor for arterial or venous thromboembolism.**

**Monitor patients for signs and symptoms of peripheral neuropathy.**

**Hepatic disorder**
Liver function should be monitored, particularly when there is history of, or concurrent viral liver infection, or when thalidomide is combined with drugs known to be associated with liver dysfunction (e.g. paracetamol).

**PREScribing AND DISPensing INFORMATION**
Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a complete Prescription Authorisation Form.

**PATIENT AND CARER ADVICE**
Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as
Photodynamic therapy responsive malignancy

PHOTOSENSITISERS

Porfimer sodium

- **DRUG ACTION** Porfimer sodium accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

- **INDICATIONS AND DOSE**
  - Photodynamic therapy of non-small cell lung cancer and obstructing oesophageal cancer
    - By slow intravenous injection
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058; concomitant photosensitising treatment; diseases exacerbated by light; elective surgery; ophthalmic slit-lamp examination for 30 days after administration

- **SIDE-EFFECTS** Alopecia; bone marrow depression; constipation; dizziness; dysphagia; haemorrhage; hyperuricaemia; nausea; oedema; pain; photosensitivity reaction (sunscreens ineffective); skin reactions; stomatitis; thromboembolism; tumour lysis syndrome; vomiting

- **PREGNANCY** Manufacturer advises avoid breastfeeding for at least 1 month after treatment—no information available.

- **BREAST FEEDING** No information available—manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment (may increase duration of photosensitivity); avoid in severe impairment (no information available).

- **PATIENT AND CARER ADVICE** Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for injection**
    - Photofrin (Axcan Pharma Inc, Pinnacle Biologics BV)
    - Photofrin 15 mg Photofrin 15mg powder for solution for injection vials | 1 vial (£0.31) (Hospital only)
    - Porfimer sodium 75 mg Photofrin 75mg powder for solution for injection vials | 1 vial (£0.31) (Hospital only)

Temoporfin

- **DRUG ACTION** Temoporfin accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

- **INDICATIONS AND DOSE** Photodynamic therapy of advanced head and neck squamous cell carcinoma refractory to, or unsuitable for, other treatments
  - By slow intravenous injection
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058; concomitant photosensitising treatment; diseases exacerbated by light; elective surgery; ophthalmic slit-lamp examination for 30 days after administration

- **SIDE-EFFECTS** Alopecia; bone marrow depression; constipation; dizziness; dysphagia; haemorrhage; hyperuricaemia; nausea; oedema; pain; photosensitivity reaction (sunscreens ineffective); skin reactions; stomatitis; thromboembolism; tumour lysis syndrome; vomiting

- **PREGNANCY** Manufacturer advises avoid pregnancy for at least 3 months after treatment.

- **BREAST FEEDING** No information available—manufacturer advises avoid breastfeeding for at least 1 month after treatment—no information available.

- **PATIENT AND CARER ADVICE** Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 15 days after administration. Avoid prolonged exposure of injection site arm for 15 days. If extravasation occurs protect area from light for at least 3 months.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - Foscan (Biolitec Pharma Ltd)
      - Temoporfin 1 mg per 1 ml Foscan 3mg/3ml solution for injection vials | 1 vial (£0.00) (Hospital only)
      - Foscan 6mg/6ml solution for injection vials | 1 vial (£0.31) (Hospital only)
      - Foscan 12mg/12ml solution for injection vials | 1 vial (£0.61) (Hospital only)

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7 Targeted therapy responsive malignancy

ANTINEOPLASTIC DRUGS > PROTEASOME INHIBITORS

Bortezomib

- **DRUG ACTION** Bortezomib is a proteasome inhibitor.
- **INDICATIONS AND DOSE** Treatment of multiple myeloma that has progressed despite the use of at least one therapy, and where the patient has already had, or is unable to have, haematopoietic stem cell transplantation (either as monotherapy, or in combination with pegylated liposomal doxorubicin or dexamethasone) | Treatment of previously untreated multiple myeloma in patients who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with melphalan and prednisolone) | Induction treatment of previously untreated multiple myeloma in patients who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with dexamethasone, or with dexamethasone and thalidomide) | ▶ BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION | ▶ Adult: (consult local protocol)

**CONTRA-INDICATIONS** Acute diffuse infiltrative pulmonary disease | pericardial disease

**CAUTIONS** Amyloidosis | cardiovascular disease | consider antiviral prophylaxis for herpes zoster infection | dehydration | diabetes (may affect blood glucose) | history of syncope | pulmonary disease (discontinue if interstitial lung disease develops) | risk factors for seizures | risk of neuropathy—consult product literature

**INTERACTIONS** ▶ Appendix 1: bortezomib

**SIDE-EFFECTS** ▶ Common or very common Anemia | anxiety | appetite abnormal | arrhythmias | asthma | chills | constipation | cough | decreased leucocytes | diabetes mellitus | diarrhoea | dizziness | dysphagia | dyspnoea | electrolyte imbalance | encephalopathy | enzyme abnormality | eye inflammation | fever | fluid imbalance | gastrointestinal discomfort | gastrointestinal disorders | haemorrhage | hair disorder | headaches | hearing impairment | heart failure | hepatic disorder | hiccup | hyperbilirubinaemia | hypersensitivity | hypertension | hypotension | increased risk of infection | ischaemic heart disease | lethargy | loss of consciousness | malaise | mood altered | muscle complaints | muscle weakness | nausea | nerve disorders | neuromuscular dysfunction | neutropenia | oedema | oral disorders | oropharyngeal complaints | pain | renal impairment | sensation abnormal | sepsis | skin reactions | sleep disorder | syncope | taste altered | thrombocytopenia | tinnitus | ventricular dysfunction | vertigo | vision disorders | vomiting | weight changes

▶ Uncommon Altered smell sensation | angioedema | antibiotic associated colitis | arthritis | azotemia | cardiac arrest | cardiomyopathy | cardiovascular disorder | cerebrovascular insufficiency | chest discomfort | circulatory impairment | circulatory collapse | coagulation | disorders | concentration impaired | confusion | Cushing’s syndrome | dry eye | dysphonia | ear discomfort | embolism and thrombosis | eye discomfort | eye disorders | failure to thrive | gait abnormal | gas exchange abnormal | genital pain | haemolytic anaemia | hallucination | hyperthyroidism | increased leucocytes | injury | irritable bowel syndrome | joint disorders | lymphadenopathy | memory loss | movement disorders | mucous membrane disorder | myopathy | neurotoxicity | palpitations | pancreatitis | pancytopenia | pericardial disorders | pericarditis | posterior reversible encephalopathy syndrome (PRES) (discontinue) | proteinuria | psychiatric disorders | psychotic disorder | pulmonary hypertension | pulmonary oedema | reflexes abnormal | respiratory disorders | rhinorrhoea | seizure | sensation of pressure | severe cutaneous adverse reactions (SCARs) | sexual dysfunction | shock | SIADH | skin mass | skin ulcers | speech disorder | sweat changes | temperature sensation altered | thirst change | tremor | tumour lysis syndrome | urinary disorders | urinary tract disorder | vascular disorders | vasculitis | vasodilation

▶ Rare or very rare Acidosis | acute coronary syndrome | alcohol intolerance | amyloidosis | apnoea | ascites | atrioventricular block | bladder irritation | blood disorders | bone disorder | bone fracture | brain oedema | breast disorder | cardiac valve disorder | cholelithiasis | CNS haemorrhage | cognitive disorder | coma | coronary artery insufficiency | delirium | drooling | ear disorder | erythromelalgia | fistula | gout | healing impaired | hypothyroidism | inflammation | lymphoedema | macrophage activation | mass | meningitis | metabolic disorder | multi organ failure | nail disorder | neoplasm malignant | neoplasms | nervous system disorder | paralysis | paresis | pelvic pain | perforation | photosensitivity reaction | platelet abnormalities | procedural complications | prostatitis | radiation injury | seborrhoea | sudden death | suicidal ideation | testicular disorders | throat complaints | ulcer | vaginal ulceration | venous insufficiency | vitamin deficiencies

▶ Frequency not known Herpes zoster reactivation | JC virus infection | progressive multifocal leukoencephalopathy (PML)

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

**PREGNANCY** Toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment—monitor for toxicity.

**Dose adjustments** Manufacturer advises reduce dose in moderate to severe impairment—consult product literature.

**RENAL IMPAIRMENT** No information available for creatinine clearance less than 20 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** ▶ Monitor blood-glucose concentration in patients on oral antidiabetics.

▶ Monitor for symptoms of progressive multifocal leukoencephalopathy (presenting as new or worsening neurological signs or symptoms)—discontinue treatment if diagnosed.

▶ Chest x-ray recommended before treatment to monitor for pulmonary disease—discontinue if interstitial lung disease develops.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions** ▶ Bortezomib for previously untreated mantle cell lymphoma (December 2015) NICE TA370

Bortezomib is recommended as an option for the treatment of previously untreated mantle cell lymphoma

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in adults for whom haematopoietic stem cell transplantation is unsuitable.

www.nice.org.uk/TA370

- **Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (April 2014)** NICE TA311

Bortezomib is recommended as an option within its marketing authorisation, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

www.nice.org.uk/TA311

- **Bortezomib and thalidomide for the first-line treatment of multiple myeloma (July 2011)** NICE TA228

Bortezomib in combination with an alkylating drug and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
- high-dose chemotherapy with stem cell transplantation is considered inappropriate and
- the person is unable to tolerate or has contra-indications to thalidomide.

www.nice.org.uk/TA228

- **Bortezomib monotherapy for relapsed multiple myeloma (October 2007)** NICE TA129

Bortezomib monotherapy is an option for the treatment of progressive multiple myeloma in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone-marrow transplantation, under the following circumstances:
- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in patients who have a reduction in serum M protein of 50% or more (where serum M protein is not measurable, an appropriate alternative biochemical measure of response should be used) and
- the manufacturer rebates the full cost of bortezomib if there is an inadequate response (as defined above) after four cycles of treatment.

www.nice.org.uk/TA129

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium, has advised (December 2013) that bortezomib (Velcade®) is accepted for restricted use within NHS Scotland in combination with dexamethasone and thalidomide for the induction treatment of adults with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Velcade** (Janssen-Cilag Ltd)

  Bortezomib 3.5 mg Velcade 3.5mg powder for solution for injection vials | 1 vial (Hosp) £762.38 (Hospital only)

**Carfilzomib**

08-Feb-2019

- **DRUG ACTION** Carfilzomib is an irreversible selective proteasome inhibitor that disrupts tumour cell turnover and induces apoptosis.

- **INDICATIONS AND DOSE** Treatment of multiple myeloma in patients who have received at least one prior therapy (in combination with dexamethasone, or with dexamethasone and lenalidomide) (specialist use only)

- **BY INTRAVENOUS INFUSION**

- **Adult:** (consult product literature or local protocols)

- **CAUTIONS**

  Elderly (over 75 years)—higher incidence of adverse effects; ensure adequate hydration; infusion-related reactions; recent history of myocardial infarction; risk of cardiac failure; risk of herpes zoster reactivation; uncontrolled angina; uncontrolled arrhythmias

  **CAUTIONS, FURTHER INFORMATION**

  Infusion-related reactions Manufacturer advises premedication with dexamethasone to reduce incidence and severity of infusion-related reactions.

  Risk of herpes zoster reactivation Manufacturer advises consider antiviral prophylaxis for herpes zoster infection.

- **INTERACTIONS** → Appendix 1: carfilzomib

- **SIDE-EFFECTS**

  - **Common or very common** Anaemia; anxiety; appetite decreased; arthralgia; arthrosis; asthma; cataract; chest pain; chills; constipation; cough; decreased leucocytes; dehydration; diarrhoea; dizziness; dysphonia; dyspnoea; electrolyte imbalance; embolism and thrombosis; fever; flushing; gastrointestinal discomfort; haemorrhage; headache; heart failure; hyperbilirubinaemia; hyperglycaemia; hyperhidrosis; hypertension; hyperuricaemia; hypoalbuminaemia; hypotension; increased risk of infection; infusion related reaction; insomnia; muscle complaints; muscle weakness; nausea; neutropenia; opharyngeal pain; pain; palpitations; peripheral neuropathy; peripheral oedema; pulmonary hypertension; pulmonary oedema; renal impairment; respiratory disorders; sensation abnormal; sepsis; skin reactions; thrombocytopenia; tinnitus; toothache; vision blurred; vomiting

  - **Uncommon** Cardiac arrest; gastrointestinal perforation; haemolytic uraemic syndrome; hepatic disorders; intracranial haemorrhage; multi organ failure; myocardial infarction; myocardial ischaemia; pericardial effusion; pericarditis; stroke; tumour lysis syndrome

  - **Rare or very rare** Posterior reversible encephalopathy syndrome (PRES); thrombotic microangiopathy

  **CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception during and for 1 month after treatment in women of childbearing potential; efficacy of oral contraceptives may be reduced, and hormonal contraceptives associated with a risk of thrombosis should be avoided. Male patients should use effective contraception during and for 3 months after treatment if their partner is pregnant or of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

  **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

  **BREAST FEEDING** Manufacturer advises avoid during and for at least 2 days after treatment—no information available.

  **HEPATIC IMPAIRMENT** Manufacturer advises caution (increased risk of side-effects), particularly in moderate to severe impairment (limited information available).

  **RENAL IMPAIRMENT** Manufacturer advises caution—increased incidence of adverse effects.

  **MONITORING REQUIREMENTS** Manufacturer advises monitoring of the following patient parameters: serum potassium concentration at least monthly; signs and symptoms of fluid overload, especially in those at risk of cardiac failure; renal function at treatment initiation and at least monthly during treatment—consider dose modification; hepatic function at treatment initiation and monthly during treatment—consider dose modification; platelet count and blood pressure. Also monitor for signs and symptoms of thrombotic microangiopathy.
Handing and storage
Manufacturer advises store in a refrigerator at 2–8°C.

Patient and carer advice
Manufacturer advises that patients and carers are warned to report signs and symptoms of thromboembolism (such as dyspnoea, chest pain, arm or leg swelling or pain).

Driving and skilled tasks
Patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of dizziness, hypotension and blurred vision.

National funding/access decisions

NICE decisions
- Carfilzomib for previously treated multiple myeloma (July 2017) NICE TA457
  Carfilzomib (Kyprolis®) in combination with lenalidomide and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if:
  - they have had only 1 previous therapy, which did not include bortezomib, and
  - the manufacturer provides carfilzomib with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

SMC No. 1171/16
The Scottish Medicines Consortium has advised (January 2017) that carfilzomib (Kyprolis®) in combination with lenalidomide and dexamethasone is not recommended for use within NHS Scotland for the treatment of adults with multiple myeloma who have received at least one prior therapy as the economic case was not demonstrated.

SMC No. 1242/17
The Scottish Medicines Consortium has advised (August 2017) that carfilzomib (Kyprolis®) is accepted for use within NHS Scotland, in combination with dexamethasone alone for the treatment of adults with multiple myeloma who have received at least one prior therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion

Electrolytes: May contain Sodium
- Kyprolis (Amgen Ltd) ▼
  Carfilzomib 10 mg  Kyprolis 10mg powder for solution for infusion vials 1 vial £176.00
  Carfilzomib 30 mg  Kyprolis 30mg powder for solution for infusion vials 1 vial £528.00
  Carfilzomib 60 mg  Kyprolis 60mg powder for solution for infusion vials 1 vial £1,056.00

Ixazomib

Drug action
Ixazomib is a proteasome inhibitor.

Indications and dose
Multiple myeloma in patients who have received at least one prior therapy, in combination with lenalidomide and dexamethasone (specialist use only)
- By mouth
- Adult: 4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle, for dose adjustments due to side-effects, consult product literature

Important safety information
Risks of incorrect dosing of oral anti-cancer medicines
See Cytotoxic drugs p. 888.

Caution, further information
- Herpes zoster reactivation
- Herpes zoster reactivation
  - Manufacture advises consider concomitant antiviral prophylaxis to decrease the risk of herpes zoster reactivation.
- Interactions
  - Appendix 1: ixazomib
- Side-effects
  - Common or very common
    - Back pain, constipation, diarrhoea, increased risk of infection, nausea, neutropenia, peripheral neuropathy (monitor for symptoms), peripheral oedema, rash, thrombocytopenia, vomiting
  - Frequency not known
    - Posterior reversible encephalopathy syndrome (PRES) (discontinue)
- Conception and contraception
  - Manufacture advises effective contraception in women of child-bearing potential and in men with a partner of child-bearing potential, during treatment and for at least 90 days after stopping treatment; additional barrier method recommended in women using hormonal contraceptives.
- Pregnancy
  - Manufacture advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- Breast feeding
  - Manufacture advises avoid—no information available.
- Hepatic impairment
  - Manufacture advises caution in moderate to severe impairment (risk of increased exposure).
  - Dose adjustments
    - Manufacture advises dose reduction to 3 mg in moderate to severe impairment.
- Renal impairment
  - Manufacture advises dose reduction to 3 mg in severe impairment (creatinine clearance less than 30 mL/min).
- Monitoring requirements
  - Manufacture advises to monitor hepatic function regularly and adjust dose accordingly—consult product literature.
- Patient and carer advice
  - Missed doses
    - Manufacture advises if less than 72 hours remain before the next scheduled dose, the missed dose should not be taken and the next dose should be taken at the normal time.
- National funding/access decisions
  - NICE decisions
    - Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (February 2018) NICE TA505
      Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if:
      - they have already had 2 or 3 lines of therapy, and
      - the conditions in the managed access agreement for ixazomib are followed.

www.getintopharma.com
Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.  
www.nice.org.uk/guidance/ta505

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS 23, 25**
  - Ninlaro (Takeda UK Ltd) ▼
  - Ixazomib (as ixazomib citrate) 2.3 mg Ninlaro 2.3mg capsules | 3 capsule £6,336.00
  - Ixazomib (as ixazomib citrate) 3 mg Ninlaro 3mg capsules | 3 capsule £6,336.00
  - Ixazomib (as ixazomib citrate) 4 mg Ninlaro 4mg capsules | 3 capsule £6,336.00

**TARGETED ANTINEOPLASTIC DRUGS > PROTEIN KINASE INHIBITORS**

**Abemaciclib**
- **INDICATIONS AND DOSE**
  - Locally advanced or metastatic breast cancer (initiated by a specialist)
    - **BY MOUTH**
    - Adult: 150 mg twice daily, for dose adjustments due to side-effects—consult product literature

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce abemaciclib dose to 100 mg twice daily; in those already taking a reduced dose, consult product literature. If the CYP3A4 inhibitor is stopped, increase the abemaciclib dose (after 3–5 half lives of the inhibitor) to the dose used before starting the CYP3A4 inhibitor.

**IMPORTANT SAFETY INFORMATION**

- **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
  - See Cytotoxic drugs p. 888.

- **INTERACTIONS**
  - Appendix 1: abemaciclib

- **SIDE-EFFECTS**
  - Common or very common: Alopecia - anaemia - appetite decreased - decreased leucocytes - diarrhoea - dizziness - embolism and thrombosis - excessive tearing - fatigue - fever - infection - muscle weakness - nausea - neutropenia - skin reactions - taste altered - thrombocytopenia - vomiting

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer advises highly effective contraception in women of childbearing potential during treatment and for at least 3 weeks after completing treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **PREGNANCY**
  - Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment. Temporary or permanent withdrawal may be needed following increases in aminotransferases—consult product literature.

**DOSE ADJUSTMENTS**
- Manufacturer advises dose reduction to 150 mg once daily in severe impairment.

**Afatinib**
- **INDICATIONS AND DOSE**
  - Treatment of locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, in patients who have not previously been treated with EGFR tyrosine kinase inhibitor
    - **BY MOUTH**
    - Adult: 40 mg once daily; increased if tolerated to up to 50 mg once daily, dose increase may be considered after 3 weeks at initial dose; consult product literature for details on dosing and dose adjustment due to side effects

**IMPORTANT SAFETY INFORMATION**

- **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
  - See Cytotoxic drugs p. 888.

- **CAUTIONS**
  - Cardiac risk factors - conditions which may affect left ventricular ejection fraction—consider cardiac monitoring, including assessment of left ventricular ejection fraction, at baseline and during treatment - diarrhoea—proactive management recommended (consult product literature) - exposure to sun (protect skin from exposure to sun) - history of keratitis - new pulmonary symptoms (including dyspnoea, cough, fever)—interrupt treatment until interstitial lung disease is excluded - severe dry eyes - signs and symptoms of keratitis— promptly refer to ophthalmologist for assessment - signs and symptoms of skin reaction—treat promptly and interrupt afatinib treatment if severe or if Stevens-Johnson syndrome suspected (consult product literature) - ulcerative keratitis - use of contact lenses - worsening pulmonary symptoms

www.getintopharma.com
Targeted therapy responsive malignancy

Afatinib (as Afatinib dimaleate) 50 mg Giotrif 50mg tablets  
28 tablet [PO] £2,023.28

Alectinib 15-Aug-2018

DRUG ACTION  Alectinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE  Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only)
▶ BY MOUTH
▶ Adult: 600 mg twice daily, for dose adjustments due to side-effects—consult product literature

PATIENT AND CARER ADVICE

INTERACTIONS  → Appendix 1: afatinib
SIDE-EFFECTS
▶ Common or very common  Appetite decreased - cystitis - dehydration - diarrhoea - dry eye - dyspepsia - epistaxis - eye inflammation - fever - hypokalaemia - muscle spasms - nausea - oral disorders - paronychia - renal impairment - rhinitis - skin reactions - taste altered - vomiting - weight decreased
▶ Uncommon  Interstitial lung disease - pancreatitis
▶ Rare or very rare  Severe cutaneous adverse reactions (SCARs)

CONCEPTION AND CONTRAINDICATIONS  Ensure effective contraception during and for at least one month after treatment in women of childbearing potential.

PREGNANCY  Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING  Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT  Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

Dose adjustments  Manufacturer advises consider dose interruption if hepatic function worsens in mild to moderate impairment—consult product literature.

RENAL IMPAIRMENT  Manufacturer advises avoid in severe renal impairment.

DIRECTIONS FOR ADMINISTRATION  Tablets should be taken whole on an empty stomach. Food should not be consumed for at least 3 hours before and at least 1 hour after each dose.

Giotrif tablets may be dispersed in approximately 100 mL of noncarbonated water by stirring occasionally for 100 hours and at least 15 minutes (must not be crushed). The dispersion should be swallowed immediately, and the glass rinsed with the same volume of water which should also be swallowed. The dispersion can also be administered via a gastric tube.

PATIENT AND CARER ADVICE  Patient counselling advised (administration). Driving and skilled tasks  Occular adverse reactions may affect performance of skilled tasks e.g. driving.

NATIONAL FUNDING/ACCESS DECISIONS  NICE decisions
▶ Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (April 2014) NICE TA310
Afatinib is recommended as an option, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer in adults:
● whose tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation, and
● who have not previously had an EGFR-TK inhibitor, and
● if the manufacturer provides afatinib with the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta310

INTERACTIONS  → Appendix 1: alectinib
SIDE-EFFECTS
▶ Common or very common  Anaemia - arrhythmias - constipation - diarrhoea - eye disorders - eye inflammation - hyperbilirubinaemia - musculoskeletal pain - myalgia - nausea - oedema - photosensitivity reaction - skin reactions - vision disorders - vomiting
▶ Uncommon  Drug-induced liver injury - respiratory disorders

CONCEPTION AND CONTRAINDICATIONS  Manufacturer advises women of child-bearing potential should use effective contraception during and for at least 3 months after stopping treatment.

PREGNANCY  Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING  Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT  Dose adjustments  Manufacturer advises reduce dose to 450 mg twice daily in severe impairment.

MONITORING REQUIREMENTS  Manufacturer advises monitor creatine phosphokinase every 2 weeks for the first month and as clinically indicated thereafter in patients reporting symptoms of myalgia.

Manufacturer advises monitor heart rate and blood pressure as clinically indicated.

Manufacturer advises monitor liver function at baseline then every 2 weeks during the first 3 months of treatment and periodically thereafter as clinically indicated; more frequent monitoring should be performed in patients who develop aminotransferase and bilirubin elevations.

Manufacturer advises monitor for symptoms of interstitial lung disease and pneumonitis.

PATIENT AND CARER ADVICE
Photosensitivity  Manufacturer advises patients should use a broad spectrum sunscreen and lip balm and be advised to avoid prolonged sun exposure during treatment, and for 7 days after discontinuation.

Myalgia  Manufacturer advises patients should be advised to report any unexplained muscle pain, tenderness or weakness.

Vomiting  Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time.

Missed doses  Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks  Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of symptomatic bradycardia and vision disorders.

www.getintopharma.com
### NATIONAL FUNDING/ACCESS DECISIONS

#### NICE decisions
- **Alectinib for untreated ALK-positive advanced non-small-cell lung cancer (August 2018)** NICE TA536
  Alectinib (Alecensa®) is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer in adults. It is recommended only if the manufacturer provides alectinib according to the commercial arrangement.
  www.nice.org.uk/guidance/ta536
- **Scottish Medicines Consortium (SMC) decisions**
  SMC No. SMC2012
  The Scottish Medicines Consortium has advised (August 2018) that alectinib (Alecensa®) is accepted for use within NHS Scotland as monotherapy for the first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
- **Capsule**
  CAUTIONARY AND ADVISORY LABELS 11, 21
  ELECTROLYTES: May contain Sodium
  - **Alecensa** Roche Products Ltd
  - **Alectinib** as Alectinib hydrochloride 150 mg Alecensa 150mg capsules | 224 capsule £5,032.00

### DRUG ACTION
Alectinib is a tyrosine kinase inhibitor.

### INDICATIONS AND DOSE
**Treatment of advanced renal cell carcinoma following failure of previous treatment with sunitinib or a cytokine (aldesleukin or interferon alfa)**
- **BY MOUTH**
- **Adult:** consult product literature

### IMPORTANT SAFETY INFORMATION
**Risks of incorrect dosing of oral anti-cancer medicines**
See Cytotoxic drugs p. 888.

### CONTRA-INDICATIONS
Recent active gastro-intestinal bleeding, untreated brain metastases

### CAUTIONS
Hypertension (blood pressure should be well-controlled before starting and monitored during treatment)

### INTERACTIONS
- **Appendix 1: alectinib**

### SIDE-EFFECTS
- **Common or very common**
  - Alopecia
  - Anaemia
  - Appetite decreased
  - Arthralgia
  - Asthenia
  - Constipation
  - Cough
  - Dehydration
  - Diarrhoea
  - Dizziness
  - Dysphonia
  - Dyspnoea
  - Electrolyte imbalance
  - Embolism and thrombosis
  - Gastrointestinal discomfort
  - Gastrointestinal disorders
  - Haemorrhage
  - Headache
  - Heart failure
  - Hyperbilirubinaemia
  - Hypertension
  - Hyperthyroidism
  - Hypothyroidism
  - Mucositis
  - Myalgia
  - Nausea
  - Oral disorders
  - Oropharyngeal pain
  - Pain in extremity
  - Polycythaemia
  - Proteinuria
  - Renal failure
  - Skin reactions
  - Taste altered
  - Thrombocytopenia
  - Tinnitus
  - Vomiting
  - Weight decreased

- **Common**
  - Leucopenia
  - Neutropenia

- **Uncommon**
  - Leucopenia
  - Neutropenia
  - Posterior reversible encephalopathy syndrome (PRES)

- **Conception and contraception**
  - Effective contraception required during and for up to 1 week after treatment.

### PREGNANCY
Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies). See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

### HEPATIC IMPAIRMENT
Manufacturer advises avoid in severe impairment—no information available.

### Dose adjustments
Manufacturer advises reduce dose in moderate impairment.

### MONITORING REQUIREMENTS
- **Monitor**
  - For thyroid dysfunction.
  - For symptoms of gastro-intestinal perforation.
  - For proteinuria before and during treatment.
  - For liver function before and during treatment.

### NATIONAL FUNDING/ACCESS DECISIONS
- **NICE decisions**
  - **Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (February 2015)**
  NICE TA333
  Axitinib (Inlyta®) is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the manufacturer provides axitinib with the discount agreed in the patient access scheme.
  www.nice.org.uk/guidance/ta333

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
- **Tablet**
  CAUTIONARY AND ADVISORY LABELS 25
  - **Inlyta** (Pfizer Ltd)
    - **Axitinib 1 mg** Inlyta 1mg tablets | 56 tablet £703.40 (Hospital only)
    - **Axitinib 3 mg** Inlyta 3mg tablets | 56 tablet £2,110.20 (Hospital only)
    - **Axitinib 5 mg** Inlyta 5mg tablets | 56 tablet £3,517.00 (Hospital only)
    - **Axitinib 7 mg** Inlyta 7mg tablets | 56 tablet £4,923.80 (Hospital only)

### Binimetinib
- **DRUG ACTION**
  Binimetinib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically mitogen-activated extracellular kinases MEK 1 and 2, thereby inhibiting BRAF V600 mutation-positive cell growth.

#### INDICATIONS AND DOSE
**Unresectable or metastatic melanoma with a BRAF V600 mutation (in combination with encorafenib)** (specialist use only)
- **BY MOUTH**
- **Adult:** 45 mg twice daily, for dose adjustments due to side-effects, consult product literature

### IMPORTANT SAFETY INFORMATION
**Risks of incorrect dosing of oral anti-cancer medicines**
See Cytotoxic drugs p. 888.

### CONTRA-INDICATIONS
**History of retinal vein occlusion**

### CAUTIONS
Left ventricular dysfunction (ejection fraction below 50%, or below the institutional lower limits of normal) - neuromuscular conditions associated with elevated creatine kinase and rhabdomyolysis - risk factors for retinal vein occlusion - risk factors for venous thromboembolism

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Targeted therapy responsive malignancy

### Bosutinib

**INDICATIONS AND DOSE**

**Previously treated chronic, accelerated and blast phase Philadelphia chromosome-positive chronic myeloid leukaemia (specialist use only)**

- **BY MOUTH**
  - Adult: 500 mg once daily, consult product literature for dose adjustment due to side-effects, or incomplete haematologic response by week 8, or incomplete cytogenetic response by week 12

**Newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myeloid leukaemia (specialist use only)**

- **BY MOUTH**
  - Adult: 400 mg once daily, consult product literature for dose adjustment due to side-effects, or failure to demonstrate breakpoint cluster region-Abelson (BCR-ABL) transcripts ≤10% by month 3

### IMPORTANT SAFETY INFORMATION

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**MHRA/CHM ADVISORY (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS**

An EU wide review has concluded that bosutinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

- **CAUTIONS**
  - Cardiac disease - hepatitis B infection - history of pancreatitis — withhold treatment if lipase elevated and abdominal symptoms occur - history of QT prolongation — monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment - recent cardiac event — monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment - risk factors for QT prolongation — monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment - significant gastrointestinal disorder

### CAUTIONS, FURTHER INFORMATION

**Hepatitis B infection**

The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

- **INTERACTIONS**  
  - Appendix 1: bosutinib

### SIDE-EFFECTS

- **Common or very common**

- **Uncommon**
  - Facial paralysis - pancreatitis - paresis

- **Frequency not known**
  - Respiratory disorders - retinal occlusion (discontinue permanently)

### MONITORING REQUIREMENTS

- **Manufacturer advises monitor liver function before and during treatment.**

- **Manufacturer advises avoid in renal failure.**

- **Manufacturer advises monitor blood pressure before and during treatment.**

- **Manufacturer advises monitor blood pressure function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

- **Manufacturer advises assess left ventricular ejection fraction before treatment, one month after starting treatment, then every 3 months or more frequently as clinically indicated.**

- **Manufacturer advises monitor for visual disturbances.**

- **Manufacturer advises monitor blood pressure before and during treatment.**

- **Manufacturer advises avoid in moderate or severe impairment (increased exposure).**

- **Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

- **Manufacturer advises assess left ventricular ejection fraction before treatment, one month after starting treatment, then every 3 months or more frequently as clinically indicated.**

- **Manufacturer advises monitor blood pressure function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

- **Manufacturer advises monitor blood pressure before and during treatment.**

- **Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

- **Manufacturer advises monitor blood pressure before and during treatment.**

- **Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

- **Manufacturer advises monitor blood pressure function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.**

### NATIONAL FUNDING/ACCESS DECISIONS

**NICE decisions**

- **Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (February 2019)**

  NICE TA562

Encorafenib with binimetinib (Mektovi) is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma in adults. It is recommended only if the manufacturer provides binimetinib according to the commercial arrangements.

www.nice.org.uk/guidance/ta562

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tr>
<td>Binimetinib 15 mg Mektovi 15mg tablets</td>
<td>84 tablet (PM)</td>
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<td>£2,240.00 (Hospital only)</td>
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This information is intended for healthcare professionals and should be used in conjunction with the product literature.
**Indications and dose**

Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously treated with crizotinib (specialist use only)

**By mouth**

- Adult: Initially 90 mg once daily for 7 days, then increased to 180 mg once daily, for dose adjustments due to dose interruption or side-effects—consult product literature.

**Dose adjustments due to interactions**

- Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce brigatinib dose to 90 mg once daily; in those starting treatment or already taking a reduced dose, consult product literature.

**Monitoring requirements**

- Manufacturer advises monitor full blood count weekly for haematological, cytogenetic, or molecular response.
- Manufacturer advises monitor liver function at baseline, then monthly for the first month and then monthly thereafter or as clinically indicated.
- Manufacturer advises monitor blood pressure, heart rate, creatine phosphokinase, amylase, and lipase regularly.
- Manufacturer advises monitor fasting serum glucose at baseline and periodically thereafter.
- Manufacturer advises monitor liver function at baseline, then every 2 weeks during the first 3 months of treatment, and periodically thereafter.
- Manufacturer advises prompt investigation if pneumonitis suspected—consult product literature.
- Manufacturer advises monitor for new or worsening respiratory symptoms, particularly in the first week of treatment—promptly investigate if pneumonitis suspected—consult product literature.
- Manufacturer advises monitor blood pressure, heart rate, creatine phosphokinase, amylase, and lipase regularly.
- Manufacturer advises monitor liver function at baseline, then every 2 weeks during the first 3 months of treatment, and periodically thereafter.
- Manufacturer advises monitor fasting serum glucose at baseline and periodically thereafter.
- Manufacturer advises patients and carers should be told to report symptoms of visual disturbance, or unexplained muscle pain, tenderness, or weakness.

**Monitoring requirements due to interactions**

- Manufacturer advises dose reduction to 40 mg once daily in severe impairment.
- Manufacturer advises dose reduction to 30 mg once daily in moderate impairment. Manufacturer advises reduce dose to 20 mg in mild impairment.

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**Drug action**

Brigatinib is a tyrosine kinase inhibitor.
Driving and skilled tasks  Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbance, dizziness, or fatigue.

• NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
- Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (March 2019) NICE TA571
- Brigatinib (Alunbrig®®) is recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer in adults who have already had crizotinib. It is recommended only if the manufacturer provides it according to the commercial arrangement.

www.nice.org.uk/guidance/ta571

• MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

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<td>£1,225.00</td>
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<td>90 mg</td>
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Cabozantinib

• DRUG ACTION Cabozantinib is an inhibitor of several protein kinases.

• INDICATIONS AND DOSE

Treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (initiated by a specialist)
- BY MOUTH USING CAPSULES
- Adult: 140 mg once daily, for dose adjustment or treatment interruption due to side-effects, consult product literature (closely monitor for first 8 weeks of therapy)

Advanced renal cell carcinoma (initiated by a specialist)
- BY MOUTH USING TABLETS
- Adult: 60 mg once daily, for dose adjustment or treatment interruption due to side-effects, consult product literature (closely monitor for first 8 weeks of therapy)

DOSE EQUIVALENCE AND CONVERSION
- Cabozantinib tablets and capsules are not bioequivalent—consult product literature when switching formulations.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

• CONTRA-INDICATIONS Reversible Posterior Leukoencephalopathy Syndrome

CAUTIONS Hypertension—discontinue treatment if uncontrolled despite medical intervention - palmar-plantar erythrodysesthesia syndrome—consider treatment interruption if severe and restart at a lower dose when resolved to grade 1. Patients at increased risk of fistulae—consult product literature - patients at increased risk of gastrointestinal perforation—consult product literature - patients at increased risk of intra-abdominal abscess—consult product literature - patients at risk of haemorrhage (including tumour involvement of the trachea or bronchus)—discontinue if symptoms develop - patients at risk of thromboembolic events including myocardial infarction—discontinue if symptoms develop - risk of osteonecrosis of the jaw—susceptibility to QT-interval prolongation (e.g. cardiac disease, electrolyte disturbances, bradycardia, concomitant use of drugs that prolong the QT interval)—monitor ECG and electrolytes periodically

CAUTIONS, FURTHER INFORMATION

- Elective surgery Withhold treatment for at least 28 days before elective surgery and restart only if adequate wound healing—discontinue in patients with wound healing complications requiring medical intervention.
- Risk of osteonecrosis of the jaw Discontinue treatment at least 28 days before elective invasive dental procedures—monitor for symptoms before and during treatment and discontinue if osteonecrosis develops.

• INTERACTIONS → Appendix 1: cabozantinib

• SIDE-EFFECTS


• CONCEPTION AND CONTRACEPTION Patients and their sexual partners must use effective contraception (in addition to barrier method) during treatment and for at least 4 months after the last dose.

• PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

• BREAST FEEDING Manufacturer advises discontinue breast-feeding during treatment and for at least 4 months after the last dose.

• HEPATIC IMPAIRMENT For capsules manufacturer advises caution in mild to moderate impairment (risk of increased exposure); avoid in severe impairment (no information available). For tablets manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

Dose adjustments For capsules manufacturer advises dose reduction to 60 mg once daily in mild to moderate impairment.

• RENAL IMPAIRMENT Manufacturer advises caution in renal impairment. Avoid in severe impairment.

• MONITORING REQUIREMENTS Monitor urine protein regularly and discontinue if nephrotic syndrome develops.

• PATIENT AND CARER ADVICE Food should not be consumed for at least 2 hours before and at least 1 hour after each dose.

Driving and skilled tasks Fatigue and weakness may affect performance of skilled tasks e.g. driving.
Ceritinib

21-Feb-2019

**DRUG ACTION** Ceritinib is a tyrosine kinase inhibitor, with particular activity against anaplastic lymphoma kinase (ALK).

**INDICATIONS AND DOSE**
First-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only) Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously treated with crizotinib (specialist use only)

- **BY MOUTH**
  - Adult: 450 mg once daily, dose interruption, dose reduction or discontinuation may be required based on individual safety and tolerability—consult product literature; discontinue treatment if patient unable to tolerate at least 150 mg daily

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce the dose by one-third (rounded to the nearest multiple of the 150 mg dosage form).

**IMPORTANT SAFETY INFORMATION**
Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 888.

**CONTRA-INDICATIONS**
Congenital long QT syndrome

**CAUTIONS**
Diabetes mellitus - history or susceptibility to QT-interval prolongation

**CAUTIONS, FURTHER INFORMATION**
- QT-interval prolongation QT-interval prolongation has been observed in clinical studies, which may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. Risk factors include pre-existing bradycardia, other relevant pre-existing cardiac disease or electrolyte disturbances; manufacturer advises monitor ECG and electrolytes periodically.

**INTERACTIONS**
  - Appendix 1: ceritinib

**SIDE-EFFECTS**
- **Common or very common** Anaemia - appetite decreased; arthralgias - arthralgias; asthma - anaphylaxis; diarrhoea - dysphagia; gastrointestinal discomfort; gastroesophageal reflux disease; hepatic disorders - hyperbilirubinaemia; hyperglycaemia; hypophosphataemia; nausea - oesophageal disorder; pericardial effusion - pericarditis; QT interval prolongation - renal impairment - respiratory disorders - skin reactions - vision disorders - vitreous floaters; vomiting; weight decreased

- **Uncommon** Pancreatitis

**SIDE-EFFECTS, FURTHER INFORMATION**
Gastro-intestinal effects

Manufacturer advises monitor for signs of gastrointestinal toxicity and consider dose reduction or discontinuation of treatment.

**INTERSTITIAL LUNG DISEASE**
Manufacturer advises monitor patients who exhibit pulmonary symptoms and consider dose reduction or discontinuation of treatment.

**CONCEPTION AND CONTRACEPTION**
Manufacturer recommends effective contraception in women of childbearing potential during treatment and for up to 3 months after discontinuation of treatment.

**PREGNANCY**
Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment (limited information available).
Ceritinib for untreated ALK-positive non-small cell lung cancer

NATIONAL FUNDING/ACCESS DECISIONS

Manufacturer advises monitor for pulmonary symptoms, then monitor every 2 weeks for the first three months of treatment and monthly thereafter; if transaminases are elevated, more frequent monitoring should be performed as clinically indicated.

Manufacturer advises monitor fasting plasma-glucose levels before treatment initiation and periodically thereafter as clinically indicated.

Manufacturer advises monitor for pulmonary symptoms indicative of interstitial lung disease and pneumonitis—discontinue treatment if diagnosis confirmed; also monitor heart rate and blood pressure regularly.

DIRECTIONS FOR ADMINISTRATION

Manufacturer advises Zykadia® capsules should be taken with food at the same time each day—consult product literature for dosing information if patients are unable to take capsules with food.

PATIENT AND CARER ADVICE

Patients and carers should be counselled on the administration of capsules.

Missed doses

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks

Manufacturer advises patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of fatigue and vision disorders.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Ceritinib for previously treated anaplastic lymphoma kinase-positive non-small cell lung cancer (June 2016) NICE TA395

Ceritinib (Zykadia®) is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase-positive non-small cell lung cancer in adults previously treated with crizotinib; only if the manufacturer provides the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta395

Ceritinib for untreated ALK-positive non-small cell lung cancer (January 2018) NICE TA500

Ceritinib (Zykadia®) is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer in adults, only if the manufacturer provides it with the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta500

Scottish Medicines Consortium (SMC) decisions

SMC No. 1097/15

The Scottish Medicines Consortium has advised (December 2015) that ceritinib (Zykadia®) is accepted for use within NHS Scotland for the treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously treated with crizotinib. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Gelatin, propylene glycol

Zykadia (Novartis Pharmaceuticals UK Ltd)

Ceritinib 150 mg Zykadia 150mg capsules | 150 capsule $8,923.45

DRUG ACTION

Cobimetinib is a mitogen-activated protein kinase (MAPK) inhibitor.

INDICATIONS AND DOSE

Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma (in combination with vemurafenib) (specialist use only)

BY MOUTH

Adult: 60 mg once daily for 21 days; subsequent cycles repeated after a 7-day interval, for dose adjustment due to side-effects—consult product literature

CAUTIONS

Left ventricular dysfunction - risk factors for bleeding

INTERACTIONS

Appendix 1: cobimetinib

SIDE EFFECTS

Common or very common

Anaemia - basal cell carcinoma - chills - dehydration - diarrhoea - electrolyte imbalance - fever - haemorrhage - hyperglycaemia - hypertension - nausea - photosensitivity reaction - pneumonitis - serous retinopathy - skin reactions - vision disorders - vomiting

Uncommon

Rhabdomyolysis

CONCEPTION AND CONTRACEPTION

Manufacturer advises use of two effective contraceptive methods during treatment and for at least 3 months after stopping treatment.

PREGNANCY

Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises caution in severe impairment—limited information available.

MONITORING REQUIREMENTS

Creatine kinase elevation Manufacturer advises baseline creatine kinase and creatinine levels should be measured before starting treatment, and then at monthly intervals during treatment or as clinically indicated—consult product literature if elevated.

Left ventricular function Manufacturer advises ejection fraction should be evaluated before initiation of treatment, then after the first month of treatment and at least every 3 months thereafter (or as clinically indicated) until treatment discontinuation.

Liver function Manufacturer advises liver function should be evaluated before initiation of treatment and monthly thereafter (or more frequently as clinically indicated).

Visual disturbances Manufacturer advises assess for new or worsening visual disturbances at each visit; if symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended.

PATIENT AND CARER ADVICE

Vomiting

Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time.

Missed doses

Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks

Manufacturer advises patients should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.

Important Safety Information

Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 888.

www.getintopharma.com
Crizotinib

**DRUG ACTION** Crizotinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only) | ROS1-positive advanced non-small cell lung cancer (specialist use only)

**BY MOUTH**

- Adult: 250 mg twice daily, consult product literature for information on dose adjustments based on individual patient safety and tolerability.

**SIDE-EFFECTS**


- Uncommon Gastrointestinal perforation (including fatal cases) - hepatic failure (including fatal cases) - renal impairment

**RECOMMENDATIONS**

- Reduce dose to 200 mg twice daily after 2 weeks, based on individual assessment of safety and tolerability.

**INTERACTIONS**

- Appendix 1: Crizotinib

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES** See Cytotoxic drugs p. 888.

**MHRA/CHM ADVICE (NOVEMBER 2015): RISK OF CARDIAC FAILURE**

Severe, sometimes fatal cases of cardiac failure have been reported in patients treated with crizotinib. The MHRA has issued the following advice:

- Monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention).
- Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur.

**CAUTIONS**

- History of diverticulitis (risk of gastrointestinal perforation)—discontinue treatment if gastrointestinal perforation occurs) - metastases of gastrointestinal tract (risk of gastro-intestinal perforation) - patients with susceptibility to QT-prolongation (including bradycardia, history of cardiac disease, concomitant use of drugs that prolong QT interval, and electrolyte disturbances)—periodic renal monitoring required - risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs - vision disorders reported—consider full ophthalmological evaluation if vision disorder worsens or persists

**CAUTIONS, FURTHER INFORMATION**

- Fatal interstitial lung disease and pneumonitis - Fatal interstitial lung disease and pneumonitis reported (monitor patients with pulmonary symptoms, withdrawal if suspected, and permanently discontinue treatment if diagnosed).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Cotellic (Roche Products Ltd) ▼

Cotellic (as Cotellic hemifumarate) 20 mg tablets 63 tablet (Po) £4,275.67

**SIDE-EFFECTS, FURTHER INFORMATION**

Consider reducing the dose, or interrupting or stopping treatment if symptoms of cardiac failure occur.

**CONCEPTION AND CONTRACEPTION**

Ensure effective contraception during and for at least 90 days after treatment.

**PREGNANCY**

Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Avoid — no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises use with caution.

Dose adjustments Manufacturer advises reduce dose in moderate to severe impairment—consult product literature.

**RENAL IMPAIRMENT**

Dose adjustments Reduce dose to 250 mg once daily in severe impairment not requiring peritoneal dialysis or hemodialysis, may be increased to 200 mg twice daily after at least 4 weeks, based on individual assessment of safety and tolerability.

**MONITORING REQUIREMENTS**

Monitor liver function once a week during the first 2 months of treatment, then at least monthly thereafter and as clinically indicated. Monitor ECG and electrolytes (correct if abnormal) in all patients before starting treatment, then periodically and as clinically indicated thereafter. Monitor for signs and symptoms of treatment emergent bradycardia (including syncope, dizziness and hypotension)—monitor blood pressure and heart rate regularly.

**PATIENT AND CARER ADVICE**

Counsel all patients on the early signs and symptoms of gastrointestinal perforation—advise to seek immediate medical attention.

Driving and skilled tasks Symptomatic bradycardia (including syncope, dizziness and hypotension), vision disorder and fatigue may affect performance of skilled tasks (e.g. driving or operating machinery).

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (September 2016) NICE TA406

Crizotinib is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults, only if the manufacturer provides it with the discount agreed in the patient access scheme.

- Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (December 2016) NICE TA422

Crizotinib is recommended, within its marketing authorisation, as an option for previously treated
anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults, only if the manufacturer provides it with the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta422

- Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (July 2018) NICE TA629

Crizotinib is recommended for use within the Cancer Drugs Fund as an option for treating ROS1-positive advanced non-small-cell lung cancer (NSCLC) in adults, only if the conditions in the managed access agreement are followed. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta529

Scottish Medicines Consortium (SMC) decisions

SMC No. 129/18

The Scottish Medicines Consortium has advised (June 2018) that crizotinib (Xalkori®) is accepted for use within NHS Scotland for the treatment of adults with ROS1-positive advanced non-small cell lung cancer. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

- MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug.

  Capsule

  CAUTIONARY AND ADVISORY LABELS 25

  • Xalkori (Pfizer Ltd) ▼
  • Crizotinib 200 mg xalkori 200mg capsules | 60 capsule ▶️
    £4,689.00 (Hospital only)
  • Crizotinib 250 mg xalkori 250mg capsules | 60 capsule ▶️
    £4,689.00 (Hospital only)

Dabrafenib

24-Jul-2018

- DRUG ACTION

  Dabrafenib is a BRAF kinase inhibitor, which inhibits BRAF V600 mutation-positive melanoma cell growth.

- INDICATIONS AND DOSE

  Unresectable or metastatic melanoma with a BRAF V600 mutation (as monotherapy or in combination with trametinib) (specialist use only) Adjuvant treatment of stage III melanoma with a BRAF V600 mutation following complete resection (in combination with trametinib) (specialist use only)

  BY MOUTH

  Adult: 150 mg every 12 hours, for dose adjustments due to side-effects, consult product literature

  Adjuvant treatment of stage III melanoma with a BRAF V600 mutation following complete resection (in combination with trametinib) (specialist use only)

  BY MOUTH

  Adult: 150 mg every 12 hours for 12 months, for dose adjustments due to side-effects, consult product literature

- SIDE-EFFECTS

  • Common or very common Alopecia - appetite decreased - arthralgia - asthenia - chills - constipation - cough - diarrhoea - fever - headache - hyperglycaemia - hypophosphataemia - influenza-like illness - myalgia - nausea - neoplasms - pain in extremity - photosensitivity reaction - skin reactions - vomiting

  • Uncommon Nephritis - pancreatitis - panniculitis - renal impairment - uveitis

- SIDE-EFFECTS, FURTHER INFORMATION

  Additional side-effects reported when used in combination with trametinib include dizziness, hyperhidrosis, hypotension, leukopenia, muscle spams, myocarditis, neutropenia, night sweats, and thrombocytopenia.

- CONCEPTION AND CONTRA-INDICATIONS

  Manufacturer advises women of child-bearing potential should use effective non-hormonal contraception during and for 4 weeks after stopping treatment.

- PREGNANCY

  Manufacturer advises avoid unless potential benefit outweighs risk—incidence in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

- BREAST FEEDING

  Manufacturer advises avoid—no information available.

- HEPATIC IMPAIRMENT

  Manufacturer advises caution in moderate to severe impairment—no information available.

- RENAL IMPAIRMENT

  Manufacturer advises caution in severe impairment—no information available.

- MONITORING REQUIREMENTS

  Manufacturer advises assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, monthly during treatment, and for 6 months after discontinuation or until initiation of alternative treatment; assess and monitor for non-cutaneous secondary or recurrent malignancy before, during, and for 6 months after discontinuation or until initiation of alternative treatment—consult product literature; monitor full blood count as clinically indicated; monitor for ophthalmologic reactions including uveitis, iridocyclitis and iritis; monitor serum creatinine.

- PATIENT AND CARER ADVICE

  Manufacturer advises patients should be informed to immediately report any skin lesions—risk of cutaneous squamous cell carcinoma and new primary melanoma.

  Missed doses

  Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

  Driving and skilled tasks

  Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of ocular adverse reactions.

- NATIONAL FUNDING/ACCESS DECISIONS

  NICE decisions

  ▶️ Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (October 2014) NICE TA321

  Dabrafenib (Tafinlar®) is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the manufacturer provides dabrafenib with the discount agreed in the patient access scheme.

  www.nice.org.uk/guidance/ta321

  ▶️ Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (June 2016) NICE TA396

  Trametinib (Mekinist®) in combination with dabrafenib (Tafinlar®) is recommended, within its marketing authorisation, as an option for treatment of melanoma only when the manufacturer provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.

  www.nice.org.uk/guidance/ta396

www.getintopharma.com
• Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (October 2018) NICE TA544

Dabrafenib (Tafinlar®) with trametinib (Mekinist®) is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults. It is recommended only if the manufacturer provides dabrafenib and trametinib with the discounts agreed in the commercial arrangements.

www.nice.org.uk/guidance/ta544

Scottish Medicines Consortium (SMC) decisions

SMC No. 1023/15

The Scottish Medicines Consortium has advised (March 2015) that dabrafenib (Tafinlar®) is accepted for restricted use within NHS Scotland, as monotherapy, for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma in adults who have received no prior therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. SMC2131

The Scottish Medicines Consortium has advised (February 2019) that dabrafenib (Tafinlar®) is accepted for use within NHS Scotland in combination with trametinib for the adjuvant treatment of adults with stage III melanoma with a BRAF V600 mutation, following complete resection. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Dasatinib

30-Apr-2019

Dasatinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Chronic phase chronic myeloid leukaemia (initiated by a specialist)

BY MOUTH USING TABLETS

Adult: 100 mg once daily, then increased if necessary up to 140 mg once daily, for dose adjustment due to side-effects—consult product literature

Accelerated and blast phase chronic myeloid leukaemia [resistant or intolerant to prior therapy] (initiated by a specialist) / Acute lymphoblastic leukaemia [resistant or intolerant to prior therapy] (initiated by a specialist)

BY MOUTH USING TABLETS

Adult: 140 mg once daily, then increased if necessary up to 180 mg once daily, for dose adjustment due to side-effects—consult product literature

CAUTIONS

Hepatitis B infection - risk of cardiac dysfunction (monitor closely) - susceptibility to QT-interval prolongation (correct hypokalaemia or hypomagnesiaemia before starting treatment)

FURTHER INFORMATION

Hepatitis B infection

The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

INTERACTIONS

Appendix 1: dasatinib

SIDE-EFFECTS

Common or very common


Uncommon


Rare or very rare

Cardiac arrest - dementia - diabetes mellitus - facial paralysis - gait abnormal - hypersensitivity vasculitis - hypothyroidism - pure red cell aplasia - seizure - thyroiditis

Frequency not known

Hepatitis B reactivation

CONCEPTION AND CONCEPTION

Effective contraception required during treatment.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution.

MONITORING REQUIREMENTS

Manufacturer advises evaluate for signs and symptoms of underlying cardiopulmonary disease before initiation of therapy—echocardiography should be performed at treatment initiation in patients with symptoms of cardiac disease and considered for patients with risk factors for cardiac or pulmonary disease.

www.getintopharma.com
Manufacturer advises monitor patients with risk factors or a history of cardiac disease for signs or symptoms of cardiac dysfunction during treatment.

When used for Accelerated or blast phase chronic myeloid leukaemia or Acute lymphoblastic leukaemia Manufacturer advises monitor full blood count weekly for the first 2 months, then monthly or as clinically indicated thereafter.

When used for Chronic phase chronic myeloid leukaemia Manufacturer advises monitor full blood count every 2 weeks for 3 months, then every 3 months or as clinically indicated thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA426 Dasatinib is recommended, within its marketing authorisation, as an option for untreated chronic phase Philadelphia-chromosome-positive CML in adults, only if the manufacturer provides it with the discount agreed in the patient access scheme.

Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425 Dasatinib is recommended as an option for treating chronic or accelerated phase Philadelphia-chromosome-positive CML in adults, if they cannot have imatinib, or their disease is imatinib-resistant and the manufacturer provides dasatinib with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta426

Scottish Medicines Consortium (SMC) decisions

**SMC No. 370/07**

The Scottish Medicines Consortium has advised (September 2016) that dasatinib (Sprycel®) is accepted for use within NHS Scotland for the treatment of adults with chronic, accelerated or blast phase chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate, only if the manufacturer provides dasatinib with the discount agreed in the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

SMC No. 1170/16

The Scottish Medicines Consortium has advised (September 2016) that dasatinib (Sprycel®) is accepted for use within NHS Scotland for the treatment of adults with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase, only if the manufacturer provides dasatinib with the discount agreed in the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 25**

Sprycel (Bristol-Myers Squibb Pharmaceuticals Ltd)

Dasatinib 20 mg Sprycel 20mg tablets | 60 tablet | POM | £1,252.48 DT | £1,252.48 (Hospital only)

Dasatinib 50 mg Sprycel 50mg tablets | 60 tablet | POM | £2,504.96 DT | £2,504.96 (Hospital only)

Dasatinib 80 mg Sprycel 80mg tablets | 30 tablet | POM | £2,504.96 DT | £2,504.96 (Hospital only)

Dasatinib 100 mg Sprycel 100mg tablets | 30 tablet | POM | £2,504.96 DT | £2,504.96 (Hospital only)

Dasatinib 140 mg Sprycel 140mg tablets | 30 tablet | POM | £2,504.96 DT | £2,504.96 (Hospital only)

Encorafenib

**DRUG ACTION** Encorafenib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically BRAF kinase, thereby inhibiting BRAF V600 mutation-positive cell growth.

**INDICATIONS AND DOSE** Unresectable or metastatic melanoma with a BRAF V600 mutation (in combination with binimetinib) (specialist use only)

- By mouth
  - Adult: 450 mg once daily, for dose adjustments due to side-effects, consult product literature

**IMPORTANT SAFETY INFORMATION**

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES See Cytotoxic drugs p. 888.

- CONTRA-INDICATIONS BRAF wild-type malignant melanoma
- CAUTIONS Prior or concurrent cancer associated with RAS mutation · risk factors for QT-interval prolongation
- INTERACTIONS Appendix 1: encorafenib
- SIDE-EFFECTS
  - Common or very common Alopecia · anaemia · angioedema · appetite decreased · arthralgia · arthrosis · constipation · detachment of retinal pigment epithelium · diarrhoea · dizziness · embolism and thrombosis · eye inflammation · facial paralysis · fatigue · fever · fluid retention · gastrointestinal discomfort · gastrointestinal disorders · haemorrhage · headache · heart failure · hypertension · hypersensitivity · hypersensitivity vasculitis · hypotension · insomnia · intracranial haemorrhage · left ventricular dysfunction · lip squamous cell carcinoma · muscle complaints · muscle weakness · myopathy · nausea · neoplasms · nerve disorders · oedema · pain · panniculitis · paresis · photosensitivity reaction · renal impairment · skin reactions · taste altered · ulcerative colitis · vision disorders · vomiting
  - Uncommon Pancreatitis
  - Frequency not known QT interval prolongation
  - CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective contraception during and for at least one month after stopping treatment; additional barrier method recommended in women using hormonal contraceptives.
  - PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - BREAST FEEDING Manufacturer advises avoid—no information available.
  - HEPATIC IMPAIRMENT Manufacturer advises caution in mild impairment (increased exposure); avoid in moderate or severe impairment (no information available).
  - Dose adjustments Manufacturer advises dose reduction to 300 mg once daily in mild impairment.
  - RENAL IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).
  - MONITORING REQUIREMENTS
    - Manufacturer advises assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, every 2 months during treatment, and for up to 6 months after discontinuation; assess for non-cutaneous malignancy and monitor full blood count before, during, and after treatment discontinuation as clinically indicated—consult product literature.
    - Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.

www.getintopharma.com
Manufacturer advises assess ECG before treatment, one month after starting treatment, then every 3 months or more frequently as clinically indicated.

Manufacturer advises monitor blood creatinine levels as clinically indicated.

Manufacturer advises monitor ophthalmologic reactions including uveitis, iridocyclitis, and iritis.

**PATIENT AND CARER ADVICE** Manufacturer advises patients should be informed to immediately report new skin lesions—risk of cutaneous squamous cell carcinoma and new primary melanoma.

**Missed doses** Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**Driving and skilled tasks** Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (February 2019) NICE TA562

Encorafenib (Braftovi®) with binimetinib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma in adults. It is recommended only if the manufacturer provides encorafenib according to the commercial arrangements. [www.nice.org.uk/guidance/ta562](http://www.nice.org.uk/guidance/ta562)

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **Braftovi (Pierre Fabre Ltd)**
- Encorafenib 50 mg (Braftovi 50mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 75 mg (Braftovi 75mg capsules) | 42 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 150 mg (Braftovi 150mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 200 mg (Braftovi 200mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 250 mg (Braftovi 250mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 280 mg (Braftovi 280mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 300 mg (Braftovi 300mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 400 mg (Braftovi 400mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 500 mg (Braftovi 500mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 600 mg (Braftovi 600mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 750 mg (Braftovi 750mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)
- Encorafenib 900 mg (Braftovi 900mg capsules) | 28 capsule [Pm](https://www.nice.org.uk/guidance/ta562)

**Drug Action**

Erlotinib is a tyrosine kinase inhibitor.

**Indications and Dose**

Treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy | Monotherapy for maintenance treatment of locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of platinum-based chemotherapy

- **By mouth**
- Adult: 150 mg once daily

Treatment of metastatic pancreatic cancer (in combination with gemcitabine)

- **By mouth**
- Adult: 100 mg once daily

**Dose Adjustments Due to Interactions**

- Manufacturer advises if concurrent use of potent inducers of CYP3A4 is unavoidable, increase dose to 300 mg daily, if well tolerated for more than 2 weeks, further increase to 450 mg daily could be considered with close monitoring.

**Important Safety Information**

**Epidermal Growth Factor Receptor (EGFR) Inhibitors: Serious Cases of Keratitis and Ulcerative Keratitis (May 2012)**

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness.

Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines** See Cytotoxic drugs p. 888.

**Cautionary and Advisory Labels**

- **Uncommon** Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness.

**Driving and Skilled Tasks**

Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.

**Conception and Contraception**

Effective contraception required during and for at least 2 weeks after treatment.

**Pregnancy**

Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**Breast Feeding**

Manufacturer advises avoid—breast feeding during treatment and for at least 2 weeks after the last dose.

**Hepatic Impairment**

Manufacturer advises caution in mild to moderate impairment—monitor liver function and interrupt treatment if changes in liver function are severe (increased risk of hepatic failure); avoid in severe impairment—no information available.

**Dose Adjustments**

Manufacturer advises consider dose reduction or interruption if serious adverse effects occur.

**Renal Impairment**

Manufacturer advises avoid in severe impairment.

**National Funding/Access Decisions**

**NICE decisions**

- Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (June 2011) NICE TA227

Erlotinib (Tarceva®) monotherapy is **not** recommended for maintenance treatment in patients with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy.

Patients currently receiving erlotinib monotherapy for maintenance treatment should have the option to continue treatment until they and their clinician consider it appropriate to stop. [www.nice.org.uk/guidance/ta227](http://www.nice.org.uk/guidance/ta227)

- Erlotinib for the first-line treatment of locally advanced or metastatic EGFR/TK mutation-positive non-small-cell lung cancer (June 2012) NICE TA258

Erlotinib (Tarceva®) is recommended as an option in patients for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer if:

- they test positive for the epidermal growth factor tyrosine kinase (EGFR-TK) mutation, and

[www.getintopharma.com](http://www.getintopharma.com)
Immune system and malignant disease

Drug action

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (December 2015) NICE TA374

Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in patients with tumours that are EGFR-TK mutation-negative.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta374

Everolimus is a protein kinase inhibitor.

Affinitor®

Neuroendocrine tumours of pancreatic origin
Neuroendocrine tumours of lung origin
Neuroendocrine tumours of gastro-intestinal origin
Renal cell carcinoma
Hormone-receptor positive HER2-negative breast cancer [in combination with exemestane]

Adult:

BY MOUTH

Adult: 10 mg once daily, for dose interruption or adjustments due to side-effects—consult product literature

Certican®

Liver transplantation

Adult:

BY MOUTH

Adult: Initially 1 mg twice daily, to be started approximately 4 weeks after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Renal transplantation | Heart transplantation

Adult:

BY MOUTH

Adult: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Votubia® dispersible tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Adjunctive treatment of refractory partial-onset seizures, with or without secondary generalisation, associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Votubia® Tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Renal angiomylipoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Everolimus

Drug action

Everolimus is a protein kinase inhibitor.

Indications and dose

Neuroendocrine tumours of pancreatic origin | Neuroendocrine tumours of gastro-intestinal origin

Adult:

BY MOUTH

Adult: 10 mg once daily, for dose interruption or adjustments due to side effects—consult product literature

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Cautionary and advisory labels 23

Tarceva (Roche Products Ltd)

Erlotinib (as Erlotinib hydrochloride) 25 mg Tarceva 25 mg tablets | 30 tablet (PO) £378.33

Erlotinib (as Erlotinib hydrochloride) 100 mg Tarceva 100 mg tablets | 30 tablet (PO) £1,324.14

Erlotinib (as Erlotinib hydrochloride) 150 mg Tarceva 150 mg tablets | 30 tablet (PO) £1,631.53

Precautions

Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 888.

Caution

History of bleeding disorders • peri-surgical period (impaired wound healing)

Interactions

Appendix 1: everolimus

Side-effects

Common or very common

Alopecia • anaemia • appetite decreased • arthralgia • asthenia • cough • decreased leucocytes • dehydration • diabetes mellitus • diarrhoea • dry mouth • dyslipidaemia • dysphagia • dyspnoea • electrolyte imbalance • eye inflammation • fever • gastrointestinal discomfort • haemorrhage • headache • hyperglycaemia • hypertension • increased risk of infection • insomnia • menstrual cycle irregularities • mucositis • nail disorders • nausea • neutropenia • oral disorders • peripheral oedema • proteinuria • renal impairment • respiratory disorders • skin reactions • taste altered • thrombocytopenia • vomiting • weight decreased

Uncommon

Congestive heart failure • embolism and thrombosis • flushing • healing impaired • hepatitis B • musculoskeletal chest pain • pancytopenia • sepsis • urinary frequency increased

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Liver transplantation

Adult:

BY MOUTH

Adult: Initially 1 mg twice daily, to be started approximately 4 weeks after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Renal transplantation | Heart transplantation

Adult:

BY MOUTH

Adult: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Votubia® dispersible tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Adjunctive treatment of refractory partial-onset seizures, with or without secondary generalisation, associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Votubia® tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Renal angiomylipoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

 EVEROLIMUS

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Renal transplantation | Heart transplantation

Adult:

BY MOUTH

Adult: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Votubia® dispersible tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Adjunctive treatment of refractory partial-onset seizures, with or without secondary generalisation, associated with tuberous sclerosis complex

Adult:

BY MOUTH USING DISPERSIBLE TABLETS

Adult: (consult product literature)

Votubia® tablets

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Renal angiomylipoma associated with tuberous sclerosis complex

Adult:

BY MOUTH USING TABLETS

Adult: (consult product literature)

Important safety information

Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 888.

Caution

History of bleeding disorders • peri-surgical period (impaired wound healing)

Interactions

Appendix 1: everolimus

Side-effects

Common or very common

Alopecia • anaemia • appetite decreased • arthralgia • asthenia • cough • decreased leucocytes • dehydration • diabetes mellitus • diarrhoea • dry mouth • dyslipidaemia • dysphagia • dyspnoea • electrolyte imbalance • eye inflammation • fever • gastrointestinal discomfort • haemorrhage • headache • hyperglycaemia • hypertension • increased risk of infection • insomnia • menstrual cycle irregularities • mucositis • nail disorders • nausea • neutropenia • oral disorders • peripheral oedema • proteinuria • renal impairment • respiratory disorders • skin reactions • taste altered • thrombocytopenia • vomiting • weight decreased

Uncommon

Congestive heart failure • embolism and thrombosis • flushing • healing impaired • hepatitis B • musculoskeletal chest pain • pancytopenia • sepsis • urinary frequency increased

BNF 78
Targeted therapy responsive malignancy 981

- Rare or very rare  
  Pure red cell aplasia
- Frequency not known  
  Hepatitis B reactivation

SIDE-EFFECTS, FURTHER INFORMATION  
Reduce dose or discontinue if severe side-effects occur—consult product literature.

- CONCEPTION AND CONTRACEPTION  
  Effective contraception must be used during and for up to 8 weeks after treatment.
- PREGNANCY  
  Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- BREAST FEEDING  
  Manufacturer advises avoid.
- HEPATIC IMPAIRMENT  
  Consult product literature.

- MONITORING REQUIREMENTS  
  For Votubia® preparations: manufacturer advises everolimus blood concentration monitoring is required—consult product literature.
  For Certican®: manufacturer advises pre-dose (‘trough’) whole blood everolimus concentration should be 3–8 nanograms/mL; monitoring should be performed every 4–5 days (using chromatographic assay) after initiation or dose adjustment until 2 consecutive stable concentrations; monitor patients with hepatic impairment taking concomitant strong CYP3A4 inducers and inhibitors when switching formulation, and/or if concomitant ciclosporin dose is reduced.
  Manufacturer advises monitor blood-glucose concentration, complete blood count, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter.
  Manufacturer advises monitor renal function before treatment and periodically thereafter.
  Manufacturer advises monitor for signs and symptoms of infection before and during treatment.

- DIRECTIONS FOR ADMINISTRATION  
  VOTUBIA® DISPERSIBLE TABLETS  
  Manufacturer advises tablets must be dispersed in water before administration—consult product literature for details.
  Tablets may be dispersed in approximately 30 mL of water by gently stirring, immediately before drinking. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed.

- PRESCRIBING AND DISPENSING INFORMATION  
  Votubia® is available as both tablets and dispersible tablets. These formulations vary in their licensed indications and are not interchangeable—consult product literature for information on switching between formulations.

- PATIENT AND CARER ADVICE  
  Pneumonitis  
  Non-infectious pneumonitis reported. Manufacturer advises patients and their carers should be informed to seek urgent medical advice if new or worsening respiratory symptoms occur.
  Infections  
  Manufacturer advises patients and their carers should be informed of the risk of infection.

- NATIONAL FUNDING/ACCESS DECISIONS  
  NICE decisions  
  Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (December 2016) NICE TA421
  Everolimus, in combination with exemestane, is recommended within its market authorisation for treating advanced human epidermal growth factor receptor 2 (HER2)-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor. Everolimus is recommended only if the manufacturer provides it with the discount agreed in the patient access scheme.
  www.nice.org.uk/TA421

- Everolimus for advanced renal cell carcinoma after previous treatment (February 2017) NICE TA432
  Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy. Everolimus is only recommended if the manufacturer provides it with the discount agreed in the patient access scheme.
  www.nice.org.uk/TA432

- Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (June 2017) NICE TA449
  Everolimus and sunitinib are recommended, within their marketing authorisations, as options for treating well- or moderately differentiated unresectable or metastatic neuroendocrine tumours (NETs) of pancreatic origin in adults with progressive disease.
  Everolimus is recommended, within its marketing authorisation, as an option for treating well-differentiated (grade 1 or grade 2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease.
  Everolimus is recommended only when the company provides it with the discount agreed in the patient access scheme.
  www.nice.org.uk/TA449

VOTUBIA® DISPERSIBLE TABLETS

Scottish Medicines Consortium (SMC) decisions  
SMC No. 1331/18
The Scottish Medicines Consortium has advised (June 2018) that everolimus (Votubia® dispersible tablets) are accepted for use within NHS Scotland for the adjunctive treatment of patients aged two years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

AFINITOR®

NICE decisions  
Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (January 2018) NICE TA498
Lenvatinib plus everolimus is recommended as an option for treating advanced renal cell carcinoma in adults who have had one previous vascular endothelial growth factor (VEGF)-targeted therapy, only if:  
- their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1, and
- the manufacturer provides lenvatinib with the discount agreed in the patient access scheme.
Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
  www.nice.org.uk/guidance/TA498

CERTICAN®

NICE decisions  
Everolimus for preventing organ rejection in liver transplantation (July 2015) NICE TA348
Everolimus (Certican®) is not recommended within its marketing authorisation for preventing organ rejection in patients who have undergone a liver transplant. Patients currently receiving everolimus for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop.
  www.nice.org.uk/guidance/TA348

www.getintopharma.com
Targeted therapy responsive malignancy

982

IMMUNOSUPPRESSIVE THERAPY FOR KIDNEY TRANSPLANT IN ADULTS (OCTOBER 2017) NICE TA481

Everolimus is not recommended as an initial treatment to prevent organ rejection in adults having a kidney transplant. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA481

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Dispersible tablet

CAUTIONARY AND ADVISORY LABELS 13

- Everolimus 2 mg Votubia 2mg dispersible tablets sugar-free | 30 tablet POTS £96.00
- Everolimus 3 mg Votubia 3mg dispersible tablets sugar-free | 30 tablet POTS £1,440.00
- Everolimus 5 mg Votubia 5mg dispersible tablets sugar-free | 30 tablet POTS £2,250.00

Tablet

CAUTIONARY AND ADVISORY LABELS 25

- Everolimus (Non-proprietary)
- Everolimus 2.5 mg Everolimus 2.5mg tablets | 30 tablet POTS £1,150.00
- Everolimus 5 mg Everolimus 5mg tablets | 30 tablet POTS £2,200.00
- Everolimus 10 mg Everolimus 10mg tablets | 30 tablet POTS £2,920.00
- Afinitor (Novartis Pharmaceuticals UK Ltd)
- Everolimus 2.5 mg Afinitor 2.5mg tablets | 30 tablet POTS £1,200.00
- Everolimus 5 mg Afinitor 5mg tablets | 30 tablet POTS £2,250.00
- Everolimus 10 mg Afinitor 10mg tablets | 30 tablet POTS £2,673.00
- Certican (Novartis Pharmaceuticals UK Ltd)
- Everolimus 250 microgram Certican 0.25mg tablets | 60 tablet POTS £148.50
- Everolimus 750 microgram Certican 0.75mg tablets | 60 tablet POTS £445.50
- Votubia (Novartis Pharmaceuticals UK Ltd)
- Everolimus 2.5 mg Votubia 2.5mg tablets | 30 tablet POTS £1,200.00
- Everolimus 5 mg Votubia 5mg tablets | 30 tablet POTS £2,250.00
- Everolimus 10 mg Votubia 10mg tablets | 30 tablet POTS £2,970.00

Gefitinib

DRUG ACTION

Gefitinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor

BY MOUTH

- Adult: 250 mg once daily

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

INTERACTIONS

Appendix 1: gefitinib

SIDE-EFFECTS

- Common or very common Alopecia - angioedema - appetite decreased - asthenia - cystitis - dehydration - diarrhoea - dry eye - dry mouth - eye inflammation - fever - haemorrhage - hyperglycaemia - interstitial lung disease - nail disorder - nausea - proteinuria - skin reactions - stomatitis - vomiting
- Uncommon Corneal erosion - gastrointestinal perforation - hepatitis - pancreatitis
- Rare or very rare Cutaneous vasculitis - severe cutaneous adverse reactions (SCARs)

CONCEPTION AND CONCEPTION

Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

PREGNANCY

Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Manufacturer advises caution in moderate to severe impairment due to cirrhosis—monitor for adverse events (risk of increased drug plasma concentrations).

RENAI IMPAIRMENT

Manufacturer advises caution if creatinine clearance less than 20 mL/minute.

MONITORING REQUIREMENTS

- Monitor for worsening of dyspnoea, cough and fever—discontinue if interstitial lung disease confirmed.
- Monitor liver function—consider discontinuing if severe changes in liver function occur.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (July 2010) NICE TA192

Gefitinib (Iressa®) is recommended as an option for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer if the patient tests positive for the epidermal growth receptor tyrosine kinase (EGFR-TK) mutation and the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

www.nice.org.uk/guidance/ta192

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (December 2015) NICE TA374

Gefitinib (Iressa®) is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in patients with tumours that are EGFR-TK mutation-positive.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta374

Scottish Medicines Consortium (SMC) decisions

SMC No. 615/10

The Scottish Medicines Consortium has advised (December 2015) that gefitinib (Iressa®) is accepted for restricted use within NHS Scotland for the treatment of adults with previously untreated locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor tyrosine kinase. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

www.getintopharma.com
Ibrutinib

**DRUG ACTION** Ibrutinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

**Treatment of relapsed or refractory mantle cell lymphoma**
- **BY MOUTH**
  - Adult: 560 mg once daily, for dose adjustments due to side effects consult product literature.

**Treatment of chronic lymphocytic leukaemia, in patients who have received at least one prior therapy, or as first-line treatment in patients with 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy**
- **BY MOUTH**
  - Adult: 420 mg once daily, for dose adjustments due to side effects consult product literature.

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**
- Manufacturer advises if concurrent use of moderate inhibitors of CYP3A4, amiodarone or ciprofloxacin is unavoidable, reduce dose to 280 mg once daily.
- Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 140 mg once daily, or withhold ibrutinib for up to 7 days.

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 888.

**MHRA/CHM ADVICE: IBRUTINIB (IMBRUVICA®): REPORTS OF VENTRICULAR TACHYARRHYTHMIA; RISK OF HEPATITIS B REACTIVATION AND OF OPPORTUNISTIC INFECTIONS (AUGUST 2017)**

Cases of ventricular tachyarrhythmia have been reported with the use of ibrutinib. The MHRA advises that ibrutinib should be temporarily discontinued in patients who develop symptoms suggestive of ventricular arrhythmia and to assess benefit-risk before restarting therapy.

Hepatitis B virus status should be established before initiating therapy—for patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before the start of treatment; monitor and manage patients according to local protocols to minimise the risk of hepatitis B virus reactivation. Prophylaxis should be considered for those at an increased risk of opportunistic infections.

**CAUTIONS**
Family history of congenital short QT syndrome • increased leucocytes—increased risk of infection • interstitial lung disease • muscle spasms • musculoskeletal pain • nausea • neoplasms • neutropenia • peripheral oedema • sepsis • skin reactions • stomatitis • thrombocytopenia • tumour lysis syndrome • vision blurred • vomiting

**SIDE-EFFECTS**
- Common or very common
  - Arrhythmias • arthralgia • broken nails • CNS haemorrhage • constipation • diarrhoea • dizziness • fever • haemorrhage • headache • hypertension • hyperuricaemia • increased leucocytes • increased risk of infection • interstitial lung disease • muscle spasms • musculoskeletal pain • nausea • neoplasms • neutropenia • peripheral oedema • sepsis • skin reactions • stomatitis • thrombocytopenia • tumour lysis syndrome • vision blurred • vomiting

**INTERACTIONS**
- Appendix 1: ibrutinib

**CONCEPTION AND CONTRACEPTION**
Highly effective contraception (must include a non-hormonal method) required during and for 3 months after stopping treatment.

**PREGNANCY**
Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises discontinue breastfeeding—no information available.

**HEPATIC IMPAIRMENT**
Manufacturer advises avoid in severe impairment (risk of increased exposure)—monitor for toxicity.

**Dose adjustments**
Manufacturer advises dose reduction to 280 mg daily in mild impairment and to 140 mg daily in moderate impairment with further adjustments if necessary—consult product literature.

**RENAL IMPAIRMENT**
Use in severe impairment only if benefit outweighs risk and with close monitoring for toxicity.

**Monitoring**
Maintain hydration and monitor serum creatinine periodically in mild to moderate renal impairment.

**MONITORING REQUIREMENTS**
- Monitor full blood count once a month.
- Monitor for atrial fibrillation (increased risk in cardiac risk factors, acute infections and history of atrial fibrillation), monitor all patients periodically and complete ECG if arrhythmic symptoms or dyspnoea develop—consult product literature for treatment options.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (January 2017) NICE TA429
  Ibrutinib (Imbruvica®) alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults who have had at least one prior therapy or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable, and only when the manufacturer provides ibrutinib with the discount agreed in the patient access scheme.
  www.nice.org.uk/guidance/ta429
- Ibrutinib for treating Waldenstrom’s macroglobulinaemia (November 2017) NICE TA491
  Ibrutinib (Imbruvica®) is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom’s macroglobulinaemia in adults who have had at least one prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.
  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
  www.nice.org.uk/guidance/ta491
 Immunology

Immune system and malignant disease

INTERACTIONS

CAUTIONS

DRUG ACTION

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS

Indications and advice on minimising the risk of infection

SIDE-EFFECTS

Common or very common Colitis · diarrhoea · fever · infection · neutropenia · pneumonitis · rash

Rare or very rare Severe cutaneous adverse reactions (SCARs)

CONCEPTION AND CONTRAINDICATIONS

Highly effective contraception (in addition to barrier method) required during and for one month after treatment.

PREGNANCY

Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises caution (risk of increased exposure—limited information available in severe impairment)—monitor for adverse reactions.

MONITORING REQUIREMENTS

Manufacturer advises monitor liver function—consult product literature.

Monitor for signs and symptoms of infection, including cytomegalovirus infection and respiratory infections; new symptoms should be reported promptly. Neutrophil count should be monitored in all patients every 2 weeks for the first 6 months of treatment; patients with neutrophil count <1000 per mm$^3$ should be monitored weekly.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Idelalisib for treating chronic lymphocytic leukaemia (October 2015) NICE TA359

Idelalisib (Zydelig®), in combination with rituximab, is recommended as an option for treatment in adults:

- who have untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation, or
- who have chronic lymphocytic leukaemia when the disease has been treated but has relapsed within 24 months, and
- if the manufacturer provides idelalisib with the discount agreed in the simple discount agreement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta359

Scottish Medicines Consortium (SMC) decisions

SMC No. 1039/15

The Scottish Medicines Consortium has advised (March 2015) that idelalisib (Zydelig®) is accepted for restricted use within NHS Scotland, in combination with rituximab, for the treatment of relapsed chronic lymphocytic leukaemia in patients who are unsuitable for chemotherapy and treatment naïve patients with 17p deletion or TP53 mutation who are unsuitable for chemotherapy and treatment only whilst idelalisib is available at the price agreed in the patient access scheme.

SMC No. 1039/15

The Scottish Medicines Consortium has advised (May 2015) that idelalisib (Zydelig®) is accepted for restricted use within NHS Scotland as monotherapy for the treatment of patients with follicular lymphoma that is refractory to two prior lines of treatment. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

All Wales Medicines Strategy Group (AWMSG) decisions

AWMSG No. 2597

The All Wales Medicines Strategy Group has advised (April 2017) that idelalisib (Zydelig®) is recommended as an option for use within NHS Wales as monotherapy for the treatment of patients with follicular lymphoma, that is refractory to two prior lines of treatment.

Idelalisib

DRUG ACTION

Idelalisib is a protein kinase inhibitor.

INDICATIONS AND DOSE

Treatment of chronic lymphocytic leukaemia in patients who have received at least one previous therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies (in combination with rituximab) | Treatment of follicular lymphoma refractory to two lines of treatment (monotherapy)

BY MOUTH

Adult: 150 mg twice daily, for dose adjustment due to side effects, consult product literature

IMPORTANT SAFETY INFORMATION

Risks of incorrect dosing of ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

MHRA/CHM ADVICE: IDEALALISIB (ZYDELIG®); UPDATED INDICATIONS AND ADVICE ON MINIMISING THE RISK OF INFECTION (SEPTEMBER 2016)

In light of a recent safety review the indications for idelalisib have been updated. Manufacturer recommendations regarding monitoring for infection and prophylaxis of Pneumocystis jirovecii pneumonia have also been updated. Patients should be advised on the risk of serious or fatal infections during treatment, and idelalisib should not be initiated in patients with any evidence of infection.

CAUTIONS

Active hepatitis · diarrhoea—symptomatic management recommended (consult product literature) · pneumonitis—withhold treatment (consult product literature)

INTERACTIONS

Appendix 1: idelalisib

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Hepatitis B infection

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

BY MOUTH

Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

BY MOUTH

Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

BY MOUTH

Adult: 600 mg once daily

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy)

BY MOUTH

Adult: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

BY MOUTH

Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protubersans | Recurrent or metastatic dermatofibrosarcoma protubersans, in patients who cannot have surgery

BY MOUTH

Adult: 800 mg daily in 2 divided doses

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

BY MOUTH

Adult: 100–400 mg once daily

Imatinib

DRUG ACTION
Imatinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

BY MOUTH

Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

BY MOUTH

Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy) | Monotherapy for relapsed or refractory acute lymphoblastic leukaemia

BY MOUTH

Adult: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

BY MOUTH

Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protubersans | Recurrent or metastatic dermatofibrosarcoma protubersans, in patients who cannot have surgery

BY MOUTH

Adult: 800 mg daily in 2 divided doses

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

BY MOUTH

Adult: 100–400 mg once daily

SIDE-EFFECTS

SIDE-EFFECTS

COMMONLY REPORTED SIDE-EFFECTS

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

BY MOUTH

Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

BY MOUTH

Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy) | Monotherapy for relapsed or refractory acute lymphoblastic leukaemia

BY MOUTH

Adult: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

BY MOUTH

Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protubersans | Recurrent or metastatic dermatofibrosarcoma protubersans, in patients who cannot have surgery

BY MOUTH

Adult: 800 mg daily in 2 divided doses

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

BY MOUTH

Adult: 100–400 mg once daily

CAUTIONS

Cardiac disease | Hepatitis B infection | history of renal failure | risk factors for heart failure

CAUTIONS, FURTHER INFORMATION

Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

INTERACTIONS

INTERACTIONS

Appendix 1: imatinib

SIDE-EFFECTS

SIDE-EFFECTS

Common or very common

Alopecia | anaemia | appetite abnormalities | asthenia | bone marrow disorders | chills | constipation | cough | diarrhea | dizziness | dry eye | dry mouth | dyspnoea | excessive tearing | eye inflammation | fever | fluid imbalance | flushing | gastrointestinal discomfort | gastrointestinal disorders | haemorrhage | headaches | insomnia | joint disorders | muscle complaints | nausea | neutropenia | oedema | pain | photosensitivity reaction | sensation abnormal | skin reactions | sweat changes | taste altered | thrombocytopenia | vision blurred | vomiting | weight changes

Uncommon

Anxiety | arrhythmias | ascites | breast abnormalities | broken nails | burping | chest pain | CNS haemorrhage | congestive heart failure | depression | drowsiness | dysphagia | electrolyte imbalance | eosinophilia | eye discomfort | gout | gynaecomastia | hearing loss | hepatic disorders | hyperbilirubinaemia | hyperglycaemia | hypertension | hyperuricaemia | hypotension | increased risk of infection | laryngeal pain | lymphadenopathy | lymphopenia | malaise | memory loss | menstrual cycle irregularities | nerve disorders | oral disorders | palpitations | pancreatitis | peripheral coldness | pulmonary oedema | Raynaud’s phenomenon | renal impairment | renal pain | respiratory disorders | restless legs | scrotal oedema | sepsis | sexual dysfunction | syncope | thrombocytosis | tinnitus | tremor | urinary frequency increased | vertigo

Rare or very rare

Angina pectoris | angiodema | arthritis | cardiac arrest | cataract | confusion | glaucoma | haemolytic anaemia | haemorrhagic ovarian cyst | hepatic failure (including fatal cases) | hypersensitivity vasculitis | inflammatory bowel disease | intracranial pressure increased | muscle weakness | myocardial infarction | myopathy | nail discoulouration | pericardial disorders | pulmonary hypertension | seizure | severe cutaneous adverse reactions (SCARs) | tumour lysis syndrome

Frequency not known

Embolism and thrombosis | hepatitis B reactivation | neoplastic complications | osteonecrosis | pericarditis

CONCEPTION AND CONTRACEPTION

Effective contraception required during treatment.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Dose adjustments Max. 400 mg daily; reduce dose further if not tolerated.

RENAI IMPAIRMENT

Dose adjustments Maximum starting dose 400 mg daily if creatinine clearance less than 60 mL/minute; reduce dose further if not tolerated.

MONITORING REQUIREMENTS

Monitor for gastrointestinal haemorrhage.

Monitor complete blood counts regularly.

Monitor for fluid retention.

Monitor liver function.

Monitor growth in children (may cause growth retardation).

DIRECTIONS FOR ADMINISTRATION

Tablets may be dispersed in water or apple juice.

PATIENT AND CARER ADVICE

Patients or carers should be given advice on how to administer imatinib tablets.

www.getintopharma.com
Dasatinib, nilotinib and imatinib for untreated chronic
Imatinib for the treatment of unresectable and/or metastatic
gastro-intestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location, and mitotic rate), for up to 3 years.

Patients currently receiving treatment initiated within the NHS with imatinib that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/TA326

Imatinib for chronic myeloid leukaemia (updated January 2016) NICE TA70
Imatinib is recommended as an option for patients with Philadelphia-chromosome-positive chronic myeloid leukaemia who initially present in the accelerated phase or with blast crisis. Imatinib is also recommended as an option for patients who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.

www.nice.org.uk/TA70

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (October 2004) NICE TA86
Imatinib 400 mg daily is recommended as first-line management of KIT (CD117)-positive unresectable or metastatic, or both, gastro-intestinal stromal tumours. Continued therapy is recommended only if a response to initial treatment (as defined by Southwest Oncology Group criteria available at www.nice.org.uk/TA86) is achieved within 12 weeks. Patients who have responded should be assessed at 12-week intervals. Discontinue if tumour ceases to respond.

www.nice.org.uk/TA86

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (November 2010) NICE TA209
Imatinib 600 mg daily or 800 mg daily is not recommended for unresectable or metastatic, or both, gastro-intestinal stromal tumours whose disease has progressed after treatment with imatinib 400 mg daily.

www.nice.org.uk/TA209

Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA425
Imatinib is recommended as an option for untreated chronic phase Philadelphia-chromosome-positive CML in adults.

www.nice.org.uk/TA426

Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425
High-dose imatinib (600 mg in the chronic phase or 800 mg in the accelerated and blast-crisis phases) is not recommended for treating Philadelphia-chromosome-positive CML in adults whose disease is imatinib-resistant.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA425

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (March 2002) that imatinib (Glivec®) should be used for chronic myeloid leukaemia only under specialist supervision in accordance with British Society of Haematology guidelines (November 2001).

The Scottish Medicines Consortium has also advised (February 2012) that nilotinib (Tasigna®) is accepted for restricted use within NHS Scotland for the treatment of adult patients who are at significant risk of relapse following resection of a KIT (CD117)-positive gastrointestinal stromal tumour (GIST) and who are at high risk of recurrence following complete resection (according to the Armed Forces Institute of Pathology (AFIP) risk criteria).

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 27

| Imatinib (Non-proprietary) | Imatinib (as imatinib mesilate) 100 mg | Imatinib 100mg tablets | 30 tablet £486.66 | 60 tablet £973.32 DT + £603.10
| Imatinib (as imatinib mesilate) 400 mg | Imatinib 400mg tablets | 30 tablet £1,946.67 DT + £1,157.46 | 60 tablet £3,893.34
| Glivec (Novartis Pharmaceuticals UK Ltd) | Imatinib (as imatinib mesilate) 100 mg | Glivec 100mg tablets | 60 tablet £973.32 DT + £603.10
| Imatinib (as imatinib mesilate) 400 mg | Glivec 400mg tablets | 30 tablet £1,946.67 DT + £1,157.46

Lapatinib

INDICATIONS AND DOSE

Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2) with hormone-receptor-negative disease who have had previous treatment with trastuzumab in combination with chemotherapy (in combination with trastuzumab)

BY MOUTH
Adult: 1 g once daily

Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for patients who have had previous treatment with an anthracycline, a taxane, and trastuzumab (in combination with capecitabine)

BY MOUTH
Adult: 1.25 g once daily

Treatment of advanced or metastatic breast cancer with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for postmenopausal women with hormone-receptor-positive disease (in combination with an aromatase inhibitor)

BY MOUTH
Adult: 1.5 g once daily

IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

CAUTIONS Diarrhoea— withhold treatment if severe (consult product literature) - low gastric pH (reduced absorption) - susceptibility to QT-interval prolongation (including electrolyte disturbances)

INTERACTIONS → Appendix 1: lapatinib

SIDE-EFFECTS
Common or very common
Alopecia - appetite decreased - arthralgia - asthenia - constipation - cough - dehydration - diarrhoea (treat promptly) - dysphagia - epistaxis - gastrointestinal discomfort - headache - hepatotoxicity (discontinue permanently if severe) - hot flush - hyperbilirubinaemia - insomnia - mucositis - nail disorder - nausea - pain - paronychia - skin reactions - stomatitis - vomiting

www.getintopharma.com
Targeted therapy responsive malignancy 987

LENVIMA®

Differentiated thyroid carcinoma (specialist use only)

• BY MOUTH
  • Adult: 24 mg once daily, dose should be taken at the same time every day, for dose adjustments due to side-effects—consult product literature

Hepatocellular carcinoma (specialist use only)

• BY MOUTH
  • Adult (body-weight up to 60 kg): 8 mg once daily, dose should be taken at the same time every day, for dose adjustments due to side-effects—consult product literature
  • Adult (body-weight 60 kg and above): 12 mg once daily, dose should be taken at the same time every day, for dose adjustments due to side-effects—consult product literature

Important safety information

Risks of incorrect dosing of oral anti-cancer medicines

See Cytotoxic drugs p. 888.

Contra-indications

Fistulae

Caution

Arterial thromboembolism within the previous 6 months—elderly (75 years and over)—reduced tolerability—hypertension—blood pressure should be well-controlled prior to treatment—impaired wound healing—consider temporary interruption of treatment for major surgical procedures

Interactions

Appendix 1: lenvatinib

Side-effects

Common or very common

Uncommon
  • Pancreatitis—pareisis—posterior reversible encephalopathy syndrome (PRES)—spleenic infarction

Frequency not known

Fistula

Side-effects, further information

Manufacturer advises gastrointestinal toxicity should be actively managed—dehydration and/or hypovolaemia caused by gastrointestinal toxicity are identified as primary risk factors for renal impairment or failure.

Conception and contraception

Manufacturer advises women of child-bearing potential should use highly effective contraception during treatment and for 1 month after the last dose, an additional barrier method of contraception should be used in women using oral hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

Pregnancy

Manufacturer advises avoid unless potential benefit outweighs risk—teratogenic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

Breast feeding

Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment

KISPLYX® Manufacturer advises caution in severe impairment (risk of increased exposure).

BNF 78

Lenvatinib

26-Feb-2019

DRUG ACTION

Lenvatinib is a multireceptor tyrosine kinase inhibitor.

INDICATIONS AND DOSE

KISPLYX®

Advanced renal cell carcinoma following one prior vascular endothelial growth factor-targeted therapy (in combination with everolimus) (specialist use only)

• BY MOUTH
  • Adult: 18 mg once daily, dose should be taken at the same time every day, for dose adjustment due to side-effects—consult product literature

CONCEPTION AND CONTRACEPTION

Contraceptive advice should be used in women using oral contraceptive. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—teratogenic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

KISPLYX® Manufacturer advises caution in severe impairment (risk of increased exposure).

MEDICATION FORMS

There can be variation in the licensing of different medicines containing the same drug.

TABLET

Tyverb (Novartis Pharmaceuticals UK Ltd)

Lapatinib (as Lapatinib ditosylate monohydrate) 250 mg Tyverb 250mg tablets 84 tablet (P39) £96.16 105 tablet (P39) £1,206.45

www.nice.org.uk/TA257

IMMUNE SYSTEM AND MALIGNANT DISEASE

www.getintopharma.com
Dose adjustments Manufacturer advises dose reduction to 10 mg once daily in severe impairment.

LENVIMA® Manufacturer advises caution.
- When used for Hepatocellular carcinoma Manufacturer advises avoid in severe impairment (no information available).

Dose adjustments When used for Differentiated thyroid carcinoma Manufacturer advises dose reduction to 14 mg once daily in severe impairment; further dose adjustments may be necessary based on tolerability—consult product literature.

RENAL IMPAIRMENT KISPLYX® Manufacturer advises avoid in end-stage renal disease.
Dose adjustments Manufacturer advises reduce dose to 10 mg once daily in severe impairment; further dose adjustments may be necessary based on tolerability—consult product literature.

MONITORING REQUIREMENTS
- Manufacturer advises monitor blood pressure after 1 month and periodically during treatment (calcium levels should be monitored at least monthly), correct electrolyte abnormalities prior to treatment; monitor thyroid function before and regularly during treatment.
- Manufacturer advises monitor liver function before treatment, then every 2 weeks for the first 2 months, and then monthly thereafter; monitor for signs and symptoms of cardiac decompensation (adjust dose as necessary—consult product literature).
- Manufacturer advises monitor liver function before treatment, then every 2 weeks for the first 2 months, and then monthly thereafter; monitor urine protein regularly.

DIRECTIONS FOR ADMINISTRATION Manufacturer advises capsules should be swallowed whole. Alternatively, capsules may be added to a tablespoon of water or apple juice in a small glass (without breaking or crushing), allowed to sit for at least 10 minutes, then stirred for at least 3 minutes to dissolve the capsule shells before swallowing; the same amount of liquid should then be added to the glass, swirled a few times, then swallowed.

PATIENT AND CARER ADVICE Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue and dizziness.

NATIONAL FUNDING/ACCESS DECISIONS NICE decisions
- Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (August 2018) NICE TASS
Lenvatinib (Lenvima®) is recommended as an option for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if:
- they have not had a tyrosine kinase inhibitor before, or
- they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity specifically, toxicity that cannot be managed by dose delay or dose modification), and
- the manufacturer provides lenvatinib according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta535

- Lenvatinib for untreated advanced hepatocellular carcinoma (December 2018) NICE TAS
Lenvatinib (Lenvima®) is recommended as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults, only if:
- they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and
- the manufacturer provides it according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta551

Scottish Medicines Consortium (SMC) decisions
SMC No. SMC2138The Scottish Medicines Consortium has advised (April 2019) that lenvatinib (Lenvima®) is accepted for use within NHS Scotland as monotherapy for the treatment of adults with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

KISPLYX® NICE decisions
- Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (January 2018) NICE TA498
Lenvatinib plus everolimus is recommended as an option for treating advanced renal cell carcinoma in adults who have had one previous vascular endothelial growth factor (VEGF)-targeted therapy, only if:
- their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1, and
- the manufacturer provides lenvatinib with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta498

LENVIMA® Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (October 2016) that lenvatinib (Lenvima®) is accepted for use within NHS Scotland for treatment of adults with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

All Wales Medicines Strategy Group (AWMSG) decisions
The All Wales Medicines Strategy Group has advised (October 2017) that lenvatinib (Lenvima®) is recommended as an option for restricted use within NHS Wales for the treatment of adults with progressive, locally advanced or metastatic, differentiated
Midostaurin

**DRUG ACTION** Midostaurin is an inhibitor of multiple tyrosine kinases.

**INDICATIONS AND DOSE**

**Acute myeloid leukaemia (specialist use only)**
- **BY MOUTH**
  - Adult: 50 mg twice daily, on days 8–21 of induction and consolidation chemotherapy cycles; for administration following consolidation chemotherapy, and dose adjustment or treatment interruption due to side-effects—consult product literature

**Aggressive systemic mastocytosis (specialist use only)**
- **Systemic mastocytosis with associated haematological neoplasm (specialist use only)**
  - **Mast cell leukaemia (specialist use only)**
  - **BY MOUTH**
  - Adult: 100 mg twice daily, for dose adjustment or treatment interruption due to side-effects—consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 888.

**CAUTIONS** Active severe infection (control before initiation of monotherapy) - elderly (limited experience) - patients at risk of congestive heart failure - risk factors for QT-interval prolongation

**INTERACTIONS** → Appendix 1: midostaurin

**SIDE-EFFECTS**
- **Common or very common**
  - Concentration impaired - constipation - cough - diarrhoea - dizziness - dyspepsia - dysphagia - fatigue - febrile neutropenia - fever - haemorrhage - headache - hypotension - infection - nausea - oropharyngeal pain - peripheral oedema - respiratory disorders - tremor - vertigo - vomiting - weight increased
- **Frequency not known**
  - Congestive heart failure - QT interval prolongation

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises perform pregnancy test in women of childbearing potential within 7 days prior to treatment initiation; effective contraception must be used during treatment and for at least 4 months after stopping treatment—additional barrier method recommended in women using hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises avoid during treatment and for 4 months after stopping treatment—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment and monitor for toxicity—no information available.

**RENAL IMPAIRMENT**
Manufacturer advises caution in severe impairment and monitor for toxicity—limited information available.

**MONITORING REQUIREMENTS**
- **Manufacturer advises monitor white blood cell count regularly, especially at treatment initiation; also monitor for signs and symptoms of infection.**
- **Manufacturer advises assess left ventricular ejection fraction in patients at risk of congestive heart failure at baseline and during treatment as clinically indicated; consider performing ECGs if concomitant use with drugs that can prolong QT-interval.**
- **Manufacturer advises monitor for pulmonary symptoms indicative of interstitial lung disease or pneumonitis.**

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- **Midostaurin for untreated acute myeloid leukaemia (June 2018) NICE TA523**

Midostaurin is recommended, within its marketing authorisation, as an option in adults for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy. It is recommended only if the manufacturer provides midostaurin with the discount agreed in the patient access scheme.

www.nice.org.uk/guidance/ta523

**Scottish Medicines Consortium (SMC) decisions**
SMC No. 1330/18

The Scottish Medicines Consortium has advised (June 2018) that midostaurin (Rydapt®) is accepted for use within NHS Scotland for the treatment of adults with newly diagnosed acute myeloid leukaemia who are FMS-like tyrosine kinase 3 (FLT3) mutation-positive, when used in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS** There is variation in the licensing of different medicines containing the same drug.

**Capsule**
- **CAUTIONARY AND ADVISORY LABELS 21, 25**
- **EXCIPIENTS: May contain Alcohol**
  - **Rydapt (Novartis Pharmaceuticals UK Ltd) ▼**
  - Midostaurin 25 mg Rydapt 25mg capsules | 56 capsule £5,609.94

Nilotinib

**DRUG ACTION**
Nilotinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

**Newly diagnosed chronic phase Philadelphia chromosome-positive chronic myeloid leukaemia (initiated by a specialist)**
- **BY MOUTH**
  - Adult: 300 mg twice daily, for dose adjustments due to side-effects—consult product literature continued →

www.getintopharma.com
PREGNANCY

CONCEPTION AND CONTRACEPTION

Frequency not known ▶ Uncommon

CAUTIONS

Clinically significant bradycardia, congestive heart failure, hepatitis B infection, history of pancreatitis, recent myocardial infarction, susceptibility to QT-interval prolongation (including electrolyte disturbances), unstable angina.

CAUTIONS, FURTHER INFORMATION

Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus in those with active infection.

INTERACTIONS → Appendix 1: nilotinib

SIDE-EFFECTS

Common or very common Alopoeia, anaemia, anemia, pectoris, anxiety, appetite abnormal, arrhythmias, arthralgia, asthenia, bone marrow disorders, cardiac conduction disorders, chest discomfort, constipation, cough, decreased leucocytes, depression, diabetes mellitus, diarrhoea, dizziness, dry eye, dyslipidaemia, dyspnoea, electrolyte imbalance, eosinophilia, eye discomfort, eye disorders, eye inflammation, fever, flushing, gastrointestinal discomfort, gastrointestinal disorders, headaches, hepatic disorders, hyperbilirubinaemia, hyperglycaemia, hypertension, increased risk of infection, insomnia, muscle complaints, muscle weakness, myocardial infarction, nausea, neoplasms, neutropenia, oedema, pain, palpitations, peripheral neuropathy, QT interval prolongation, respiratory disorders, sensation abnormal, skin reactions, sweat changes, taste altered, thrombocytopenia, vertigo, vomiting, weight changes.

Uncommon Atherosclerosis, cerebrovascular insufficiency, chills, cyanosis, erectile dysfunction, gout, haemorrhage, heart failure, hyperaemia, malaise, oral disorders, pancreatitis, peripheral vascular disease, temperature sensation altered, vision disorders.

Frequency not known Breast abnormalities, chorioretinopathy, diastolic dysfunction, dry mouth, facial swelling, gynaecomastia, hepatitis B reactivation, hyperparathyroidism, hyperuricaemia, hypoglycaemia, lethargy, memory loss, menorrhagia, oesophageal pain, oopharyngeal pain, pericardial effusion, pericarditis, restless legs, sebaceous hyperplasia, syncope, tremor, urinary disorders, urine discolouration.

CONCEPTION AND CONTRACEPTION

Manufacturer advises highly effective contraception in women of childbearing potential during treatment and for up to two weeks after stopping treatment.

PREGNANCY

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; see also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

CAUTIONS

Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution (risk of increased exposure).

MONITORING REQUIREMENTS

Manufacturer advises monitor lipid profiles before initiating treatment, at 3 and 6 months, and then yearly thereafter; monitor blood glucose before initiating treatment and then periodically during treatment, as clinically indicated.

Manufacturer advises monitor full blood count every 2 weeks for the first 2 months of treatment, then monthly thereafter, or as clinically indicated.

Manufacturer advises perform baseline ECG before treatment and as clinically indicated thereafter; correct any electrolyte disturbances before treatment and monitor periodically during treatment.

Manufacturer advises monitor and actively manage cardiovascular risk factors during treatment.

DIRECTIONS FOR ADMINISTRATION

Manufacturer advises capsules should either be swallowed whole or the contents of each capsule may be dispersed in one teaspoon of apple sauce and taken immediately.

PRESCRIBING AND DISPENSING INFORMATION

All prescribers should be familiar with the Summary of Key Safety Recommendations for Tasigna® (nilotinib) provided by the manufacturer.

PATIENT AND CARER ADVICE

Manufacturer advises patients and carers should seek immediate medical attention if signs or symptoms of cardiovascular events occur.

All patients should be provided with the Important Information About How to Take Your Medication leaflet provided by the manufacturer.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA426

Nilotinib (Tasigna®) is recommended, within its marketing authorisation, as an option for untreated chronic phase Philadelphia-chromosome-positive CML in adults, only if the manufacturer provides it with the discount agreed in the patient access scheme. www.nice.org.uk/guidance/ta426

Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425

Nilotinib (Tasigna®) is recommended as an option for treating chronic or accelerated phase Philadelphia-chromosome-positive CML in adults, if they cannot have imatinib, or their disease is imatinib-resistant, and the manufacturer provides nilotinib with the discount agreed in the patient access scheme. www.nice.org.uk/guidance/ta425

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 23, 25, 27

Tasigna (Novartis Pharmaceuticals UK Ltd)

Nilotinib (as Nilotinib hydrochloride monohydrate)

150 mg Tasigna 150mg capsules | 112 capsule Pkt £2,432.85

Nilotinib (as Nilotinib hydrochloride monohydrate)

200 mg Tasigna 200mg capsules | 112 capsule Pkt £2,432.85

www.getintopharma.com
**Nintedanib**

**INDICATIONS AND DOSE**

**OFEV®**

**Treatment of idiopathic pulmonary fibrosis**
- **By mouth**
- Adult: 150 mg twice daily, reduced if not tolerated to 100 mg twice daily, for dose adjustments due to side-effects, consult product literature

**VARGATEF®**

**Treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel) (initiated under specialist supervision)**
- **By mouth**
- Adult: 200 mg twice daily on days 2–21 of a standard 21 day docetaxel cycle, for treatment following discontinuation of docetaxel and for dose adjustments due to side-effects, consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISks OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**CAUTIONS**

History or risk factors for QT prolongation - impaired wound healing - increased risk of bleeding - patients at high risk of cardiovascular disease - previous abdominal surgery - recent history of hollow organ perforation - theoretical increased risk of gastrointestinal perforation - theoretical increased risk of venous thromboembolism

**INTERACTIONS** → Appendix 1: nintedanib

**SIDE-EFFECTS**

- Common or very common Abdominal pain - abscess - appetite decreased - dehydratation - diarrhoea - electrolyte imbalance - haemorrhage - hyperbilirubinaemia - hypertension - mucositis - nausea - neutropenia - peripheral neuropathy - sepsis - skin reactions - stomatitis - thrombocytopenia - venous thromboembolism - vomiting - weight decreased
- Uncommon Drug-induced liver injury - gastrointestinal perforation - myocardial infarction - pancreatitis - renal impairment

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with peanut or soya hypersensitivity.

**CONCEPTION AND CONTRA IndICATION**

Manufacturer advises exclude pregnancy before treatment and ensure effective contraception (in addition to barrier method) during treatment and for at least 3 months after last dose.

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in mild impairment (risk of increased exposure); avoid in moderate to severe impairment (limited information available).

**OFEV®**

**DOSE ADJUSTMENTS**

Manufacturer advises dose reduction to 100 mg twice daily in mild impairment.

**RENAL IMPAIRMENT**

Manufacturer advises caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- For OFEV®, manufacturer advises monitor full blood count before each treatment cycle and regularly thereafter; monitor hepatic function before each treatment cycle during combination therapy and monthly during monotherapy; monitor renal function during treatment; monitor for thromboembolic events; monitor prothrombin time, INR and for bleeding if used concomitantly with anticoagulants; monitor for cerebral bleeding in patients with stable brain metastases.
- For OFEV®, manufacturer advises monitor hepatic function before treatment initiation and during the first month of treatment, then at regular intervals during the subsequent 2 months and as clinically indicated thereafter; monitor renal function during treatment; monitor blood pressure as clinically indicated.

**PRESCRIBING AND DISPENSING INFORMATION**

**VARGATEF®**

Not to be taken on the same day as docetaxel therapy.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small cell lung cancer (July 2015) NICE TA347
- Nintedanib (Vargatef®), in combination with docetaxel is recommended as an option for the treatment of patients with locally advanced, metastatic, or locally recurrent non-small-cell lung cancer of adenocarcinoma histology, that has progressed after first-line chemotherapy, only if the manufacturer provides nintedanib with the discount agreed in the patient access scheme.
  
  www.nice.org.uk/guidance/ta347

- Nintedanib for treating idiopathic pulmonary fibrosis (January 2016) NICE TA379
- Nintedanib (Ofev®) is recommended as an option for treating idiopathic pulmonary fibrosis, only if:
  - the patient has a forced vital capacity (FVC) between 50% and 80% of predicted,
  - the manufacturer provides nintedanib with the discount agreed in the patient access scheme, and,
  - treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period.

- Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.
  
  www.nice.org.uk/guidance/ta379

- Scottish Medicines Consortium (SMC) decisions

  SMC No. 1076/15
  The Scottish Medicines Consortium has advised (October 2015) that nintedanib (Ofev®) is accepted for restricted use within NHS Scotland for the treatment of idiopathic pulmonary fibrosis in patients with a predicted forced vital capacity less than or equal to 80%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

**EXCIPIENTS:** May contain Lecithin

- **Ofev** (Boehringer Ingelheim Ltd) ▼
  - Nintedanib (as Nintedanib esilate) 100 mg Ofev 100mg capsules | 60 capsule [£88] £1,151.10 (Hospital only)
  - Nintedanib (as Nintedanib esilate) 150 mg Ofev 150mg capsules | 60 capsule [£88] £1,151.10 (Hospital only)

- **Vargatef** (Boehringer Ingelheim Ltd) ▼
  - Nintedanib (as Nintedanib esilate) 100 mg Vargatef 100mg capsules | 120 capsule [£88] £1,151.10 (Hospital only)
  - Nintedanib (as Nintedanib esilate) 150 mg Vargatef 150mg capsules | 60 capsule [£88] £1,151.10 (Hospital only)

www.getintopharma.com
Osimertinib

**DRUG ACTION**
Osimertinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**
Locally advanced or metastatic epidermal growth factor receptor T790M mutation-positive non-small-cell lung cancer (specialist use only)
- **BY MOUTH**
  - Adult: 80 mg once daily, for dose adjustment due to side-effects—consult product literature

**SIDE-EFFECTS**
- Common or very common
  - Diarrhoea - eyelid pruritus - increased risk of infection - nail discolouration - nail disorders - respiratory disorders - skin reactions - stomatitis
- Uncommon
  - Eye disorders - eye inflammation - QT interval prolongation

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**
Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**
Manufacturer advises avoid—may be present in milk based on animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**
Manufacturer advises caution in severe and end-stage impairment—limited information available.

**MONITORING REQUIREMENTS**
Manufacturer advises monitor ECG and electrolytes periodically in patients with risk factors for QTc interval prolongation; dose adjustment is advised if QTc interval is more than 500 milliseconds on at least 2 separate ECGs—consult product literature.

**DIRECTIONS FOR ADMINISTRATION**
Manufacturer advises tablet may be dispersed in 50 mL of non-carbonated water, by stirring until dispersed and swallowed immediately (do not crush). The residue must then be re-dispersed in an additional half a glass of water and immediately swallowed. Manufacturer advises if administration via a nasogastric tube is required, the tablet may be dispersed in 15 mL of non-carbonated water, by stirring until dispersed and the residue re-dispersed in an additional 15 mL of water (do not crush). The total 30 mL of liquid should then be administered as per the nasogastric tube manufacturer’s instructions with appropriate water flushes; the solution should be administered within 30 minutes of adding the tablets to water.

**PATIENT AND CARER ADVICE**
Missed doses
Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**CONTRA-INDICATIONS**
Congenital long QT syndrome

**CAUTIONS**
Elderly (more frequent dose adjustments may be required) - history of interstitial lung disease - radiation pneumonitis requiring steroid treatment - risk factors for QTc interval prolongation

**INTERACTIONS**
→ Appendix 1: osimertinib

**IMPORTANT SAFETY INFORMATION**
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

**Scottish Medicines Consortium (SMC) decisions**
The Scottish Medicines Consortium (SMC) decisions

**NATIONAL FUNDING/ACCESS DECISIONS**
**NICE decisions**
- Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (October 2016) NICE TA416
Osimertinib is recommended as an option, for use within the Cancer Drugs Fund, for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer in adults whose disease has progressed only:
- after first-line treatment with an EGFR tyrosine kinase inhibitor, and
- if the conditions in the managed access agreement for osimertinib are followed.

Palbociclib

**DRUG ACTION**
Palbociclib is a highly selective inhibitor of cyclin-dependent kinases 4 and 6, which leads to disruption of cancer cell proliferation.

**INDICATIONS AND DOSE**
Locally advanced or metastatic breast cancer (initiated by a specialist)
- **BY MOUTH**
  - Adult: 125 mg once daily for 21 consecutive days of repeated 28 day cycles, for dose adjustments due to side-effects—consult product literature

**SIDE-EFFECTS**
- Common or very common
  - Alopecia - anaemia - appetite decreased - asthenia - diarrhoea - dry eye - epistaxis - excessive tearing - fever - infection - leucopenia - mucositis

**INTERACTIONS**
→ Appendix 1: palbociclib

**IMPORTANT SAFETY INFORMATION**
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.
Targeted therapy responsive malignancy

Pazopanib

27-Apr-2019

- Drug action
  - Pazopanib is a tyrosine kinase inhibitor.

- Indications and dose
  - First-line treatment of advanced renal cell carcinoma
  - Treatment of advanced renal cell carcinoma in patients who have had previous treatment with cytokine therapy
    - By mouth
      - Adult: 888 mg daily, adjust dose in steps of 200 mg according to tolerability; maximum 800 mg per day

- Treatment of selective subtypes of advanced soft-tissue sarcoma
  - By mouth
  - Adult: (consult product literature)

- Dose adjustments due to interactions
  - Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 400 mg daily.

- Important safety information
  - Risks of incorrect dosing of oral anti-cancer medicines
    - See Cytotoxic drugs p. 888.

- Contra-indications
  - Cerebral haemorrhage - clinically significant gastrointestinal haemorrhage - haemoptysis in the past 6 months

- Caution
  - Cardiac disease - increased risk of gastrointestinal fistula - increased risk of gastro-intestinal perforation - increased risk of haemorrhage - increased risk of thrombotic microangiopathy - permanently discontinue if symptoms develop - ischaemic stroke - myocardial infarction - risk of thrombotic events - susceptibility to QT-interval prolongation (including electrolyte disturbances) - transient ischaemic attack

- Common or very common

- Uncommon
  - Cerebrovascular insufficiency - eye disorders - haemolytic uraemic syndrome - menstrual cycle irregularities - myocardial infarction - myocardial ischaemia - oropharyngeal pain - pancreatitis - photosensitivity reaction - polycythaemia - QT interval prolongation - rhinorrhea - skin ulcer - thrombotic microangiopathy

- Side effects
  - There can be variation in the licensing of different medicines containing the same drug.

- Capsule
  - caution and advisory labels 1, 2, 25
  - Ibrance (Pfizer Ltd)

  - Palbociclib 75 mg
    - Ibrance 75mg capsules | 21 capsule (PFS) £2,950.00 (Hospital only) | 63 capsule (PFS) £8,850.00 (Hospital only)

  - Palbociclib 100 mg
    - Ibrance 100mg capsules | 21 capsule (PFS) £2,950.00 (Hospital only) | 63 capsule (PFS) £8,850.00 (Hospital only)

- Further information
  - Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (December 2017)
  - NICE TA495

  - Palbociclib, with an aromatase inhibitor, is recommended within its marketing authorisation, as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults. Palbociclib is recommended only if the manufacturer provides it with the discount agreed in the patient access scheme.

  - www.nice.org.uk/guidance/ta495

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2017) that palbociclib (Ibrance®) is accepted for restricted use within NHS Scotland in combination with an aromatase inhibitor for the first-line treatment of hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer. This advice is contingent upon the ongoing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

- Medicinal forms
  - There can be variation in the licensing of different medicines containing the same drug.

- Capsule
Targeted therapy responsive malignancy

Rare or very rare  Posterior reversible encephalopathy syndrome (PRES)

CONCEPTION AND CONTRACEPTION  Effective contraception advised during treatment.

PREGNANCY  Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

BREAST FEEDING  Discontinue breast-feeding.

HEPATIC IMPAIRMENT  Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment. Dose adjustments: Manufacturer advises dose reduction to 200 mg daily in moderate impairment.

RENAL IMPAIRMENT  Use with caution if creatinine clearance less than 30 mL/minute—no information available.

MONITORING REQUIREMENTS

Monitor liver function before treatment and at weeks 3, 5, 7, and 9, then at months 3 and 4, and periodically thereafter as clinically indicated—consult product literature if elevated liver enzymes observed.

Monitor blood pressure within 1 week of treatment initiation, then frequently throughout treatment (consider dose reduction or interruption if hypertension uncontrolled despite anti-hypertensive therapy; discontinue if blood pressure persistently elevated despite anti-hypertensive therapy and pazopanib dose reduction—consult product literature).

Monitor for signs or symptoms of congestive heart failure—monitor left ventricular ejection fraction in patients at risk of heart failure before and during treatment.

Monitor for proteinuria.

Monitor thyroid function.

Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including headache, hypertension, seizure, lethargy, confusion, visual and neurological disturbances)—permanently discontinue treatment if symptoms occur.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Pazopanib for the first-line treatment of advanced renal cell carcinoma (updated August 2013) NICE TA215

Pazopanib (Votrient™) is recommended as a first-line treatment option for people with advanced renal cell carcinoma:

- who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1, and

- if the manufacturer provides pazopanib at the discounted price agreed under the patient access scheme.

People who are currently being treated with pazopanib for advanced metastatic renal cell carcinoma but who do not meet this criteria should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

www.nice.org.uk/guidance/ta215

Scottish Medicines Consortium (SMC) decisions

SMC No. 676/11

The Scottish Medicines Consortium has advised (March 2011) that pazopanib (Votrient™) is accepted for restricted use within NHS Scotland for the first-line treatment of advanced renal cell carcinoma. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

SMC No. 820/12

The Scottish Medicines Consortium has advised (December 2012) that pazopanib (Votrient™) is not recommended for use within NHS Scotland for the treatment of selective subtypes of advanced soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after neoadjuvant therapy as the economic case was not demonstrated.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS  23, 25

Votrient (Novartis Pharmaceuticals UK Ltd)

Pazopanib (as Pazopanib hydrochloride) 200 mg  Votrient 200mg tablets  | 30 tablet (PDR) £560.50

Pazopanib (as Pazopanib hydrochloride) 400 mg  Votrient 400mg tablets  | 30 tablet (PDR) £1,121.00

Ponatinib

INDICATIONS AND DOSE

Treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate.

Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate.

BY MOUTH

Adult: 45 mg once daily, for dose reductions due to side-effects or dose reduction due to risk of vascular occlusive events, consult product literature.

DOSE ADJUSTMENTS DUE TO INTERACTIONS

Manufacturer advises consider a reduced initial dose of 30 mg daily with concurrent use of potent inhibitors of CYP3A4.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: PONATINIB: RISK OF VASCULAR OCCLUSIVE EVENTS—UPDATED ADVICE ON POSSIBLE DOSE REDUCTION (UPDATED APRIL 2017)

The benefits and risks of ponatinib were reviewed by the European Medicines Agency’s Committee on Medicinal Products for Human Use in 2014, which recommended that strengthened warnings should be added to the product information aimed at minimising the risk of blood clots and blockages in the arteries. Additional long-term follow-up data are now available that supports new advice on dose modification to reduce this risk. The MHRA advise that although the recommended starting dose of ponatinib remains unchanged, prescribers should consider reducing the dose for patients with chronic phase chronic myeloid leukaemia (CP-CML) who have achieved a major cytogenetic response while on treatment. The following factors should be taken into account in the individual patient assessment:

- cardiovascular risk;
- side-effects of ponatinib therapy (including cardiovascular and other dose-related toxicity);
- time to cytogenetic response;
- BCR-ABL transcript levels.

The MHRA recommends close monitoring of response, if dose reduction is undertaken.

MHRA/CHM ADVICE: RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS (MAY 2016)

An EU wide review has concluded that ponatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.
PREGNANCY

Uncommon

SIDE-EFFECTS

Cardiovascular status


- Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection through HBsAg treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

INTERACTIONS

Appendix 1: ponatinib

SIDE-EFFECTS

- Common or very common
  - Acute coronary syndrome
  - Alopecia
  - Anaemia
  - Appetite decreased
  - Arthralgia
  - Asthenia
  - Cerebrovascular insufficiency
  - Chills
  - Constipation
  - Cough
  - Diarrhoea
  - Dizziness
  - Dry eye
  - Dry mouth
  - Dysphonia
  - Dyspnoea
  - Electrolyte imbalance
  - Embolism and thrombosis
  - Erectile dysfunction
  - Eye inflammation
  - Febrile neutropenia
  - Fever
  - Fluid imbalance
  - Gastrointestinal discomfort
  - Gastroesophageal reflux disease
  - Haemorrhage
  - Headaches
  - Heart failure
  - Hyperglycaemia
  - Hypertension
  - Hypertrophiccardioma
  - Hyperuricaemia
  - Hypothyroidism
  - Increased risk of infection
  - Influenza like illness
  - Insomnia
  - Ischaemic heart disease
  - Lethargy
  - Mass
  - Muscle complaints
  - Nausea
  - Oedema
  - Pain
  - Pancreatitis
  - Pancytopenia
  - Pericardial effusion
  - Peripheral neuropathy
  - Peripheral vascular disease
  - Pleural effusion
  - Pulmonary hypertension
  - Sensation abnormal
  - Seizis
  - Skin reactions
  - Stomatitis
  - Sweath changes
  - Vasodilation
  - Vision disorders
  - Vomiting
  - Weight decreased

- Uncommon
  - Cardiac discomfort
  - Cardiomyopathy
  - Ischaemic coronary vasospasm
  - Hepatic disorders
  - Hepatic failure (including fatal cases)
  - Intracranial haemorrhage
  - Left ventricular dysfunction
  - Posterior reversible encephalopathy syndrome
  - Renal artery stenosis
  - Splenic infarction
  - Tumour lysis syndrome

CONCEPTION AND CONTRACEPTION

Ensure effective contraception during treatment in men and women; effectiveness of hormonal contraception unknown—alternative or additional methods of contraception should be used.

PREGNANCY

Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
Regorafenib

**DRUG ACTION** Regorafenib is an inhibitor of several protein kinases.

**INDICATIONS AND DOSE**

- **Metastatic colorectal cancer (specialist use only)**
- **Unresectable or metastatic gastrointestinal stromal tumours (specialist use only)**
- **Hepatocellular carcinoma (specialist use only)**

**BY MOUTH**

- Adult: 160 mg once daily for 21 consecutive days of repeated 28-day cycles, for dose adjustment due to side effects—consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**CAUTIONS** Ensure measures to prevent hand-foot skin reaction - Gilbert’s syndrome—risk of hyperbilirubinaemia - history of ischaemic heart disease—monitor for signs and symptoms of myocardial ischaemia and intermittent treatment if signs of ischaemia or infarction develop - hypertension—control blood pressure before treatment initiation and monitor as clinically indicated during treatment (review dose and consider treatment interruption if severe or persistent hypertension develops; discontinue treatment if hypertensive crisis occurs) - may impair wound healing—withdraw treatment for major surgical procedures - predisposition to bleeding

**INTERACTIONS** → Appendix 1: regorafenib

**SIDE-EFFECTS**

- **Common or very common** Alopecia - anemia - appetite decreased - asthenia - diarrhea - dry mouth - dysphonia - electrolyte imbalance - fever - gastroesophageal reflux disease - headache - hyperbilirubinaemia - hypertension - hyperuricaemia - hypothyroidism - increased risk of infection - leucopenia - mucositis - musculoskeletal stiffness - nausea - pain - proteinuria - skin reactions - stomatitis - taste altered - thrombocytopenia - tremor - vomiting - weight decreased

- **Uncommon** Gastrointestinal fistula (discontinue) - gastrointestinal perforation (including fatal cases, discontinue) - hepatic disorders - myocardial infarction - myocardial ischaemia - nail disorder

- **Rare or very rare** Neoplasms - posterior reversible encephalopathy syndrome (PRES) - severe cutaneous adverse reactions (SCARs)

**CONCEPTION AND CONCEPTION**

Women of childbearing potential and men must use effective contraception during treatment and up to 8 weeks after last dose.

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**

Caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor blood count and coagulation parameters and consider permanent discontinuation in event of severe bleeding.
- Monitor hepatic function before treatment, then at least every two weeks for the first 2 months, then at least monthly thereafter and as clinically indicated—consult product literature if changes in liver function observed.

- Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including seizure, headache, altered mental status, visual disturbances or cortical blindness, with or without hypertension)—discontinue treatment if symptoms occur.

- Monitor biochemical, electrolyte and metabolic parameters during treatment; ensure measures to prevent hand-foot skin reaction—consult product literature if signs or symptoms develop.

**DIRECTIONS FOR ADMINISTRATION**

- Tablets should be taken at the same time each day, swallowed whole with water after a light meal that contains less than 30% fat.

**PATIENT AND CARER ADVICE**

Counselling advised (administration).

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE decisions

- **Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours (November 2017)**

NICE TA488

Regorafenib (Stivarga®) is recommended as an option for treating unresectable or metastatic gastrointestinal stromal tumours in adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if:

- their Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 1, and
- the manufacturer provides regorafenib with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta488

- **Regorafenib for previously treated advanced hepatocellular carcinoma (January 2019)** NICE TA555

Regorafenib (Stivarga®) is recommended as an option for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib, only if:

- they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and
- the manufacturer provides it according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta555

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 1316/18

The Scottish Medicines Consortium has advised (May 2018) that regorafenib (Stivarga®) is accepted for use within NHS Scotland as monotherapy for the treatment of adults with hepatocellular carcinoma who have been previously treated with sorafenib. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

- **ELECTROLYTES:** May contain Sodium

- **Stivarga (Bayer Plc)**

  Regorafenib 40 mg Stivarga 40mg tablets | 84 tablet £3,744.00 (Hospital only)
Ribociclib

DRUG ACTION Ribociclib is an inhibitor of cyclin-dependent kinases 4 and 6, which are involved in cancer cell proliferation; their inhibition results in prevention of cancer cell growth.

INDICATIONS AND DOSE
Locally advanced or metastatic breast cancer (specialist use only)

BY MOUTH
Adult: 600 mg once daily for 21 consecutive days of repeated 28 day cycles, to be taken at approximately the same time each day, preferably in the morning, for dose adjustments due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 400 mg once daily; in those already taking 400 mg once daily, reduce dose to 200 mg once daily.

IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

CONTRA-INDICATIONS
Pre-existing QTc prolongation - risk factors for QTc prolongation (including concomitant use of drugs known to prolong QTc interval)

INTERACTIONS → Appendix 1: ribociclib

SIDE-EFFECTS
Common or very common Alopecia - anaemia - appetite decreased - asthenia - back pain - constipation - decreased leucocytes - diarrhoea - dry eye - dyspnoea - electrolyte imbalance - epistaxis - excessive tearing - fever - gastrointestinal discomfort - headache - hepatotoxicity - insomnia - nausea - neutropenia - peripheral oedema - QT interval prolongation - skin reactions - stomatitis - syncope - taste altered - thrombocytopenia - urinary tract infection - vomiting - weight decreased

ALLERGY AND CROSS-SENSITIVITY
Contra-indicated in patients with hypersensitivity to peanut or soya products.

HEPATIC IMPAIRMENT
Manufacturer advises caution in moderate to severe impairment (risk of increased exposure). Dose adjustments Manufacturer advises initial dose reduction to 400 mg once daily in moderate to severe impairment.

RENAL IMPAIRMENT
Manufacturer advises use with caution in severe renal impairment—limited information available.

MONITORING REQUIREMENTS
Manufacturer advises to perform full blood counts and liver function tests before initiating treatment, every 2 weeks for the first 2 cycles, at the beginning of the subsequent 4 cycles, and then as clinically indicated thereafter.

Manufacturer advises to assess ECG before initiating treatment (only initiate treatment in patients with QTcF values < 450 milliseconds); ECG should be repeated at approx. day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

Manufacturer advises to monitor serum electrolytes (including potassium, calcium, phosphorus and magnesium) before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated; any abnormality should be corrected before initiating treatment.

NATIONAL FUNDING/ACCESS DECISIONS
NICE decisions
Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (December 2017) NICE TA496

Ribociclib, with an aromatase inhibitor, is recommended within its marketing authorisation, as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults. Ribociclib is recommended only if the manufacturer provides it with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions
SMC No. 1295/18
The Scottish Medicines Consortium has advised (March 2018) that ribociclib (Kisqali®) is accepted for use within NHS Scotland in combination with an aromatase inhibitor, for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet CAUTIONARY AND ADVISORY LABELS 3, 25
Ruxolitinib (as Ruxolitinib succinate) 200 mg Kisqali 200mg tablets | 21 tablet PDP £983.33 | 42 tablet PDP £1,966.67 | 63 tablet PDP £2,950.00

Ruxolitinib

DRUG ACTION Ruxolitinib is a selective inhibitor of the Janus-associate tyrosine kinases JAK1 and JAK2.

INDICATIONS AND DOSE
Treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis

BY MOUTH
Adult: (consult product literature or local protocols)

IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 888.

CAUTIONS
Assess risk of developing infection before treatment—do not initiate until active serious infections are resolved

CAUTIONS, FURTHER INFORMATION
Tuberculosis Patients should be evaluated for latent and active tuberculosis before starting treatment and monitored for signs and symptoms of tuberculosis during treatment.

INTERACTIONS → Appendix 1: ruxolitinib

SIDE-EFFECTS
Common or very common Anaemia - bruising - constipation - dizziness - dyslipidaemia - flatulence - haemorrhage - headache - hypotension - increased risk of infection - intracranial haemorrhage - neutropenia - sepsis - thrombocytopenia - weight increased

www.getintopharma.com
**Sorafenib**

**DRUG ACTION** Sorafenib is an inhibitor of multiple kinases.

**INDICATIONS AND DOSE**
- **Treatment of advanced renal cell carcinoma** when treatment with interferon α or interleukin-2 has failed or is unsuitable
- **Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine**
- **Treatment of hepatocellular carcinoma**

**INDICATIONS**
- By mouth
- Adult: 400 mg twice daily, for dose adjustments due to side effects, consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxic drugs p. 888.

**CAUTIONS**
- Cardiac ischaemia
- Major surgical procedures
- Potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding—susceptibility to QT-interval prolongation

**INTERACTIONS**
- Appendix 1: sorafenib

**SIDE EFFECTS**
- Common or very common
  - Alopecia
  - Anaemia
  - Appetite decreased
  - Arthralgia
  - Asthenia
  - Congestive heart failure
  - Constipation
  - Decreased leucocytes
  - Depression
  - Diarrhoea
  - Dry mouth
  - Dysphagia
  - Dysphonia
  - Electrolyte imbalance
  - Erectile dysfunction
  - Fever
  - Flushing
  - Gastrointestinal discomfort
  - Gastrointestinal disorders
  - Haemorrhage
  - Headache
  - Hypertension
  - Hypothyroidism
  - Increased risk of infection
  - Influenza-like illness
  - Intracranial haemorrhage
  - Mucositis
  - Muscle complaints
  - Myocardial infarction
  - Myocardial ischaemia
  - Nausea
  - Neoplasms
  - Neutropenia
  - Oral disorders
  - Pain
  - Peripheral neuropathy
  - Proteinuria
  - Renal failure
  - Rhabdomyolysis
  - Skin reactions
  - Taste altered
  - Thrombocytopaenia
  - Tinnitus
  - Weight decreased

- Uncommon
  - Cholangitis
  - Cholecystitis
  - Dehydration
  - Encephalopathy
  - Gynaecomastia
  - Hepatic disorders
  - Hypersensitivity vasculitis
  - Nephrotic syndrome
  - QT interval prolongation
  - Radiation injuries
  - Respiratory disorders

- Rare or very rare
  - Angioedema
  - Hypersensitivity vasculitis
  - Nephrotic syndrome
  - QT interval prolongation
  - Rhabdomyolysis
  - Severe cutaneous adverse reactions (SCARs)

**CONCEPTION AND CONTRACEPTION**
- Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888

**PREGNANCY**
- Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888

**BREAST FEEDING**
- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in severe impairment (no information available).

**MONITORING REQUIREMENTS**
- Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation.
- Monitor blood pressure regularly and consider permanent discontinuation of sorafenib if resistant to antihypertensive therapy.
- Monitor plasma-calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroidism).
- Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.

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**TARGETED THERAPY RESPONSIVE MALIGNANCY**

**CONCEPTION AND CONTRACEPTION** Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT**
- Reduce dose in severe impairment (consult product literature).

**MONITORING REQUIREMENTS**
- Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
- Monitor for infection during treatment.
- Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (March 2016)

**Ruxolitinib** (Jakavi®) is recommended as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis, or post essential thrombocythaemia myelofibrosis, only if the patient has intermediate-2 or high-risk disease, and if the manufacturer provides ruxolitinib with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta386

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Jakavi (Novartis Pharmaceuticals UK Ltd)
- Ruxolitinib (as Ruxolitinib phosphate) 5 mg Jakavi 5mg tablets
  - 56 tablet pack £1.428.00 DT = £1.428.00
- Ruxolitinib (as Ruxolitinib phosphate) 10 mg Jakavi 10mg tablets
  - 56 tablet pack £2.856.00 DT = £2.856.00
- Ruxolitinib (as Ruxolitinib phosphate) 15 mg Jakavi 15mg tablets
  - 56 tablet pack £2.856.00 DT = £2.856.00
- Ruxolitinib (as Ruxolitinib phosphate) 20 mg Jakavi 20mg tablets
  - 56 tablet pack £2.856.00 DT = £2.856.00

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www.getintopharma.com
Sunitinib

**Drug Action** Sunitinib is a tyrosine kinase inhibitor.

**Indications and Dose**

**Treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib**

- **Treatment of advanced or metastatic renal cell carcinoma**

- **Treatment of unresectable or metastatic pancreatic neuroendocrine tumours**

**Drug Interaction**

See Appendix I: Sunitinib

**Side-Effects**

- Cardiovascular disease: discontinue if congestive heart failure develops, hypertension, increased risk of bleeding, susceptibility to QT-interval prolongation

**Dose Adjustments due to Interactions**

- Manufacturer advises if concurrent use of potent inducers of CYP3A4 is unavoidable, dose may need to be increased in steps of 12.5 mg to a max. dose of 87.5 mg per day for gastro-intestinal stromal tumours or renal cell carcinoma, or to a max. dose of 62.5 mg per day for pancreatic neuroendocrine tumours.

**Aims for a healthy lifestyle**

- Maintain a healthy body weight
- Use non-oral contraception if female and of childbearing potential

**Medicinal Form**

- **Tablet**
  - Sunitinib (as Sorafenib tosylate) 200 mg Nexavar 200mg tablets
  - 112 tablet pack £13.576.56

**Selected Clinical Studies**

- BEVAZUMAB (first-line) and sorafenib (second-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009) NICE TA178
- Source: Source: NICE TA178

**SMC No. 482/08**

**Scottish Medicines Consortium (SMC) decisions**

**Scottish Medicines Consortium (SMC) decisions**

- **NICE decisions**

  - Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma.
  - Source: www.nice.org.uk/guidance/ta535

- **Sorafenib (as Sorafenib tosylate) 200 mg Nexavar 200mg tablets**

- **Tablet**
  - **Cautionary and Advisory Labels:**
    - Nexavar (Bayer Plc)
    - Source: www.nice.org.uk/guidance/ta474

- **Sorafenib for treating advanced hepatocellular carcinoma (September 2017)** NICE TA474

- **Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for patients with Child-Pugh grade A liver impairment, only if the manufacturer provides sorafenib within the agreed commercial access arrangement. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.**

- **Manufacturer advises if concurrent use of potent inducers of CYP3A4 is unavoidable, dose may need to be increased in steps of 12.5 mg to a max. dose of 87.5 mg per day for gastro-intestinal stromal tumours or renal cell carcinoma, or to a max. dose of 62.5 mg per day for pancreatic neuroendocrine tumours.**

**IMPORTANT SAFETY INFORMATION**

**RISK OF OSTEOONECROSIS OF THE JAW (JANUARY 2011)**

- Treatment with sunitinib may be a risk factor for the development of osteonecrosis of the jaw. Patients treated with sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk.

- Dental examination and appropriate preventive dentistry should be considered before treatment with sunitinib.

- If possible, invasive dental procedures should be avoided in patients treated with sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

**Risks of incorrect dosing of oral anti-cancer medicines**

See Cytotoxic drugs p. 888.

**Caution**

- Cardiovascular disease—discontinue if congestive heart failure develops, hypertension, increased risk of bleeding, susceptibility to QT-interval prolongation
1000 Targeted therapy responsive malignancy

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 14

Sunitinib (as Sunitinib malate) 25 mg
Sunitinib (as Sunitinib malate) 12.5 mg
Sunitinib (as Sunitinib malate) 50 mg

SIDE-EFFECTS

Common or very common Abscess • anaemia • anxiety • appetite decreased • arthralgia • asthenia • chest pain • chill • conjunctivitis • constipation • cough • cystitis • decreased leucocytes • dehydration • depression • diabetes mellitus • diarrhoea • dizziness • drowsiness • dyslipidaemia • dysphagia • dyspnoea • electrolyte imbalance • embolism and thrombosis • fever • gastrointestinal discomfort • gastrointestinal disorders • genital oedema • haemorrhage • headache • hypersensitivity • hypertension • increased risk of infection • insomnia • lacrimation disorder • mucositis • myalgia • nail disorder • nausea • neutropenia • oedema • oral disorders • pain • paraesthesia • post procedural infection • renal failure • respiratory disorders • scrotal oedema • sepsis • skin reactions • taste altered • thrombocytopenia • vomiting

Uncommon Healing impaired • intracranial haemorrhage • pericardial effusion

Tensirolimus

DRUG ACTION Tensirolimus is a protein kinase inhibitor.

INDICATIONS AND DOSE

First-line treatment of advanced renal cell carcinoma | Treatment of relapsed or refractory mantle cell lymphoma

BY INTRAVENOUS INFUSION

Adult: (consult product literature or local protocols)

INTERACTIONS → Appendix 1: tensirolimus

SIDE-EFFECTS

Common or very common Abscess • anaemia • anxiety • appetite decreased • arthralgia • asthenia • chest pain • chill • conjunctivitis • constipation • cough • cystitis • decreased leucocytes • dehydration • depression • diabetes mellitus • diarrhoea • dizziness • drowsiness • dyslipidaemia • dysphagia • dyspnoea • electrolyte imbalance • embolism and thrombosis • fever • gastrointestinal discomfort • gastrointestinal disorders • genital oedema • haemorrhage • headache • hypersensitivity • hypertension • increased risk of infection • insomnia • lacrimation disorder • mucositis • myalgia • nail disorder • nausea • neutropenia • oedema • oral disorders • pain • paraesthesia • post procedural infection • renal failure • respiratory disorders • scrotal oedema • sepsis • skin reactions • taste altered • thrombocytopenia • vomiting

Uncommon Healing impaired • intracranial haemorrhage • pericardial effusion

Sunitinib (as Sunitinib malate) 25 mg
Sunitinib (as Sunitinib malate) 50 mg

Sunitinib is recommended as an option for treatment in patients with unresectable or metastatic gastrointestinal tumours if imatinib treatment has failed because of resistance or intolerance, and the cost of sunitinib for the first treatment cycle is met by the manufacturer.

Sunitinib (as Sunitinib malate) 12.5 mg
Sunitinib (as Sunitinib malate) 50 mg

Sunitinib is recommended as first-line treatment for advanced renal cell carcinoma in patients who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1.

www.nice.org.uk/TA169

Sunitinib is recommended as first-line treatment for patients with unresectable or metastatic gastrointestinal tumours if imatinib treatment has failed because of resistance or intolerance, and the cost of sunitinib for the first treatment cycle is met by the manufacturer.

www.nice.org.uk/TA179

Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma.

www.nice.org.uk/TA178

Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (June 2017) NICE T4A49

Everolimus and sunitinib are recommended, within their marketing authorisations, as options for treating well- or moderately differentiated unresectable or metastatic neuroendocrine tumours (NETs) of pancreatic origin in adults with progressive disease.

www.nice.org.uk/guidance/T4A49

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (November 2009) that sunitinib (Sutent®) is accepted for use within NHS Scotland for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours after failure of imatinib. The Scottish Medicines Consortium has advised (May 2011) that sunitinib (Sutent®) is accepted for use within NHS Scotland for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.
Targeted therapy responsive malignancy 1001

- **RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.
- **MONITORING REQUIREMENTS**
  - Monitor respiratory function.
  - Monitor blood lipids.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Bevacizumab (first-line), sorafenib (first- and second-line), and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009) NICE TA178
  
  Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced and/or metastatic renal cell carcinoma.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
  
  www.nice.org.uk/guidance/ta178

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for infusion**
    - **EXCIPIENTS:** May contain Ethanol, propylene glycol
      - Torisel (Pfizer Ltd)
        - Temsirolimus 25 mg per 1 ml
          - Torisel 30mg/1.2ml concentrate for solution for infusion vials and diluent | 1 vial (PO) £620.00 (Hospital only)

Tivozanib

- **DRUG ACTION** Tivozanib is a tyrosine kinase inhibitor.

- **INDICATIONS AND DOSE**
  - **Advanced renal cell carcinoma (specialist use only)**
    - **BY MOUTH**
      - **Adult:** 1340 micrograms once daily for 21 consecutive days of repeated 28 day cycles, for dose adjustments due to side effects—consult product literature

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

- **CAUTIONS** History of arterial thromboembolic events - history of bleeding disorders - history of posterior reversible encephalopathy syndrome following tivozanib treatment - history of QT-interval prolongation - history of venous thromboembolic events - major surgical procedures—interrupt treatment - patients aged over 65 years—increased risk of adverse effects - pre-existing cardiac disease - risk factors for arterial thromboembolic events - risk factors for gastro-intestinal fistula - risk factors for gastro-intestinal perforation - risk factors for venous thromboembolic events - risk of bleeding

- **INTERACTIONS** → Appendix 1: tivozanib

- **SIDE EFFECTS**
  - **Common or very common** Alopecia - anaemia - angina pectoris - appetite decreased - arthralgia - asthma - chills - constipation - cough - diarrhoea - dizziness - dry mouth - dysphagia - dysphonia - dyspnoea - embolism and thrombosis - fever - flushing - gastrointestinal discomfort - gastrointestinal disorders - haemorrhage - headache - hypertension - hypothyroidism - increased risk of infection - insomnia - myalgia - myocardial infarction - nasal complaints - nausea - oral disorders - pain - pancreatitis - peripheral neuropathy - peripheral oedema - proteinuria - skin reactions - tachycardia - taste altered - tinnitus - vertigo - visual impairment - vomiting - weight decreased
  - **Uncommon** Ear congestion - excessive tearing - goitre - hyperhidrosis - hyperthyroidism - memory loss - mucositis - muscle weakness - pulmonary oedema - QT interval prolongation - thrombocytopenia - transient ischaemic attack
  - **Rare or very rare** Posterior reversible encephalopathy syndrome (PRES)

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception in men, women of childbearing potential, and their partners during treatment and for at least one month after the last dose; an additional barrier method of contraception should be used in women using hormonal contraceptives. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies. See also *Pregnancy and reproductive function* in Cytotoxic drugs p. 888.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild-to-moderate impairment—monitor patients for tolerability; avoid in severe impairment.

- **Dose adjustments** Manufacturer advises reduce dose to 1340 micrograms on alternate days in moderate impairment—increased risk of adverse effects due to increased exposure.

- **RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—limited information available.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises perform liver function tests
  - Monitor patients for symptoms of gastro-intestinal perforation or fistula.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Tivozanib for treating advanced renal cell carcinoma (March 2018) NICE TA512

Tivozanib is recommended as an option for treating advanced renal cell carcinoma in adults, only if:

  - they have had no previous treatment, and
  - the manufacturer provides tivozanib with the discount agreed in the patient access scheme.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta512

Scottish Medicines Consortium (SMC) decisions

SMC No. 1335/18

The Scottish Medicines Consortium has advised (July 2018) that tivozanib (Fotivda®) is accepted for restricted use within NHS Scotland for the first line treatment of adults with advanced renal cell carcinoma. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

www.getintopharma.com
Trametinib

12-Jul-2018

**DRUG ACTION**
Trametinib is a protein kinase inhibitor.

**INDICATIONS AND DOSE**
Unresectable or metastatic melanoma with a BRAF V600 mutation (as monotherapy or in combination with dabrafenib) (specialist use only) Advanced non-small cell lung cancer with a BRAF V600 mutation (in combination with dabrafenib) (specialist use only)

**SIDE-EFFECTS**
Increased risk of haemorrhage — increased risk of infection — intracranial haemorrhage — left ventricular dysfunction — lymphoedema — mucositis — nausea — oedema — respiratory disorders — skin reactions — stomatitis — vision disorders — vomiting

**INTERACTIONS**
Chorioretinopathy - gastrointestinal disorders - heart failure - retinal detachment - retinal occlusion - rhabdomyolysis

**CONTRA-INDICATIONS**
History of retinal vein occlusion — predisposing factors for retinal vein occlusion — left ventricular dysfunction — breast cancer — impaired left ventricular function — diabetes mellitus — hypertension

**HANDLING AND STORAGE**
Store in an ambient temperature of 2–8°C; once opened, bottle may be stored for 30 days at not more than 30°C.

**IMPRESSANT SAFETY INFORMATION**
MHRA/CHM ADVICE (MARCH 2016): TRAMETINIB: RISK OF GASTROINTESTINAL PERFORATION AND COLITIS
A review by EU medicines regulators has concluded that trametinib can cause gastrointestinal perforation or colitis.

**CONTRA-INDICATIONS**
History of retinal vein occlusion — predisposing factors for retinal vein occlusion — left ventricular dysfunction — breast cancer — impaired left ventricular function — diabetes mellitus — hypertension

**CAUTIONS**
Concomitant antiplatelet or anticoagulant therapy—increased risk of haemorrhage — conditions that could impair left ventricular function — elderly (more frequent dose adjustments may be required) — impaired left ventricular function — predisposing factors for retinal vein occlusion — risk factors for gastrointestinal perforation

**INTERACTIONS**
Appendix 1: trametinib

**SIDE-EFFECTS**
Common or very common Abdominal pain — alopecia — anaemia — asthenia — bradycardia — constipation — cough — dehydration — diarrhoea — dry mouth — dyspnoea — eye inflammation — fever — haemorrhage — hypersensitivity — hypertension — increased risk of infection — intracranial haemorrhage — left ventricular dysfunction — lymphoedema — mucositis — nausea — oedema — respiratory disorders — skin reactions — stomatitis — vision disorders — vomiting

**NICE decisions**
Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (June 2016) NICE TA396
Trametinib (Mekinist®) in combination with dabrafenib (Tafinlar®) is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation when the manufacturer provides trametinib and dabrafenib with the discounts agreed in the patient access schemes.

www.nice.org.uk/guidance/ta396

Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (October 2018) NICE TA544
Dabrafenib (Tafinlar®) with trametinib (Mekinist®) is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults. It is recommended only if the manufacturer provides dabrafenib and trametinib with the discounts agreed in the commercial arrangements.

www.nice.org.uk/guidance/ta544
Targeted therapy responsive malignancy

Scottish Medicines Consortium (SMC) decisions
SMC No. 1161/16
The Scottish Medicines Consortium has advised (August 2016) that trametinib (Mekinist®), in combination with dabrafenib, is accepted for restricted use within NHS Scotland for first-line treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 3, 23, 25
    - Trametinib 500 microgram Mekinist 0.5mg tablets | 7 tablet POM £280.00 | 30 tablet POM £1,200.00
    - Trametinib 2 mg Mekinist 2mg tablets | 7 tablet POM £1,120.00 | 30 tablet POM £4,800.00

Vandetanib

- **DRUG ACTION** Vandetanib is a tyrosine kinase inhibitor.

- **INDICATIONS AND DOSE**
  - Treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease
  - **BY MOUTH**
    - Adult: 300 mg once daily, for dose adjustment due to side effects—consult product literature

- **CONTRA-INDICATIONS** Congenital long QT syndrome - QT interval greater than 480 milliseconds
- **CAUTIONS** Brain metastases (intracranial haemorrhage reported) - electrolyte disturbances - history of torsades de pointes - hypertension - phototoxicity reactions reported (wear protective clothing and/or sunscreen) - susceptibility to QT-prolongation
- **INTERACTIONS** → Appendix 1: vandetanib
- **SIDE-EFFECTS**
- **CONCESSION AND CONTRACEPTION** Effective contraception required during and for at least 4 months after treatment.

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk. Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment (serum bilirubin greater than 1.5 times the upper limit of normal).
- **RENAL IMPAIRMENT** Avoid if creatinine clearance less than 30 mL/minute.
  - **Dose adjustments** Reduce dose to 200 mg if creatinine clearance 30–49 mL/minute.
- **MONITORING REQUIREMENTS** Monitor ECG, serum potassium, calcium, magnesium and thyroid stimulating hormone before treatment, then 1, 3, 6 and 12 weeks after starting treatment and following dose adjustment or interruption, then every 3 months for at least 1 year.
- **DIRECTIONS FOR ADMINISTRATION** Tablets may be dispersed in half a glass of water by stirring until dispersed (approximately 10 minutes), immediately before drinking (do not crush). After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed. The solution can also be administered via nasogastric or gastrostomy tubes.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer vandetanib tablets. Phototoxicity reaction Patients should be advised to wear protective clothing and/or sunscreen.
  - Alert card An alert card should be provided.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - Vandetanib for treating medullary thyroid cancer (December 2018) NICE TA550 Vandetanib (Caprelsa®) is **not** recommended, within its marketing authorisation, for treating aggressive and symptomatic medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease.
    - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
    - www.nice.org.uk/guidance/ta550

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Caprelsa (Genzyme Therapeutics Ltd) ▼
      - Vandetanib 100 mg Caprelsa 100mg tablets | 30 tablet POM £2,500.00
      - Vandetanib 300 mg Caprelsa 300mg tablets | 30 tablet POM £5,000.00
Vemurafenib

- **DRUG ACTION** Vemurafenib is a BRAF kinase inhibitor.

- **INDICATIONS AND DOSE**
  Monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma
  - **BY MOUTH**
  - Adult: 960 mg twice daily, for dose adjustment due to side effects—consult product literature

- **SIDE-EFFECTS**
  - Common or very common: Acute tubular necrosis, nephritis, acute interstitial
  - Frequency not known: Acute kidney injury
  - **CONCEPTION AND CONTRACEPTION** Effective contraception required during for at least 6 months after treatment.
  - **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.
  - **BREAST FEEDING** Avoid—no information available.
  - **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment (risk of increased exposure)—monitor ECG monthly during the first 3 months of treatment, followed by at least every 3 months thereafter (if QTc interval is prolonged, consult product literature).
  - **RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment.
  - **MONITORING REQUIREMENTS**
    - Monitor ECG and electrolytes before treatment, after one month and following dose adjustment (treatment not recommended if QT interval greater than 500 milliseconds at baseline).
    - Monitor liver function before treatment and periodically thereafter.
    - Monitor for uveitis, iritis and retinal vein occlusion.
    - Monitor for cutaneous and non-cutaneous squamous cell carcinoma and new primary melanoma before, during and for up to 6 months after treatment—consult product literature.

- **DIRECTIONS FOR ADMINISTRATION** Food may affect absorption (take at the same time with respect to food).

- **PATIENT AND CARER ADVICE** Counselling advised (administration).
  - Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) Patients should be advised to stop taking vemurafenib and consult their doctor immediately if skin rash develops.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - **NICE decisions**
      - Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (December 2012) NICE TA269
      - Vemurafenib is recommended as an option for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.
      - www.nice.org.uk/TA269
    - **Scottish Medicines Consortium (SMC) decisions**
      - The Scottish Medicines Consortium has advised (November 2013) that vemurafenib (Zelboraf®) is accepted for restricted use within NHS Scotland as monotherapy for the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

- **CONTRA-INDICATIONS** Wild-type BRAF malignant melanoma

- **CAUTIONS** Electrolyte disturbances - prior or concurrent cancer associated with RAS mutations—increased risk of tumour progression - susceptibility to QT-prolongation

- **INTERACTIONS**
  - Common or very common 7th nerve paralysis - alopecia - appetite decreased - arthralgia - arthritis - asthenia - connective tissue disorders - constipation - cough - diarrhoea - dizziness - eye inflammation - fever - folliculitis - headache - myalgia - nausea - neoplasms - pain - panniculitis - peripheral oedema - photosensitivity reaction - QT interval prolongation - radiation injuries - skin reactions - taste altered - vomiting - weight decreased
  - Uncommon Liver injury - neutropenia - pancreatitis - peripheral neupathy - retinal occlusion - severe cutaneous adverse reactions (SCARs) - vasculitis
  - Rare or very rare Acute tubular necrosis - nephritis acute interstitial
  - Frequency not known Acute kidney injury

- **ANTINEOPLASTICS, OTHER**
  - **Niraparib**
    - **DRUG ACTION** Niraparib is an inhibitor of PARP enzymes which are involved in DNA repair. PARP inhibition results in disruption of cellular homoeostasis and cell death.

- **INDICATIONS AND DOSE**
  - Ovarian cancer (initiated by a specialist) | Fallopian tube cancer (initiated by a specialist) | Peritoneal cancer (initiated by a specialist)
    - **BY MOUTH**
    - Adult: 300 mg once daily, consider initial dose of 200 mg in patients with body-weight less than 58 kg, for dose adjustments due to side-effects—consult product literature

- **IMPROT SAFETY INFORMATION**
  - **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**
    - See Cytotoxic drugs p. 888.
  - **CAUTIONS** Pre-existing hypertension (control before treatment initiation)
  - **SIDE-EFFECTS**
    - Common or very common Anorexia - anxiety - appetite decreased - arthralgia - back pain - conjunctivitis -

▸ Uncommon Pancytopenia
▸ Frequency not known Neoplasms

CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception in women of childbearing potential during treatment and for 1 month after receiving the last dose.

PREGNANCY

Manufacturer advises avoid—limited information available.

BREAST FEEDING

Manufacturer advises avoid during treatment and for 1 month after last dose—no information available.

HEPATIC IMPAIRMENT

Manufacturer advises caution in severe impairment (no information available).

RENAL IMPAIRMENT

Manufacturer advises caution in severe impairment—no information available.

MONITORING REQUIREMENTS

▸ Manufacturer advises monitor full blood count weekly for the first month of treatment, then monthly for the next 10 months and periodically thereafter.
▸ Manufacturer advises monitor blood pressure monthly for the first year of treatment and periodically thereafter.

PATIENT AND CARER ADVICE

Driving and skilled tasks

Manufacturer advises patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of dizziness and fatigue.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

▸ Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (July 2018) NICE TA528

Niraparib (Zejula 8) is recommended for use within the Cancer Drugs Fund as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if:

▸ they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy, or
▸ they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy, and

▸ the conditions in the managed access agreement for niraparib are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

wm:nice.org.uk/guidance/ta528

Scottish Medicines Consortium (SMC) decisions

SMC No. 1341/18

The Scottish Medicines Consortium has advised (August 2018) that niraparib (Zejula 8) is accepted for restricted use within NHS Scotland as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. It is restricted to those patients who do not have a germline BRCA mutation. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

▸ Zejula (Tesaro UK Ltd)

Niraparib (as Niraparib tosylate monohydrate) 100 mg Zejula 100 mg capsules | 56 capsule (PO) £4,500.00 (Hospital only) | 84 capsule (PO) £6,750.00 (Hospital only)

Olaparib

DRUG ACTION

Olaparib is a PARP inhibitor. PARP are enzymes that repair damaged DNA in cancer cells and, in the absence of functional BRCA, inhibition of PARP results in an inability of cancer cells to repair. Therefore, inhibition of PARP results in an antineoplastic effect.

INDICATIONS AND DOSE

Ovarian cancer (initiated by a specialist) | Fallopian tube cancer (initiated by a specialist) | Peritoneal cancer (initiated by a specialist)

▸ BY MOUTH USING CAPSULES
▸ Adult: 400 mg twice daily, patients should start treatment no later than 8 weeks after completion of their final dose of the platinum-containing regimen, for dose adjustments due to side-effects—consult product literature
▸ BY MOUTH USING TABLETS
▸ Adult: 300 mg twice daily, patients should start treatment no later than 8 weeks after completion of their final dose of the platinum-containing regimen, for dose adjustments due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▸ Manufacturer advises if concurrent use of moderate inhibitors of CYP3A4 is unavoidable, reduce dose of capsules to 200 mg twice daily and tablets to 150 mg twice daily.
▸ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose of capsules to 150 mg twice daily and tablets to 100 mg twice daily.

DOSE EQUIVALENCE AND CONVERSION

▸ Manufacturer advises capsules and tablets are not interchangeable on a milligram-for-milligram basis due to differences in dosing and bioavailability.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 888.

MHRA/CHM ADVICE: LYNPARZA 8 (OLAPARIB): RISK OF MEDICATION ERRORS WITH NEW PHARMACEUTICAL FORM (MAY 2018)

A tablet formulation of olaparib was approved by the European Commission in May 2018. Capsules and tablets are not to be substituted on a milligram-to-milligram basis due to differences in dosing and bioavailability of each formulation. Prescribers should specify the formulation and dosage of olaparib on each prescription and pharmacists should ensure that the correct formulation and dose is dispensed. Patients should be instructed on the correct dose they should take for their capsules or tablets and if switched, informed of the difference in dosing.

INTERACTIONS → Appendix 1: olaparib

SIDE-EFFECTS

▸ Common or very common Anaemia - appetite decreased - diarrhoea - dizziness - fatigue - gastrointestinal discomfort - headache - lymphopenia - nausea - neutropenia - skin
**Targeted therapy responsive malignancy**

Rucaparib

**DRUG ACTION** Rucaparib is a PARP inhibitor. PARP are enzymes that repair damaged DNA in cancer cells and, in the absence of functional BRCA, inhibition of PARP results in an inability of cancer cells to repair. Therefore inhibition of PARP results in an antineoplastic effect.

**INDICATIONS AND DOSE**
- **Ovarian cancer (initiated by a specialist)**
- **Fallopian tube cancer (initiated by a specialist):**
  - Peritoneal cancer (initiated by a specialist)

<table>
<thead>
<tr>
<th>By Mouth</th>
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<tr>
<td>Adults: 600 mg twice daily, for dose adjustments due to side-effects—consult product literature</td>
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</table>

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxics p. 888.

**INTERACTIONS** Appendix 1: rucaparib

**SIDE-EFFECTS**
- **Common or very common**
  - Anaemia
  - Appetite decreased
  - Asthenia
  - Decreased leucocytes
  - Diarrhoea
  - Dizziness
  - Dyspepsia
  - Dyspnoea
  - Fever
  - Hypercholesterolaemia
  - Nausea
  - Neutropenia
  - Photosensitivity reaction
  - Skin reactions
  - Taste altered
  - Thrombocytopenia
  - Vomiting
- **Uncommon**
  - Acute myeloid leukaemia (discontinue)
  - Myleodysplastic syndrome (discontinue)
- **Frequency not known**
  - Memory loss

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises effective contraception in women of childbearing potential during treatment and for 6 months after receiving the last dose.

**PREGNANCY**
- Manufacturer advises avoid—totoxicity in animal studies.

**BREAST FEEDING**
- Manufacturer advises avoid during treatment and for 2 weeks after last dose—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises avoid during treatment and for 1 month after last dose—no information available.

**RENAL IMPAIRMENT**
- Manufacturer advises avoid in severe impairment unless benefit outweighs potential risk—no information available.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Haematological toxicity**

**Conception and Access Decisions**

**NICE decisions**

- Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (January 2016) NICE TA381 Olaparib is recommended as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if:
  - they have had 3 or more courses of platinum-based chemotherapy and;
  - the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company. www.nice.org.uk/guidance/ta381

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (November 2016) that olaparib (Lynparza®) is accepted for use within NHS Scotland as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

**MEDICINAL FORMS**

- **There can be variation in the licensing of different medicines containing the same drug.**

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 25 |
| Lyncparza (AstraZeneca UK Ltd) |
| Olaparib 100 mg | Lynparza 100mg tablets | 56 tablet | POM | £2,317.50 |
| Olaparib 150 mg | Lynparza 150mg tablets | 56 tablet | POM | £2,317.50 |

**Capsule**

| CAUTIONARY AND ADVISORY LABELS 25 |
| Lyncparza (AstraZeneca UK Ltd) |
| Olaparib 50 mg | Lynparza 50mg capsules | 448 capsule | POM | £3,550.00 |

**INTERACTIONS**

- Appendix 1: rucaparib

**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Lyncparza (AstraZeneca UK Ltd)**
  - Olaparib 100 mg | Lynparza 100mg tablets | 56 tablet | POM | £2,317.50 |
  - Olaparib 150 mg | Lynparza 150mg tablets | 56 tablet | POM | £2,317.50 |

**Capsule**

- **Lyncparza (AstraZeneca UK Ltd)**
  - Olaparib 50 mg | Lynparza 50mg capsules | 448 capsule | POM | £3,550.00 |

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxics p. 888.

**INTERACTIONS**
- Appendix 1: rucaparib

**SIDE-EFFECTS**
- **Common or very common**
  - Anaemia
  - Appetite decreased
  - Asthenia
  - Decreased leucocytes
  - Diarrhoea
  - Dizziness
  - Dyspepsia
  - Dyspnoea
  - Fever
  - Hypercholesterolaemia
  - Nausea
  - Neutropenia
  - Photosensitivity reaction
  - Skin reactions
  - Taste altered
  - Thrombocytopenia
  - Vomiting
- **Uncommon**
  - Acute myeloid leukaemia (discontinue)
  - Myleodysplastic syndrome (discontinue)
- **Frequency not known**
  - Memory loss

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises effective contraception in women of childbearing potential during treatment and for 6 months after receiving the last dose.

**PREGNANCY**
- Manufacturer advises avoid—totoxicity in animal studies.

**BREAST FEEDING**
- Manufacturer advises avoid during treatment and for 2 weeks after last dose—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises avoid during treatment and for 1 month after last dose—no information available.

**RENAL IMPAIRMENT**
- Manufacturer advises avoid in severe impairment unless benefit outweighs potential risk—no information available.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Haematological toxicity**

**Conception and Access Decisions**

**NICE decisions**

- Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (January 2016) NICE TA381 Olaparib is recommended as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if:
  - they have had 3 or more courses of platinum-based chemotherapy and;
  - the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company. www.nice.org.uk/guidance/ta381

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (November 2016) that olaparib (Lynparza®) is accepted for use within NHS Scotland as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

**MEDICINAL FORMS**

- **There can be variation in the licensing of different medicines containing the same drug.**

**Tablet**

- **Lyncparza (AstraZeneca UK Ltd)**
  - Olaparib 100 mg | Lynparza 100mg tablets | 56 tablet | POM | £2,317.50 |
  - Olaparib 150 mg | Lynparza 150mg tablets | 56 tablet | POM | £2,317.50 |

**Capsule**

- **Lyncparza (AstraZeneca UK Ltd)**
  - Olaparib 50 mg | Lynparza 50mg capsules | 448 capsule | POM | £3,550.00 |

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSSING OF ORAL ANTI-CANCER MEDICINES**
See Cytotoxics p. 888.

**INTERACTIONS**
- Appendix 1: rucaparib

**SIDE-EFFECTS**
- **Common or very common**
  - Anaemia
  - Appetite decreased
  - Asthenia
  - Decreased leucocytes
  - Diarrhoea
  - Dizziness
  - Dyspepsia
  - Dyspnoea
  - Fever
  - Hypercholesterolaemia
  - Nausea
  - Neutropenia
  - Photosensitivity reaction
  - Skin reactions
  - Taste altered
  - Thrombocytopenia
  - Vomiting
- **Uncommon**
  - Acute myeloid leukaemia (discontinue)
  - Myleodysplastic syndrome (discontinue)
- **Frequency not known**
  - Memory loss

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises effective contraception in women of childbearing potential during treatment and for 6 months after receiving the last dose.

**PREGNANCY**
- Manufacturer advises avoid—totoxicity in animal studies.

**BREAST FEEDING**
- Manufacturer advises avoid during treatment and for 2 weeks after last dose—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises avoid during treatment and for 1 month after last dose—no information available.

**RENAL IMPAIRMENT**
- Manufacturer advises avoid in severe impairment unless benefit outweighs potential risk—no information available.

**MONITORING REQUIREMENTS**
- Manufacturer advises monitor full blood count before treatment initiation, then monthly thereafter.

**PATIENT AND CARER ADVICE**
- **Driving and skilled tasks**
  - Manufacturer advises patients and their carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and fatigue.
Targeted therapy responsive malignancy 1007

Venetoclax 07-Sep-2017

**DRUG ACTION** Venetoclax is a potent, selective inhibitor of B-cell lymphoma-2 (BCL-2).

**INDICATIONS AND DOSE**

Chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation when a B-cell receptor pathway inhibitor is unsuitable or ineffective (specialist use only): Chronic lymphocytic leukaemia in the absence of 17p deletion or TP53 mutation when both chemoimmunotherapy and a B-cell receptor pathway inhibitor has been ineffective (specialist use only)

- **BY MOUTH**
  - Adult: (consult product literature)
  - Chronic lymphocytic leukaemia in patients who have received at least one prior therapy in combination with rituximab (specialist use only)
  - BY MOUTH
  - Adult: (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**

See Cytotoxic drugs p. 888.

**CAUTIONS**

Ensure adequate hydration

**INTERACTIONS**

- Appendix 1: venetoclax

**SIDE-EFFECTS**

- Common or very common: Anaemia - constipation - diarrhoea - electrolyte imbalance - fatigue - hyperuricaemia - increased risk of infection - lymphopenia - nausea - neutropenia - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises ensure effective, non-hormonal contraception during and for 30 days after treatment in women of child-bearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 888.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment (increased risk of toxicity); avoid in severe impairment (no information available).

**RENAL IMPAIRMENT**

Manufacturer advises close monitoring (increased risk of tumour lysis syndrome); use only if potential benefit outweighs risk in severe impairment—no information available.

**MONITORING REQUIREMENTS**

Manufacturer advises monitor renal function before starting treatment.

**PATIENT AND CARER ADVICE**

Hydration

Manufacturer advises patients should drink 1.5–2 L of water daily, starting 2 days before and throughout the dose-titration phase; intravenous fluids should be administered for those who cannot maintain an adequate level of oral hydration with consideration of overall risk of tumour lysis syndrome.

Vomiting

Manufacturer advises that if vomiting occurs following dose administration, no additional doses should be taken on that day and the next dose should be taken at the normal time.

**Missed doses**

Manufacturer advises that if a dose is more than 8 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Venetoclax for treating chronic lymphocytic leukaemia (November 2017) NICE TA487

Venetoclax is recommended for use within the Cancer Drugs Fund, within its authorisation, as an option for treating chronic lymphocytic leukaemia in adults:

- with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or
- without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemoimmunotherapy and a B-cell receptor pathway inhibitor, and
- only if the conditions in the managed access agreement are followed.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/TA487

- Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (February 2019) NICE TA561

Venetoclax (Venclyxto®) with rituximab is recommended, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy. It is recommended only if the manufacturer provides it according to the commercial arrangement.

www.nice.org.uk/guidance/ta561

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (August 2017) that venetoclax (Venclyxto®) is accepted for use within NHS Scotland as monotherapy for the treatment of chronic lymphocytic leukaemia:

- in the presence of 17p deletion or TP53 mutation in patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor; or
- in the absence of 17p deletion or TP53 mutation in patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 21, 25 |
| __________________________ | ____________ |
| Venetoclax (AbbVie Ltd) | ▼ |

- Venetoclax 10 mg (AbbVie Ltd) | 14 tablet P 59.87 |
- Venetoclax 50 mg (AbbVie Ltd) | 7 tablet P 149.67 |
- Venetoclax 100 mg (AbbVie Ltd) | 7 tablet P 299.34 | 14 tablet P 598.68 | 112 tablet P 4,785.47 |

www.getintopharma.com
**Vismodegib**

- **DRUG ACTION** Vismodegib is a hedgehog pathway inhibitor.

- **INDICATIONS AND DOSE**
  
  Symptomatic metastatic basal cell carcinoma | Locally advanced basal cell carcinoma not appropriate for surgery or radiotherapy
  
  ▶ **BY MOUTH**
  
  Adult: 150 mg once daily

- **SIDE-EFFECTS**

  - Common or very common 
    
    Alopecia - amenorrhea - appetite decreased - arthralgia - asthenia - constipation - dehydration - diarrhoea - gastrointestinal discomfort - hair growth abnormal - muscle complaints - nausea - pain - skin reactions - taste altered - vomiting - weight decreased
  
  - Frequency not known 
    
    Epiphyses premature fusion

- **CONCEPTION AND CONTRACEPTION**

  Women must use contraceptive methods while taking vismodegib and for 3 months after the final dose of vismodegib. Men must use a condom during treatment and for 3 months after the last dose.

- **PREGNANCY**

  Important: teratogenic risk—may cause severe birth defects and embryo-fetal death.

- **BREAST FEEDING**

  Avoid during treatment and for 3 months after the final dose.

- **RENAI IMPAIRMENT**

  No information available—manufacturer advises caution in severe impairment.

- **PRESCRIBING AND DISPENSING INFORMATION**

  Prescribers and pharmacists must comply with prescribing and dispensing restrictions as specified in the manufacturer’s Pregnancy Prevention Programme, and ensure that the patient fully acknowledges the programme’s pregnancy prevention measures—consult product literature for further information.

- **PATIENT AND CARER ADVICE**

  Conception and contraception Counselling on pregnancy and contraception advised. Patients must comply with the manufacturer’s pregnancy prevention programme.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE decisions**
    
    Vismodegib for treating basal cell carcinoma (November 2017) NICE TA489
    
    Vismodegib is not recommended within its marketing authorisation for treating symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma that is inappropriate for surgery or radiotherapy, in adults. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.[12]

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  CAUTIONARY AND ADVISORY LABELS 25

  - Erivedge (Roche Products Ltd) ▼

  **Vismodegib 150 mg** Erivedge 150mg capsules | 28 capsule pack £6,285.00 (Hospital only)

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**Afiblercept**

- **DRUG ACTION** Afiblercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Afiblercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

- **INDICATIONS AND DOSE**

  In combination with irinotecan, fluorouracil and folinic acid (FOLFIRI) chemotherapy, in metastatic colorectal cancer that is resistant to, or has progressed after, an oxaliplatin-containing regimen

  ▶ **BY INTRAVENOUS INFUSION**

  Adult: (consult local protocol)

- **CONTRA-INDICATIONS**

  Moderate or severe congestive heart failure - uncontrolled hypertension

- **CAUTIONS**

  Febrile neutropenia - history of cardiovascular disease (may be exacerbated by hypertension) - increased risk of haemorrhage (including fatal events) - increased risk of hypertension - increased risk of thromboembolic events (consult product literature if event occurs) - may impair wound healing— withhold treatment for at least 4 weeks before elective surgery and for at least 4 weeks after major surgery, or until wound fully healed - neutropenic infection - risk of fistula formation (discontinue if fistula develops) - risk of neutropenia - risk of thrombocytopenia

- **INTERACTIONS**

  ▶ Appendix 1: afiblercept

- **SIDE-EFFECTS**

  - Common or very common 
    
    Cataract - eye discomfort - eye disorders - eye inflammation - haemorrhage - retinal pigment epithelial tear - vision disorders
  
  - Uncommon 
    
    Lens opacity

- **CONCEPTION AND CONTRACEPTION**

  Exclude pregnancy before treatment. Effective contraception required during and for at least 6 months after treatment in men and women. Contraceptive advice should be given to men and women before therapy begins (and should cover the duration of contraception required after therapy has ended).

- **PREGNANCY**

  Manufacturer advises avoid—toxicity in animal studies. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

- **BREAST FEEDING**

  Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**

  Manufacturer advises caution in severe impairment (no information available).

- **RENAL IMPAIRMENT**

  Caution in severe impairment— no information available.

- **MONITORING REQUIREMENTS**

  ▶ Monitor blood pressure at initiation and at least fortnightly during treatment (do not initiate treatment if pre-existing hypertension is uncontrolled) – consult product literature if hypertension develops during treatment.

  ▶ Monitor for signs of gastro-intestinal perforation (discontinue if perforation develops).

  ▶ Monitor full blood count, including differential count and platelets at baseline and before each treatment cycle.
Monitor for proteinuria before each treatment administration (consult product literature if symptoms develop).

Monitor for signs and symptoms of diarrhoea and dehydration, particularly in elderly—consult product literature if severe diarrhoea occurs.

Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, altered mental status, nausea, vomiting, headache, or visual disturbance).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE decisions**

    - Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (March 2014) NICE TA307

    Aflibercept in combination with irinotecan and fluorouracil-based therapy is **not** recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.

    [www.nice.org.uk/guidance/TA307](http://www.nice.org.uk/guidance/TA307)

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**

  - **Zaltrap (Sanofi)**

    - **Aflibercept 25 mg per 1 ml Zaltrap 200mg/8ml concentrate for solution for infusion vials | 1 vial [POA] £591.30 (Hospital only)**

    - **Zaltrap 100mg/4ml concentrate for solution for infusion vials | 1 vial [POA] £295.65 (Hospital only)**
Chapter 9
Blood and nutrition

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Blood and blood-forming organs

1 Anaemias

Anaemias

Anaemia treatment considerations
Before initiating treatment for anaemia it is essential to determine which type is present. Iron salts may be harmful and result in iron overload if given alone to patients with anaemias other than those due to iron deficiency.

Sickle-cell anaemia
Sickle-cell disease is caused by a structural abnormality of haemoglobin resulting in deformed, less flexible red blood cells. Acute complications in the more severe forms include sickle-cell crisis, where infarction of the microvasculature and blood supply to organs results in severe pain. Sickle-cell crisis requires hospitalisation, intravenous fluids, analgesia and treatment of any concurrent infection. Chronic complications include skin ulceration, renal failure, and increased susceptibility to infection. Pneumococcal vaccine, haemophilus influenzae type b vaccine, an annual influenza vaccine and prophylactic penicillin reduce the risk of infection. Hepatitis B vaccine should be considered if the patient is not immune.

In most forms of sickle-cell disease, varying degrees of haemolytic anaemia are present accompanied by increased erythropoiesis; this may increase folate requirements and folate supplementation may be necessary.

Hydroxyurea may reduce the frequency of crises and the need for blood transfusions in sickle-cell disease. The beneficial effects of hydroxyurea may not become evident for several months.

G6PD deficiency
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is highly prevalent in individuals originating from most parts of Africa, from most parts of Asia, from Oceania, and from Southern Europe; it can also occur, rarely, in any other individuals. G6PD deficiency is more common in males than it is in females.

Individuals with G6PD deficiency are susceptible to developing acute haemolytic anaemia when they take a number of common drugs. They are also susceptible to developing acute haemolytic anaemia when they eat fava beans (broad beans, *Vicia faba*); this is termed favism and can be more severe in children or when the fresh fava beans are eaten raw.

When prescribing drugs for patients with G6PD deficiency, the following three points should be kept in mind:
Hypoplastic, haemolytic, and renal anaemias

1011

It is unlikely that dietary deprivation of pyridoxine hydrochloride produces clinically relevant haematological effects. However, certain forms of sideroblastic anaemia respond to pharmacological doses, possibly reflecting its role as a co-enzyme during haemoglobin synthesis. Pyridoxine hydrochloride is indicated in both idiopathic acquired and hereditary sideroblastic anaemias. Although complete cures have not been reported, some increase in haemoglobin can occur; the dose required is usually high. Reversible sideroblastic anaemias respond to treatment of the underlying cause but in pregnancy, haemolytic anaemias, and alcohol dependence, or during isoniazid p. 587 treatment, pyridoxine hydrochloride is also indicated.

Corticosteroids

Anabolic steroids, pyridoxine hydrochloride p. 587

1.1 Hypoplastic, haemolytic, and renal anaemias

Other drugs used for Hypoplastic, haemolytic, and renal anaemias

Eltrombopag, p. 1032

ANABOLIC STEROIDS > ANDROSTAN DERIVATIVES

Oxymetholone

- INDICATIONS AND DOSE
  - Aplastic anaemia
  - Adult: 1–5 mg/kg daily for 3 to 6 months

- INTERACTIONS → Appendix 1: oxymetholone

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension
  - Capsule
    - Oxymetholone (Non-proprietary)
    - Oxymetholone 50 mg Oxymetholone 50mg capsules | 50 capsule £47.50 £0.95

Fluoroquinolones (including ciprofloxacin, moxifloxacin)

Dapsone and other sulfones (higher doses for dermatitis herpetiformis more likely to cause problems)

- Anticyclichemotherapy
- Antilymphocyte immunoglobulin, rituximab p. 882

Hypoplastic, haemolytic, and renal anaemias

Anabolic steroids, pyridoxine hydrochloride p. 1080, antilymphocyte immunoglobulin, rituximab p. 882 (unlicensed indication), and various corticosteroids are used in hypoplastic and haemolytic anaemias.

Antilymphocyte immunoglobulin given intravenously through a central line over 12–18 hours each day for 5 days produces a response in about 50% of cases of acquired aplastic anaemia; the response rate may be increased when ciclosporin p. 838 is given as well. Severe reactions are common in the first 2 days and profound immunosuppression can occur; antilymphocyte immunoglobulin should be given under specialist supervision with appropriate resuscitation facilities. Alternatively, oxymetholone tablets (available from ‘special order’ manufacturers or specialist importing companies) can be used in aplastic anaemia for 3 to 6 months.
**EPOETINS**

**Epoetins**

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: RECOMBINANT HUMAN ERYTHROPOIETINS: VERY RARE RISK OF SEVERE CUTANEOUS ADVERSE REACTIONS (UPDATED JANUARY 2018)**

The MHRA is aware of very rare cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, in patients treated with erythropoietins; some cases were fatal. More severe cases were recorded with long-acting agents (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta).

Patients and their carers should be advised of the signs and symptoms of severe skin reactions when starting treatment and instructed to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often follow fever or flu-like symptoms—discontinue treatment permanently if such reactions occur.

**MHRA/CHM ADVICE (DECEMBER 2007) ERYTHROPOIETINS—HAEMOGLOBIN CONCENTRATION**

Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events, and in patients with cancer may increase the risk of thrombosis and related complications:

- patients should not be treated with erythropoietins for the licensed indications in chronic kidney disease or cancer in patients receiving chemotherapy unless symptoms of anaemia are present
- the haemoglobin concentration should be maintained within the range 10–12 g/100 mL
- haemoglobin concentrations higher than 12 g/100 mL should be avoided
- the aim of treatment is to relieve symptoms of anaemia, and in patients with chronic kidney disease to avoid the need for blood transfusion; the haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia (in some patients, this may be achieved at concentrations lower than the recommended range)

**MHRA/CHM ADVICE (DECEMBER 2007 AND JULY 2008) ERYTHROPOIETINS—TUMOUR PROGRESSION AND SURVIVAL IN PATIENTS WITH CANCER**

Clinical trial data show an unexplained excess mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. Many of these trials used erythropoietins outside of the licensed indications (i.e. overcorrected haemoglobin concentration or given to patients who have not received chemotherapy):

- erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy
- the decision to use erythropoietins should be based on an assessment of the benefits and risks for individual patients; blood transfusion may be the preferred treatment for anaemia associated with cancer chemotherapy, particularly in those with a good cancer prognosis

**CONTRA-INDICATIONS**

- Patients unable to receive thromboprophylaxis - pure red cell aplasia following erythropoietin therapy - uncontrolled hypertension

**CAUTIONS**

- Aluminium toxicity (can impair the response to erythropoietin) - concurrent infection (can impair the response to erythropoietin) - correct factors that contribute to the anaemia of chronic renal failure, such as iron or folate deficiency, before treatment. - during dialysis (increase in unfractionated or low molecular weight heparin dose may be needed) - epilepsy - inadequately treated or poorly controlled blood pressure—interrupt treatment if blood pressure uncontrolled - ischaemic vascular disease - malignant disease - other inflammatory disease (can impair the response to erythropoietin) - risk of thrombosis may be increased when used for anaemia before orthopaedic surgery—avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident - risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy - sickle-cell disease (lower target haemoglobin concentration may be appropriate) - sudden stabbing migraine-like pain (warning of a hypertensive crisis) - thrombocytosis (monitor platelet count for first 8 weeks)

**SIDE-EFFECTS**

- **Common or very common**
  - Arthralgia - embolism and thrombosis - headache - hypertension (dose-dependent) - influenza like illness - skin reactions - stroke
- **Uncommon**
  - Hypertensive crisis (in isolated patients with normal or low blood pressure) - respiratory tract congestion - seizure
- **Rare or very rare**
  - Thrombocytosis
- **Frequency not known**
  - Pure red cell aplasia (more common following subcutaneous administration in patients with chronic renal failure)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypertensive crisis**

In isolated patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention has occurred with epoetin. Pure red cell aplasia There have been very rare reports of pure red cell aplasia in patients treated with erythropoietins. In patients who develop a lack of efficacy with erythropoietin therapy and with a diagnosis of pure red cell aplasia, treatment with erythropoietins must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoietin.

**MONITORING REQUIREMENTS**

- Monitor closely blood pressure, reticulocyte counts, haemoglobin, and electrolytes—interrupt treatment if blood pressure uncontrolled.
- Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure should be corrected before treatment and monitored during therapy. Supplemental iron may improve the response in resistant patients.

**Darbepoetin alfa**

**INDICATIONS AND DOSE**

**Symptomatic anaemia associated with chronic renal failure in patients on dialysis**

- **BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INJECTION**
  - Adult: Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose to be given once weekly or once every 2 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL.; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when
PREGNANCY
Manufacturer advises avoid.

Adult: BY INTRAVENOUS INJECTION
Adult: BY SUBCUTANEOUS INJECTION

BNF manufacturer advises caution.

malignancies receiving chemotherapy (November 2014) NICE TA323
Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.
www.nice.org.uk/guidance/ta323

● NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323
Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/guidance/ta323

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

● Aranesp (Amgen Ltd)
Darbepoetin alfa 25 microgram per 1 ml Aranesp 10micrograms/0.4ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £58.72 DT + £58.72
Darbepoetin alfa 40 microgram per 1 ml Aranesp 20micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £117.45 DT + £117.45
Darbepoetin alfa 100 microgram per 1 ml Aranesp 50micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £293.62 DT + £293.62
Darbepoetin alfa 40 microgram per 1 ml Aranesp 40micrograms/0.4ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £234.90 DT + £234.90
Darbepoetin alfa 30micrograms/0.3ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £176.17 DT + £176.17
Darbepoetin alfa 200 microgram per 1 ml Aranesp 130micrograms/0.65ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £763.42 DT + £763.42
Darbepoetin alfa 100micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £332.35 DT + £332.35
Darbepoetin alfa 60micrograms/0.3ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PST) £469.79 DT + £469.79
Darbepoetin alfa 500 microgram per 1 ml Aranesp 300micrograms/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PST) £734.05 DT + £734.05
Darbepoetin alfa 50micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PST) £808.86 DT + £880.86
Darbepoetin alfa 40 microgram per 1 ml Aranesp SureClick 20micrograms/0.5ml solution for injection pre-filled pens | 1 pre-filled disposable injection (PST) £440.43 DT + £440.43
Darbepoetin alfa 50micrograms/0.3ml solution for injection pre-filled pens | 1 pre-filled disposable injection (PST) £432.35 DT + £432.35
Darbepoetin alfa 100 microgram per 1 ml Aranesp SureClick 100micrograms/0.5ml solution for injection pre-filled pens | 1 pre-filled disposable injection (PST) £117.45 DT + £117.45
Darbepoetin alfa 200 microgram per 1 ml Aranesp SureClick 200micrograms/0.5ml solution for injection pre-filled pens | 1 pre-filled disposable injection (PST) £293.62 DT + £293.62
Darbepoetin alfa 500 microgram per 1 ml Aranesp SureClick 500micrograms/1ml solution for injection pre-filled pens | 1 pre-filled disposable injection (PST) £734.05 DT + £734.05

● INTERACTIONS
Appendix 1: darbepoetin alfa

● SIDE-EFFECTS
Common or very common Hypersensitivity - oedema
PREGNANCY
No evidence of harm in animal studies—manufacturer advises caution.

● BREAST FEEDING
Manufacturer advises avoid—no information available.

● HEPATIC IMPAIRMENT
Manufacturer advises caution (no information available).

www.getintopharma.com
Blood and nutrition

Epoetin alfa

**INDICATIONS AND DOSE**

**Eprex® PRE-FILLED SYRINGES**

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg 3 times a week, adjusted in steps of 25 units/kg 3 times a week, dose adjusted according to response at intervals of at least 4 weeks; maintenance 75–300 units/kg once weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, maintenance dose can be given as a single dose or in divided doses, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg 3 times a week, increased in steps of 25 units/kg 3 times a week, adjusted according to response, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 mL per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia in adults receiving cancer chemotherapy

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, subcutaneous injection maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**INTERACTIONS** → Appendix 1: epoetin alfa

**SIDE-EFFECTS**

- Common or very common: Chills, cough, diarrhoea, fever, myalgia, nausea, pain, peripheral oedema, vomiting.
- Uncommon: Hyperkalaemia.

**BREAST FEEDING**: Unlikely to be present in milk. Minimal effect on infant.

**HEPATIC IMPAIRMENT**: Manufacturer advises caution in chronic hepatic failure.

**PRESCRIBING AND DISPENSING INFORMATION**: Epoetin alfa is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see **Biological medicines and Biosimilar medicines**, under Guidance on prescribing p. 1.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/guidance/ta323

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Eprex** (Janssen-Cilag Ltd)
  - Epoetin alfa 2000 unit per 1 mL Eprex 1,000 units/0.5 mL solution for injection pre-filled syringes | £ pre-filled disposable injection
  - £33.18 DT = £33.18
  - Epoetin alfa 4000 unit per 1 mL Eprex 2,000 units/0.5 mL solution for injection pre-filled syringes | £ pre-filled disposable injection
  - £66.37 DT = £66.37

www.getintopharma.com
Epoetin beta 10000 unit per ml

Eprex 6,000 units/0.6 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £199.11 DT = £199.11

Eprex 4,000 units/0.4 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £132.74 DT = £132.74

Eprex 5,000 units/0.5 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £165.92 DT = £165.92

Eprex 1,000 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £99.55 DT = £99.55

Eprex 10,000 units/1 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £331.85 DT = £331.85

Eprex 8,000 units/0.8 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £265.48 DT = £265.48

Epoetin beta 40000 unit per ml

Eprex 20,000 units/0.5 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (P) £110.62 DT = £110.62

Eprex 30,000 units/0.75 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (P) £139.11 DT = £139.11

Eprex 40,000 units/1 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (P) £256.48 DT = £256.48

INDICATIONS AND DOSE

Symptomatic anaemia associated with chronic renal failure

BY SUBCUTANEOUS INJECTION

Adult: Initially 20 units/kg 3 times a week for 4 weeks, increased in steps of 20 units/kg 3 times a week according to response at intervals of 4 weeks, total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks, total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses. Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 ml over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 ml; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week

BY INTRAVENOUS INJECTION

Adult: Initially 40 units/kg 3 times a week for 4 weeks, then increased to 80 units/kg 3 times a week, then increased in steps of 20 units/kg 3 times a week if required, at intervals of 4 weeks; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks. Intravenous injection to be administered over 2 minutes. Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 ml over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 ml; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy

BY SUBCUTANEOUS INJECTION

Adults: Initially 450 units/kg once weekly for 4 weeks, dose to be given weekly as a single dose or in 3–7 divided doses, increase dose after 4 weeks (if a rise in haemoglobin of at least 1 g/100 ml not achieved), increased to 900 units/kg once weekly, dose to be given weekly as a single dose or in 3–7 divided doses, if adequate response obtained reduce dose by 25–50%, discontinue treatment if haemoglobin concentration does not increase by at least 1 g/100 ml after 8 weeks of therapy (response unlikely). Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 ml over 4 weeks or if haemoglobin concentration exceeds 12 g/100 ml; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy; maximum 60 000 units per week

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia when blood-conserving procedures are insufficient or unavailable

BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION

Adult: consult product literature

SIDE-EFFECTS

Unlikely to be present in milk. Minimal effect on infant.

HEPATIC IMPAIRMENT

Manufacturer advises caution in chronic hepatic failure.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

ERYthropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

ERYthropoiesis-stimulating agents (epoetin beta, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/guidance/ta323

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Phenylalanine

NeoRecormon (Roche Products Ltd)

Epoetin beta 1667 unit per 1 ml NeoRecormon 500 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £21.05 DT = £21.05

Epoetin beta 6667 unit per 1 ml NeoRecormon 2000 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £84.17 DT = £84.17

Epoetin beta 10000 unit per 1 ml NeoRecormon 3000 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £168.34 DT = £168.34

Epoetin beta 16667 unit per 1 ml NeoRecormon 10,000 units/0.6 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £85.50 DT = £85.50

Epoetin beta 20000 unit per 1 ml NeoRecormon 6,000 units/0.3 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £252.50 DT = £252.50

Epoetin beta 33333 unit per 1 ml NeoRecormon 20,000 units/0.6 ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) £991.71 DT = £984.71

Epoetin beta 50000 unit per 1 ml NeoRecormon 30,000 units/0.6 ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (P) £991.71 DT = £984.71

www.getintopharma.com
Epoetin zeta

**INDICATIONS AND DOSE**

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg 3 times a week, adjusted according to response, in steps of 25 units/kg 3 times a week, dose to be adjusted at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

- **BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 50 units/kg 3 times a week, adjusted according to response, in steps of 25 units/kg 3 times a week, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Symptomatic anaemia in adults receiving cancer chemotherapy

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, only increase dose if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks; restart at a dose approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

- **BY INTRAVENOUS INJECTION**
  - Adult: 600 units/kg twice weekly for 3 weeks before surgery, intravenous injection to be given over 1–5 minutes, consult product literature for details and advice on ensuring high iron stores

**INTERACTIONS**: Appendix 1: epoetin zeta

**SIDE-EFFECTS**

- Common or very common: Asthenia, dizziness
- Uncommon: Intracranial haemorrhage

**PRECAUTIONS**

- **PREGNANCY**: No evidence of harm. Benefits probably outweigh risk of anaemia and of blood transfusion in pregnancy.
- **BREAST FEEDING**: Unlikely to be present in milk. Minimal effect on infant.
- **HEPATIC IMPAIRMENT**: Manufacturer advises caution in chronic hepatic failure.

**PREScribing AND DISPensing INFORMATION** Epoetin zeta is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE decisions

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy. If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

www.nice.org.uk/guidance/ta323

**MEDICINAL FORMS** There can be a variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS**: May contain Phenylalanine

- Retacrit (Pfizer Ltd)

  **Epoetin zeta 3333 unit per 1 ml**
  -Retacrit 2.000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £57.70 (Hospital only)
  -Retacrit 3.000units/0.9ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £86.55 (Hospital only)
  -Retacrit 1.000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £28.85 (Hospital only)
  -Epoetin zeta 10000 unit per 1 ml Retacrit 6.000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £173.09 (Hospital only)
  -Retacrit 10.000units/ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £288.48 (Hospital only)
  -Retacrit 8.000units/0.8ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £230.79 (Hospital only)
  -Retacrit 4.000units/0.4ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £115.40 (Hospital only)
  -Retacrit 5.000units/0.5ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (P?o) £144.25 (Hospital only)

- **Epoetin zeta 40000 unit per 1 ml**
  -Retacrit 20.000units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (P?o) £96.16 (Hospital only)
Symptomatic anaemia associated with chronic kidney disease in patients on dialysis and not currently treated with erythropoietins

- **INDICATIONS AND DOSE**
  - **Symptomatic anaemia associated with chronic kidney disease in patients on dialysis and not currently treated with erythropoietins**
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAVENOUS INJECTION**
    - **Adult:** Initially 600 nanograms/kg every 2 weeks, subcutaneous route preferred in patients not on haemodialysis; dose to be adjusted according to response at intervals of at least 1 month, maintenance dose of double the previous fortnightly dose may be given once a month if haemoglobin concentration is above 10 g/100 mL, reduce dose by approximately 25% if rate of rise in haemoglobin concentration exceeds 2 g/100 mL in 1 month or if haemoglobin concentration is increasing or approaching 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, dose may be increased by approximately 25% if the rate of rise in haemoglobin concentration is less than 1 g/100 mL over 1 month; further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin concentration is obtained.

  - **Symptomatic anaemia associated with chronic kidney disease in patients not on dialysis and not currently treated with erythropoietins**
    - **INITIALLY BY SUBCUTANEOUS INJECTION**
    - **Adult:** Initially 1.2 micrograms/kg every month, alternatively (by subcutaneous injection or by intravenous injection) initially 600 nanograms/kg every 2 weeks, subcutaneous route preferred in patients not on haemodialysis, dose to be adjusted according to response at intervals of at least 1 month, patients treated once every 2 weeks may be given a maintenance dose of double the previous fortnightly dose once a month if haemoglobin concentration is above 10 g/100 mL, reduce dose by approximately 25% if rate of rise in haemoglobin concentration exceeds 2 g/100 mL in 1 month or if haemoglobin concentration is increasing or approaching 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, dose may be increased by approximately 25% if the rate of rise in haemoglobin concentration is less than 1 g/100 mL over 1 month; further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin concentration is obtained.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: RECOMBINANT HUMAN ERYTHROPOIETINS: VERY RARE RISK OF SEVERE CUTANEOUS ADVERSE REACTIONS (UPDATED JANUARY 2018)

The MHRA is aware of very rare cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, in patients treated with erythropoietins; some cases were fatal. More severe cases were recorded with long-acting agents (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta).

Patients and their carers should be advised of the signs and symptoms of severe skin reactions when starting treatment and instructed to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often follow fever or flu-like symptoms—discontinue treatment permanently if such reactions occur.

MHRA/CHM ADVICE (DECEMBER 2007) ERYTHROPOIETINS—HAEMOGLOBIN CONCENTRATION

Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events, and in patients with cancer may increase the risk of thrombosis and related complications:

- patients should not be treated with erythropoietins for the licensed indications in chronic kidney disease or cancer in patients receiving chemotherapy unless symptoms of anaemia are present
- the haemoglobin concentration should be maintained within the range 10–12 g/100 mL
- haemoglobin concentrations higher than 12 g/100 mL should be avoided
- the aim of treatment is to relieve symptoms of anaemia, and in patients with chronic kidney disease to avoid the need for blood transfusion; the haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia (in some patients, this may be achieved at concentrations lower than the recommended range)

**CONTRA-INDICATIONS** Pure red cell aplasia following erythropoietin therapy; uncontrolled hypertension

**CAUTIONS** Bone marrow fibrosis (can impair the response to erythropoietin) - concurrent infection (can impair the response to erythropoietin) - haematological disease (can impair the response to erythropoietin) - haemolysis (can impair the response to erythropoietin) - inflammatory or traumatic episodes (can impair the response to erythropoietin) - malignant disease - occult blood loss (can impair the response to erythropoietin) - severe aluminium toxicity (can impair the response to erythropoietin)

**SIDE-EFFECTS**

- **Common or very common** Hypertension (dose-dependent)
- **Uncommon** Embolism and thrombosis - headache
- **Rare or very rare** Hot flush - hypertensive encephalopathy - rash maculopapular
- **Frequency not known** Pure red cell aplasia (discontinue) - severe cutaneous adverse reactions (SCARs) - thrombocytopenia

**PREGNANCY** No evidence of harm in animal studies—manufacturer advises caution.
Blood and nutrition

### MEDICATION FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection

- **Mircera (Roche Products Ltd)**
  - Methoxy polyethylene glycol-epoetin beta 100 microgram per 1 ml Mircera 100micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £44.05
  - Methoxy polyethylene glycol-epoetin beta 166.667 microgram per 1 ml Mircera 50micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £73.41
  - Methoxy polyethylene glycol-epoetin beta 250 microgram per 1 ml Mircera 50micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £110.11
  - Methoxy polyethylene glycol-epoetin beta 333.333 microgram per 1 ml Mircera 100micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £146.81
  - Methoxy polyethylene glycol-epoetin beta 400 microgram per 1 ml Mircera 120micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £176.18
  - Methoxy polyethylene glycol-epoetin beta 500 microgram per 1 ml Mircera 150micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £220.22
  - Methoxy polyethylene glycol-epoetin beta 600 microgram per 1 ml Mircera 200micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £258.56
  - Methoxy polyethylene glycol-epoetin beta 666.667 microgram per 1 ml Mircera 200micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £293.62
  - Methoxy polyethylene glycol-epoetin beta 833.333 microgram per 1 ml Mircera 250micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (amp) £367.03

#### IMMUNOSUPPRESSANTS > MONOCLONAL ANTIBODIES

### Eculizumab

- **DRUG ACTION**
  - Eculizumab, a recombinant monoclonal antibody, inhibits terminal complement activation at the C5 protein and thereby reduces haemolysis and thrombotic microangiopathy.

#### INDICATIONS AND DOSE

**Reduce haemolysis in paroxysmal nocturnal haemoglobinuria (PNH), in those with a history of blood transfusions (under expert supervision)**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 600 mg once weekly for 4 weeks, then increased to 900 mg once weekly for 1 week; maintenance 900 mg every 12–16 days

**Reduce thrombotic microangiopathy in atypical haemolytic uraemic syndrome (aHUS) (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 900 mg once weekly for 4 weeks, then increased to 1.2 g once weekly for 1 week; maintenance 1.2 g every 12–16 days

#### CONTRA-INDICATIONS

- Patients unvaccinated against *Neisseria meningitidis* • unresolved *Neisseria meningitidis* infection

#### CAUTIONS

- Active systemic infection

### CAUTIONS, FURTHER INFORMATION

- Meningococcal infection: Vaccinate against *Neisseria meningitidis* at least 2 weeks before treatment (tetravalent vaccine against serotypes A, C, W135 and Y recommended); revaccinate according to current medical guidelines. Patients receiving eculizumab less than 2 weeks after receiving meningococcal vaccine must be given prophylactic antibiotics until 2 weeks after vaccination. Advise patient to report promptly any signs of meningococcal infection. Other immunisations should also be up to date.

#### INTERACTIONS

- Appendix 1: monoclonal antibodies

#### SIDE-EFFECTS

- **Common or very common**
  - Alopecia • asthenia • chills • cough • decreased leucocytes • diarrhoea • dizziness • fever • gastrointestinal discomfort • headache • hypertension • increased risk of infection • influenza like illness • joint disorders • muscle complaints • nausea • oropharyngeal pain • pain • skin reactions • sleep disorders • taste altered • tremor • vomiting

- **Uncommon**
  - Abscess • anxiety • appetite decreased • chest discomfort • constipation • cystitis • depression • dysuria • haemorrhage • hot flush • hyperhidrosis • hypersensitivity • hypotension • meningitis meningococcal • mood swings • nasal complaints • oedema • palpitations • paraesthesia • sepsis • spontaneous penile erection • throat irritation • tinnitus • vascular disorders • vertigo • vision blurred

- **Rare or very rare**
  - Abnormal clotting factor • conjunctival irritation • feeling hot • gastrooesophageal reflux disease • gingival discomfort • Grave’s disease • infusion related reaction • jaundice • malignant melanoma • menstrual disorder • syncope • urogenital tract gonococcal infection
1.2 Iron deficiency anaemia

Anaemia, iron deficiency

Iron deficiency, treatment and prophylaxis

Treatment with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anaemia (e.g., gastric erosion, gastrointestinal cancer).

Prophylaxis with an iron preparation may be appropriate in malabsorption, menorrhagia, pregnancy, after subtotal or total gastrectomy, in haemodialysis patients, and in the management of low birth-weight infants such as preterm neonates.

Oral iron
Iron salts should be given by mouth unless there are good reasons for using another route.

Iron salts show only marginal differences between one another in efficiency of absorption of iron. Haemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the speed of response is not critical. Choice of preparation is thus usually decided by the incidence of side-effects and cost.

The oral dose of elemental iron for iron-deficiency anaemia should be 100 to 200 mg daily. It is customary to give this as dried ferrous sulfate; for prophylaxis of iron-deficiency anaemia, ferrous sulfate may be effective.

### Iron content of different iron salts

<table>
<thead>
<tr>
<th>Iron salt/amount</th>
<th>Content of ferrous iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>ferrous fumarate 200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>ferrous gluconate 300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>ferrous sulfate 300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>ferrous sulfate, dried 200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>

**Compound preparations**

Preparations containing iron and folic acid p. 1025 are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency; they should be distinguished from those used for the prevention of neural tube defects in women planning a pregnancy.

It is important to note that the small doses of folic acid contained in these preparations are inadequate for the treatment of megaloblastic anaemias.

Some oral preparations contain ascorbic acid p. 1082 to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the B group of vitamins (except folic acid for pregnant women).

**Modified-release preparations**

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

**Parenteral iron**

Iron can be administered parenterally as iron dextran p. 1020, iron sucrose p. 1021, ferric carboxymaltose p. 1020, or iron isomaltoside 1000 p. 1021. Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or does not require iron immediately.
Anaemias

Iron (injectable)

INDICATIONS AND DOSE
Iron-deficiency anaemia
- BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION

SIDE-EFFECTS
- Rare or very rare Face oedema - flatulence
- CAUTIONS Allergic disorders - eczema - hepatic dysfunction - immune conditions - infection (discontinue if ongoing bacteraemia) - inflammatory conditions - oral iron should not be given during or for at least 5 days after the last injection - severe asthma

SIDE-EFFECTS
- Common or very common Dizziness - flushing - headache - hypertension - hypophosphataemia - hypotension - nausea - taste altered
- Rare or very rare Angioedema - anxiety - circulatory collapse - influenza like illness - malaise - pallor - palpitations - psychiatric disorder - seizure - syncope - tremor

INTERACTIONS
- Appendix 1: iron (injectable)
- PRESCRIBING AND DISPENSING INFORMATION A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron.

INTERACTIONS
- By slow intravenous injection, or by intravenous infusion
- Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

SIDE-EFFECTS
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- CAUTIONS Allergic disorders - eczema - hepatic dysfunction - immune conditions - infection (discontinue if ongoing bacteraemia) - inflammatory conditions - oral iron should not be given during or for at least 5 days after the last injection - severe asthma

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INTERACTIONS
- Appendix 1: iron (injectable)
- PRESCRIBING AND DISPENSING INFORMATION A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron.
Iron deficiency anaemia 1021

DIRECTIONS FOR ADMINISTRATION
- With intravenous use: For intravenous infusion (Cosmofer®), give intermittently in Glucose 5% or Sodium chloride 0.9%, dilute 100–200 mg in 100 mL infusion fluid; give 25 mg over 15 minutes initially, then at a rate not exceeding 6.67 mg/minute; total dose infusion diluted in 500 mL infusion fluid and given over 4–6 hours (initial dose 25 mg over 15 minutes).

PRESCRIBING AND DISPENSING INFORMATION
- A complex of ferric hydroxide with dextran containing 5% (50 mg/mL) of iron.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Cosmofer (Pharmacosmos UK Ltd) ▴
  - Iron (as iron dextran) 50 mg per 1 mL Cosmofer 500 mg/10 mL solution for injection ampoules | 2 ampoule (£29.45) £79.70
  - Cosmofer 100 mg/2 mL solution for injection ampoules | 5 ampoule (£30.85)

Iron isomaltoside 1000

INDICATIONS AND DOSE
- Iron-deficiency anaemia
- By intravenous injection
- Adult: (consult product literature)

INTERACTIONS
- Appendix 1: iron (injectable)

SIDE-EFFECTS
- Uncommon: Asthenia
- Rare or very rare: Drowsiness, urine discolouration

PREGNANCY
- Avoid in first trimester.

HEPATIC IMPAIRMENT
- Manufacturer advises caution—monitor iron status to avoid iron overload; avoid where iron overload is a precipitating factor (particularly porphyria cutanea tarda).

DIRECTIONS FOR ADMINISTRATION
- For intravenous infusion (Venoferr®), give intermittently in Sodium chloride 0.9%, dilute 100 mg in up to 100 mL infusion fluid; give 25 mg over 15 minutes initially, then give at a rate not exceeding 3.33 mg/minute.

PRESCRIBING AND DISPENSING INFORMATION
- A complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Venoferr (Vifor Pharma UK Ltd, Imported (United States)) ▴
  - Iron (as iron sucrose) 20 mg per 1 mL Venoferr 100 mg/5 mL solution for injection vials | 5 vial (£43.52) £217.60
  - Venoferr 50 mg/2.5 mL solution for injection vials | 5 vial (£39.00)

MINERALS AND TRACE ELEMENTS
- Iron (oral)

SIDE-EFFECTS
- Common or very common: Constipation, diarrhoea, gastrointestinal discomfort, nausea
- Uncommon: Vomiting
- Frequency not known: Appetite decreased, faeces discoloured

SIDE-EFFECTS, FURTHER INFORMATION
- Iron can be constipating and occasionally lead to faecal impaction. Oral iron, particularly modified-release preparations, can exacerbate diarrhoea in patients with inflammatory bowel disease; care is also needed in patients with intestinal strictures and diverticular disease.

Overdose
- For details on the management of poisoning, see Iron salts, under Emergency treatment of poisoning p. 1359.

MONITORING REQUIREMENTS
- Therapeutic response: The haemoglobin concentration should rise by about 100–200 mg/100 mL (1–2 g/litre) per day or 2 g/100 mL (20 g/litre) over 3–4 weeks. When the haemoglobin is in the normal range, treatment should be continued for a further 3 months to replenish the iron stores. Epithelial tissue changes such as atrophic glossitis and koilonychia are usually improved, but the response is often slow.

PRESCRIBING AND DISPENSING INFORMATION
- In children: Express the dose in terms of elemental iron and iron salt and select the most appropriate preparation; specify both the iron salt and formulation on the prescription. The iron content of artificial formula feeds should also be considered. The most common reason for lack of response in children is poor compliance; poor absorption is rare in children.

PATIENT AND CARER ADVICE
- Although iron preparations are best absorbed on an empty stomach they can be taken after food to reduce gastro-intestinal side-effects. May discoulour stools.

Iron sucrose

INDICATIONS AND DOSE
- Iron-deficiency anaemia
- By slow intravenous injection, or by intravenous infusion
- Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

INTERACTIONS
- Appendix 1: iron (injectable)
**Ferric maltol**

**INDICATIONS AND DOSE**

*Iron-deficiency anaemia*

- **BY MOUTH**
  - Adult: 30 mg twice daily continued until iron stores are replenished; usual duration at least 12 weeks

**CONTRA-INDICATIONS**

Exacerbation of inflammatory bowel disease; haemochromatosis; haemoglobin less than 9.5 g/dL; iron overload syndromes; repeated blood transfusions

**INTERACTIONS** → Appendix 1: iron (oral)

**SIDE-EFFECTS**

- Common or very common: Flatulence
- Uncommon: Headache, joint stiffness, pain in extremity, skin reactions; small intestinal bacterial overgrowth, thirst

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2016) that ferric maltol (Feraccru®) is not recommended for use within NHS Scotland for the treatment of iron deficiency anaemia in adults with inflammatory bowel disease as the economic case was not demonstrated.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 23

- Feraccru® (Shield Therapeutics UK Ltd)
  - Iron (as Ferric maltol) 30 mg
  - Feraccru 30mg capsules
  - 56 capsule (Rx) £47.60 + VAT £47.60

**Ferrous fumarate**

**INDICATIONS AND DOSE**

*Iron-deficiency anaemia (prophylactic)*

- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 210 mg 1–2 times a day
  - Adult: 210 mg 1–2 times a day
- **BY MOUTH USING SYRUP**
  - Child 12-17 years: 280 mg twice daily
  - Adult: 280 mg twice daily

*Iron-deficiency anaemia (therapeutic)*

- **BY MOUTH USING TABLETS**
  - Child 12-17 years: 210 mg 2–3 times a day
  - Adult: 210 mg 2–3 times a day
- **BY MOUTH USING SYRUP**
  - Child 12-17 years: 280 mg twice daily
  - Adult: 280 mg twice daily

**GALFER® CAPSULES**

*Iron-deficiency anaemia (prophylactic)*

- **BY MOUTH**
  - Child 12-17 years: 305 mg daily
  - Adult: 305 mg daily

*Iron-deficiency anaemia (therapeutic)*

- **BY MOUTH**
  - Child 12-17 years: 305 mg twice daily
  - Adult: 305 mg twice daily

**GALFER® SYRUP**

*Iron-deficiency anaemia (prophylaxis)*

- **BY MOUTH**
  - Child 1 month–11 years: 0.25 mL/kilogram twice daily, the total daily dose may alternatively be given in 3 divided doses, prophylactic iron supplementation may be required in babies of low birth-weight who are solely breast-fed; supplementation is started 4–6 weeks after birth and continued until mixed feeding is established; maximum 20 mL per day
  - Child 12-17 years: 10 mL once daily
  - Adult: 10 mL once daily

*Iron-deficiency anaemia (therapeutic)*

- **BY MOUTH**
  - Child 1 month–11 years: 0.25 mL/kilogram twice daily, the total daily dose may alternatively be given in 3 divided doses; maximum 20 mL per day
  - Child 12-17 years: 10 mL 1–2 times a day
  - Adult: 10 mL 1–2 times a day

**INTERACTIONS** → Appendix 1: iron (oral)

**SIDE-EFFECTS**

- Faecal impaction; haematosiderosis

**PRESCRIBING AND DISPENSING INFORMATION**

Non-proprietary ferrous fumarate tablets may contain 210 mg (68 mg iron), syrup may contain approx. 140 mg (45 mg iron)/5 mL; Galfer® capsules contain ferrous fumarate 305 mg (100 mg iron).

**PATIENT AND CARER ADVICE**


**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

- Ferrous fumarate (Non-proprietary)
  - Ferrous fumarate 28 mg per 1 ml Ferrous fumarate 140mg/5ml oral solution | 200 ml (£) £3.92 DT = £3.92
  - Galfer® (Thornton & Ross Ltd)
  - Ferrous fumarate 28 mg per 1 ml Galfer 140mg/5ml syrup sugar-free | 300 ml (£) £5.33 DT = £5.33

**Tablet**

- Ferrous fumarate (Non-proprietary)
  - Ferrous fumarate 210 mg Ferrous fumarate 210mg tablets | 84 tablet (£) £3.50 DT = £3.50
  - Ferrous fumarate 322 mg Ferrous fumarate 322mg tablets | 28 tablet (£) £1.00 DT = £1.00
  - FerroEss® (Essential-Healthcare Ltd)
  - Ferrous fumarate 210 mg FerroEss 210mg tablets | 84 tablet £2.47 DT = £3.50
  - Ferrous fumarate 322 mg FerroEss 322mg tablets | 28 tablet £0.83 DT = £1.00

**Capsule**

- Galfer® (Thornton & Ross Ltd)
  - Ferrous fumarate 305 mg Galfer 305mg capsules | 100 capsule (£) £2.33 DT = £2.33 | 250 capsule (£) £5.00

**Ferrous fumarate with folic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, Ferrous fumarate above, folic acid p. 1025.

**INDICATIONS AND DOSE**

*Iron-deficiency anaemia*

- **BY MOUTH USING CAPSULES**
  - Adult: 1 capsule daily, to be taken before food

**INTERACTIONS** → Appendix 1: folic acid (oral)

**PRESCRIBING AND DISPENSING INFORMATION**

Pregaday® contains ferrous fumarate 322 mg (100 mg iron), folic acid 350 micrograms; Galfer FA® contains ferrous fumarate 305 mg (100 mg iron), folic acid 350 micrograms.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Pregaday 322mg/350microgram tablets (RPH Pharmaceuticals AB)
  - Folic acid 350 microgram, Ferrous fumarate 322 mg Pregaday 322mg/350microgram tablets | 28 tablet (£) £1.25 DT = £1.25
Iron deficiency anaemia 1023

Capsule
- Galfer FA (Thorneton & Ross Ltd)
  Folic acid 350 microgram, Ferrous fumarate 305 mg
  Galfer FA capsules 100 capsule £3.25 DT = £3.25

Ferrous gluconate

- INDICATIONS AND DOSE
  Prophylaxis of iron-deficiency anaemia
  - BY MOUTH USING TABLETS
    Child 6-11 years: 300–900 mg daily
    Child 12-17 years: 600 mg daily
    Adult: 600 mg daily
  Treatment of iron-deficiency anaemia
  - BY MOUTH USING TABLETS
    Child 1-7 years: 1.2–1.8 g daily in divided doses
    Adult: 1.2–1.8 g daily in divided doses

- INTERACTIONS → Appendix 1: iron (oral)
- SIDE-EFFECTS Gastrointestinal disorders
- PRESCRIBING AND DISPENSING INFORMATION Ferrous gluconate 300 mg contains 35 mg iron.
- PATIENT AND CARER ADVICE
  Medicines for Children leaflet: Ferrous gluconate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-gluconate-iron-deficiency-anaemia

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Tablet
  - Ferrous gluconate (Non-proprietary)
    Ferrous gluconate 300 mg Ferrous gluconate 300mg tablets
    28 tablet £3.35 DT = £0.84 | 1000 tablet £7.50–£11.64

Ferrous sulfate

- INDICATIONS AND DOSE
  Iron-deficiency anaemia (prophylactic)
  - BY MOUTH USING TABLETS
    Child 6-17 years: 200 mg daily
    Adult: 200 mg daily
  Iron-deficiency anaemia (therapeutic)
  - BY MOUTH USING TABLETS
    Child 6-17 years: 200 mg 2–3 times a day
    Adult: 200 mg 2–3 times a day

- FEOSPAN®
  Iron-deficiency anaemia
  - BY MOUTH
    Child 1-7 years: 1 capsule daily, capsule can be opened and sprinkled on food
    Adult: 1–2 capsules daily, capsule can be opened and sprinkled on food

- FERROGRAD®
  Iron-deficiency anaemia (prophylactic and therapeutic)
  - BY MOUTH
    Child 6-17 years: 1 tablet daily
    Adult: 1 tablet daily

- IRONORM® DROPS
  Iron-deficiency anaemia (prophylactic)
  - BY MOUTH
    Adult: 2.4–4.8 mL daily
  Iron-deficiency anaemia (therapeutic)
  - BY MOUTH
    Adult: 4 mL 1–2 times a day

- INTERACTIONS → Appendix 1: iron (oral)
- SIDE-EFFECTS Tooth discoloration

- PRESCRIBING AND DISPENSING INFORMATION
  Iron content
  Ferrous sulfate 200 mg is equivalent to 65 mg iron; Ironorm® drops contain ferrous sulfate 125 mg (equivalent to 25 mg iron)/mL; Feospan® suspensions contain ferrous sulfate 150 mg (47 mg iron) (spansule = capsules m/r); Ferrograd® tablets contain ferrous sulfate 255 mg (105 mg iron).
  With oral use in adults Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.
- PATIENT AND CARER ADVICE
  Medicines for Children leaflet: Ferrous sulfate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-sulfate-iron-deficiency-anaemia

- NATIONAL FUNDING/ACCESS DECISIONS
  NHS restrictions Feospan® is not prescribable in NHS primary care.

- LESS SUITABLE FOR PRESCRIBING
  Feospan® is less suitable for prescribing. Ferrograd® is less suitable for prescribing.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Modified-release tablet
  CAUTIONARY AND ADVISORY LABELS 25
  - Feospan (Nordamra)
    Ferrous sulfate dried 150 mg Feospan 150mg modified-release tablets | 30 tablet £3.25
  - Feospan dried 325 mg Feospan 325mg modified-release tablets | 30 tablet £3.25
  Tablet
  - Feospan dried 200 mg Feospan 200mg tablets
  28 tablet £8.15 DT = £1.06 | 60 tablet £1.78–£3.05
  100 tablet £3.68–£10.80 | 1000 tablet £37.86–£108.00

  Modified-release capsule
  CAUTIONARY AND ADVISORY LABELS 25
  - Feospan Suspanses (intrafarm Laboratories Ltd)
    Ferrous sulfate dried 150 mg Feospan 150mg Suspanses
    30 capsule £3.95
  Oral drops
  - Ironorm (Wallace Manufacturing Chemists Ltd)
    Ferrous sulfate 125 mg per 1 mL Ironorm 125mg/ml oral drops sugar-free | 15 mL £30.00

Ferrous sulfate with ascorbic acid

- INDICATIONS AND DOSE
  Iron-deficiency anaemia
  - BY MOUTH USING MODIFIED-RELEASE TABLETS
    Adult: 1 tablet daily, dose to be taken before food

- INTERACTIONS → Appendix 1: ascorbic acid - iron (oral)

- NATIONAL FUNDING/ACCESS DECISIONS
  NHS restrictions Ferrograd C® is not prescribable in NHS primary care.

- LESS SUITABLE FOR PRESCRIBING
  Ferrograd C® is less suitable for prescribing.

The properties listed below are those particular to the combination only. For the properties of the components please consider, ferrous sulfate above, ascorbic acid p. 1082.
1024 Anaemias

1.3 Megaloblastic anaemia

Anaemia, megaloblastic

Overview
Most megaloblastic anaemias result from a lack of either vitamin B12 or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should not be instituted until the results of tests are available.

One cause of megaloblastic anaemia in the UK is pernicious anaemia in which lack of gastric intrinsic factor resulting from an autoimmune gastritis causes malabsorption of vitamin B12.

Vitamin B12 is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare syndrome of congenital transcobalamin II deficiency.

Vitamin B12 should be given prophylactically after total gastrectomy or total ileal resection (or after partial gastrectomy if a vitamin B12 absorption test shows vitamin B12 malabsorption). Apart from dietary deficiency, all other causes of vitamin B12 deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B12 orally and none for vitamin B12 intrinsic factor complexes given by mouth. Vitamin B12 in larger oral doses [unlicensed] may be effective.

Hydroxocobalamin p. 1026 has completely replaced cyanocobalamin p. 1025 as the form of vitamin B12 of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B12 neuropathy.

Folic acid p. 1025 has few indications for long-term therapy since most causes of folate deficiency are self-limiting or will yield to a short course of treatment. It should not be used in undiagnosed megaloblastic anaemia unless vitamin B12 is administered concurrently otherwise neuropathy may be precipitated.

In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or antiepileptic drugs), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores.

For prophylaxis in chronic haemolytic states, malabsorption, or in renal dialysis, folic acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis.

Folic acid is also used for the prevention of methotrexate-induced side-effects in severe Crohn’s disease, rheumatic disease, and severe psoriasis.

Folinic acid p. 941 is also effective in the treatment of folate deficient megaloblastic anaemia but it is generally used in association with cytotoxic drugs; it is given as calcium folinate.

There is no justification for prescribing multiple ingredient vitamin preparations containing vitamin B12 or folic acid.

For the use of folic acid before and during pregnancy, see Neural tube defects (prevention in pregnancy) p. 1089.
**VITAMINS AND TRACE ELEMENTS** > **FOLATES**

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**Folic acid**

**INDICATIONS AND DOSE**

**Folate-deficient megaloblastic anaemia**

- **BY MOUTH**
  - Adult: 5 mg once weekly, to be taken before conception and until week 12 of pregnancy.
  - Females of childbearing potential: 5 mg daily, to be taken before conception and until week 12 of pregnancy.

**Prevention of neural tube defects (in those at a low risk of conceiving a child with a neural tube defect see Neural tube defects (prevention in pregnancy) p. 1089)**

- **BY MOUTH**
  - Females of childbearing potential: 400 micrograms daily, to be taken before conception and until week 12 of pregnancy.

**Prevention of neural tube defects (in those in the high-risk group who wish to become pregnant or who are at risk of becoming pregnant see Neural tube defects (prevention in pregnancy) p. 1089)**

- **BY MOUTH**
  - Females of childbearing potential: 5 mg daily, to be taken before conception and until week 12 of pregnancy.

**Prevention of methotrexate-induced side-effects in rheumatoid disease**

- **BY MOUTH**
  - Adult: 5 mg once weekly, dose to be taken on a different day to methotrexate dose.

**Prevention of methotrexate side-effects in severe Crohn’s disease**

- **BY MOUTH**
  - Adult: 5 mg once weekly, dose to be taken on a different day to methotrexate dose.

**Prophylaxis in chronic haemolytic states**

- **BY MOUTH**
  - Adult: 5 mg every 1–7 days, frequency dependent on underlying disease.

**Prophylaxis of folate deficiency in dialysis**

- **BY MOUTH**
  - Child 1 month–11 years: 250 micrograms/kg once daily (max. per dose 10 mg).
  - Child 12–17 years: 5–10 mg once daily.
  - Adult: 5 mg every 1–7 days.

**Prophylaxis of folate deficiency in patients receiving parenteral nutrition**

- **BY INTRAVENOUS INFUSION**
  - Adult: 15 mg 1–2 times a week, usually given by intravenous infusion in the parenteral nutrition solution.

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**SIDE-EFFECTS**

Possible side-effects of folic acid include nausea, vomiting, and diarrhea. Rarely, it can cause an allergic reaction.

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**PRESCRIBING AND DISPENSING INFORMATION**

Available as capsules, oral suspensions, solution for injection, tablets, and sugar-free solutions. Dosages range from 400 micrograms to 5 mg daily, depending on the condition.

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**MEDICINAL FORMS**

- **Tablet**
  - Folic acid (Non-proprietary)
  - Folic acid 400 microgram
  - Folic acid 400 microgram tablets | 90 tablet | £3.16 DT + £3.16 sugar-free
  - Folic acid 5 mg
  - Folic acid 5 mg tablets | 28 tablet | £2.00 DT + £0.73 1000 tablet | £22.86–£26.07

- **Oral solution**
  - Folic acid (Non-proprietary)
  - Folic acid 500 microgram per 1 ml
  - Folic acid 2.5 mg/5 ml oral solution sugar free | 150 ml | £13.74–£14.37 DT + £34.63
  - Folic acid 1 mg per 1 ml
  - Folic acid 5 mg/5 ml oral solution sugar free | 150 ml | £13.74–£14.37 DT + £34.63
  - Leppec (Rosemont Pharmaceuticals Ltd)
  - Folic acid 500 microgram per 1 ml
  - Leppec Folic Acid 2.5 mg/5 ml oral solution sugar free | 150 ml | £9.16 DT + £9.16

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**VITAMINS AND TRACE ELEMENTS** > **VITAMIN B GROUP**

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**Cyanocobalamin**

**INDICATIONS AND DOSE**

**Vitamin B12 deficiency of dietary origin**

- **BY MOUTH**
  - Adult: 50–150 micrograms daily, dose to be taken between meals.
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 1 mg every 2–3 days for 11 doses; maintenance 1 mg every month.

**PRESCRIBING AND DISPENSING INFORMATION**

Currently available brands of the tablet may not be suitable for vegans.

- The BP directs that when vitamin B12 injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NHSS restrictions** Cyanocobalamin solution and Cytamen® injection are not prescribable in NHS primary care.

**LESS SUITABLE FOR PRESCRIBING**

Cyanocobalamin is less suitable for prescribing.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, solution for injection, tablet, suspensions, sugar-free solutions.

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**UNLICENSED USE**

Not licensed for prevention of methotrexate-induced side-effects in severe Crohn’s disease.

**REFERENCES**

- **medicinesforchildren.org.uk/folic-acid-megaloblastic-anaemia-caused-folate-deficiency-and-haemolytic-anaemia**

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www.getintopharma.com
Iron overload

Overview
Severe tissue iron overload can occur in aplastic and other refractory anaemias, mainly as the result of repeated blood transfusions. It is a particular problem in refractory anaemias with hyperplastic bone marrow, especially thalassaemia major, where excessive iron absorption from the gut and inappropriate iron therapy can add to the tissue siderosis.

Iron overload associated with haemochromatosis can be treated with repeated venesection. Veneesction may also be used for patients who have received multiple transfusions and whose bone marrow has recovered. Where venesection is contra-indicated, the long-term administration of the iron chelating compound desferrioxamine mesilate p. 1028 is useful. Desferrioxamine mesilate (up to 2 g per unit of blood) may also be given at the time of blood transfusion, provided that the desferrioxamine mesilate is not added to the blood and is not given through the same line as the blood (but the two may be given through the same cannula).

Iron excretion induced by desferrioxamine mesilate is enhanced by administration of ascorbic acid p. 1082 (vitamin C) daily by mouth; it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to patients with cardiac dysfunction; in patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine mesilate.
Desferrioxamine mesilate infusion can be used to treat aluminium overload in dialysis patients; theoretically 100 mg of desferrioxamine binds with 4.1 mg of aluminium.

ANTIDOTES AND CHELATORS ▶ IRON CHELATORS

<table>
<thead>
<tr>
<th>Deferasirox</th>
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<tbody>
<tr>
<td><strong>DRUG ACTION</strong> Deferasirox is an oral iron chelator.</td>
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</tbody>
</table>

**INDICATIONS AND DOSE**

Transfusion-related chronic iron overload in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells) (specialist use only)

- **BY MOUTH**
  - Adult: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day; Usual maximum 21 mg/kg
  - Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with beta thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells) (specialist use only)
    - **BY MOUTH**
      - Adult: Initially 7 mg/kg once daily, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day; Usual maximum 21 mg/kg

**CHRONIC IRON OVERLOAD WHEN DESFERRIOXAMINE IS CONTRA-INDICATED OR INADEQUATE IN NON-TRANSFUSION-DEPENDENT THALASSEMIAS SYNDROMES (SPECIALIST USE ONLY)**

- **BY MOUTH**
  - Adult: Initially 7 mg/kg once daily, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration and liver iron concentration (consult product literature); maximum 14 mg/kg per day

**CAUTIONS**

- Elderly (increased risk of side-effects) - history of liver cirrhosis - not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes) - platelet count less than 50x10^9/litre - risk of gastro-intestinal ulceration and haemorrhage - unexplained cytopenia—consider treatment interruption

**INTERACTIONS** ▶ Appendix 1: Iron chelators

**SIDE-EFFECTS**

- Common or very common Constipation - diarrhoea - gastrointestinal discomfort - headache - nausea - skin reactions - urine abnormalities - vomiting
- Uncommon Anxiety - catarrh - cholelithiasis - deafness - dizziness - fatigue - fever - gastrointestinal disorders - gastrointestinal haemorrhage (including fatal cases) - hepatic disorders - laryngeal pain - maculopathy - oedema - renal tubular disorders - sleep disorder
- Rare or very rare Optic neuritis
- Frequency not known Acute kidney injury - alopecia - anaemia aggravated - angioedema - hypersensitivity vasculitis - metabolic acidosis - nephritis tubulo-interstitial - nephrolithiasis - neutropenia - pancreatitis acute - pancytopenia - renal tubular necrosis - severe cutaneous adverse reactions (SCARs) - thrombocytopenia

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **CAUTIONARY AND ADVISORY LABELS** 25
      - Exjade (Novartis Pharmaceuticals UK Ltd) ▼
        - Deferasirox 90 mg | Exjade 90mg tablets | 30 tablet pack £126.00 DT = £126.00
        - Deferasirox 180 mg | Exjade 180mg tablets | 30 tablet pack £252.00 DT = £252.00
        - Deferasirox 360 mg | Exjade 360mg tablets | 30 tablet pack £504.00 DT = £504.00

**Deferiprone**

- **DRUG ACTION** Deferiprone is an oral iron chelator.

**INDICATIONS AND DOSE**

Treatment of iron overload in patients with thalassaemia major in whom desferrioxamine is contra-indicated or is inadequate

- **BY MOUTH**
  - Adult: 25 mg/kg 3 times a day; maximum 100 mg/kg per day
Desferrioxamine mesilate
(Deferoxamine Mesilate)

- **INDICATIONS AND DOSE**
  - **Iron poisoning**
    - By continuous intravenous infusion
  - **Adult:** Initially up to 15 mg/kg/hour, max. 80 mg/kg in 24 hours, dose to be reduced after 4–6 hours, in severe cases, higher doses may be given on advice from the National Poisons Information Service
  - **Aluminium overload in dialysis patients**
    - By intravenous infusion
    - Adult: (consult product literature or local protocols)

<table>
<thead>
<tr>
<th><strong>Chronic iron overload (low iron overload)</strong></th>
<th><strong>Chronic iron overload (established overload)</strong></th>
</tr>
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<tbody>
<tr>
<td>▶ By subcutaneous infusion</td>
<td>▶ By subcutaneous infusion</td>
</tr>
<tr>
<td>Adult: The dose should reflect the degree of iron overload</td>
<td>Adult: 20–50 mg/kg daily</td>
</tr>
</tbody>
</table>

- **CAUTIONS**
  - Aluminium-related encephalopathy (may exacerbate neurological dysfunction)

- **INTERACTIONS**
  - Appendix 1: iron chelators

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain (reducing dose and increasing gradually may improve tolerance) - agranulocytosis - appetite increased - arthralgia - diarrhoea (reducing dose and increasing gradually may improve tolerance) - fatigue - headache - nausea (reducing dose and increasing gradually may improve tolerance) - neutropenia - urinary discoulouration - vomiting (reducing dose and increasing gradually may improve tolerance)
  - Frequency not known
    - Skin reactions - zinc deficiency

- **CONCEPTION AND CONTRACEPTION**

- **PREGNANCY**
  - Manufacturer advises avoid during pregnancy—teratogenic and embryotoxic in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises monitor liver function—interrupt treatment if persistent elevation in serum alanine aminotransferase.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor neutrophil count weekly and discontinue treatment if neutropenia develops.
  - Monitor plasma-zinc concentration.

- **PATIENT AND CARER ADVICE**
  - Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever or sore throat develop.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

- **Oral solution**
  - CAUTIONARY AND ADVISORY LABELS 14
    - Ferriprox (Swedish Orphan Biovitrum Ltd)
      - Ferriprone 100 mg per 1 ml Ferriprone 100mg/ml oral solution sugar-free | 500 ml £152.39 DT + £152.39
  - Ferriprox 500 mg Ferriprox 500mg tablets | 100 tablet £175.20 DT + £152.39
  - Ferriprox 1 gram Ferriprox 1000mg tablets | 50 tablet £48.15

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 14
    - Ferriprox (Swedish Orphan Biovitrum Ltd)
    - Ferriprox 500 mg Ferriprox 500mg tablets | 100 tablet £175.20 DT + £152.39
    - Ferriprox 1 gram Ferriprox 1000mg tablets | 50 tablet £175.25 DT + £175.25

3 Neutropenia and stem cell mobilisation
3.1 Neutropenia

Neutropenia

Management

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia.
and thereby reduce the incidence of associated sepsis; there is as yet no evidence that it improves overall survival. Filgrastim below (unglycosylated rhG-CSF) and lenograstim p. 1030 (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings, but they do not have any clear-cut routine indications. In congenital neutropenia filgrastim usually increases the neutrophil count with an appropriate clinical response. Pegfilgrastim p. 1031 is a polyethylene glycol-conjugated (‘pegylated’) derivative of filgrastim; pegylation increases the duration of filgrastim activity. Lipegfilgrastim p. 1031 is a polyethylene glycol-conjugated via a glycine linker derivative of filgrastim. Granulocyte-colony stimulating factors should only be prescribed by those experienced in their use.

**IMMUNOSTIMULANTS**

Granulocyte-colony stimulating factors

- **DRUG ACTION** Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils.
- **CAUTIONS** Malignant myeloid conditions - pre-malignant myeloid conditions - risk of splenomegaly and rupture—spleen size should be monitored—sickle-cell disease
- **SIDE-EFFECTS**
  - Common or very common: Arthralgia - cutaneous vasculitis - dyspnoea - haemoptysis - headache - hypersensitivity - leucocytosis - pain - spleen abnormalities - thrombocytopenia
  - Uncommon: Acute febrile neutrophilic dermatosis - capillary leak syndrome - hypoxia - pulmonary oedema - respiratory disorders - sickle cell anaemia with crisis
- **PREGNANCY** Manufacturers advise avoid—toxicity in animal studies.
- **BREAST FEEDING** There is no evidence for the use of granulocyte-colony stimulating factors during breast-feeding and manufacturers advise avoiding their use.
- **MONITORING REQUIREMENTS**
  - Full blood counts including differential white cell and platelet counts should be monitored.
  - Spleen size should be monitored during treatment—risk of splenomegaly and rupture.

Filgrastim

(Recombinant human granulocyte-colony stimulating factor; G-CSF)

- **INDICATIONS AND DOSE**
  - Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)
  - Adult: 5 micrograms/kg daily until neutrophil count in normal range, usually for up to 14 days (up to 38 days in acute myeloid leukaemia), to be started at least 24 hours after cytotoxic chemotherapy. Preferably given by subcutaneous injection; if given by intravenous infusion, administer over 30 minutes
  - Reduction in duration of neutropenia (and associated sequelae) in myeloablative therapy followed by bone-marrow transplantation (specialist use only)
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRavenous INFUSION**
      - Adult: 10 micrograms/kg daily, to be started at least 24 hours following cytotoxic chemotherapy and within 24 hours of bone-marrow infusion, then adjusted according to neutrophil count—consult product literature, doses administered over 30 minutes or 24 hours via intravenous route and over 24 hours via subcutaneous route
      - **Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone (specialist use only)**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult: 10 micrograms/kg daily for 5–7 days, to be administered over 24 hours if given by subcutaneous infusion
      - **Mobilisation of peripheral blood progenitor cells for autologous infusion, used following adjunctive myelosuppressive chemotherapy—to improve yield (specialist use only)**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult: 5 micrograms/kg daily until neutrophil count in normal range, to be started the day after completing chemotherapy, for timing of leucopheresis, consult product literature
      - **Mobilisation of peripheral blood progenitor cells in normal donors for allogeneic infusion (specialist use only)**
        - **BY SUBCUTANEOUS INJECTION**
          - Adult 18–59 years: 10 micrograms/kg daily for 4–5 days, for timing of leucopheresis, consult product literature
  - Severe congenital neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders) (specialist use only)
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Initially 12 micrograms/kg daily, adjusted according to response, can be given in single or divided doses, consult product literature and local protocol
  - Severe cyclic neutropenia, or idiopathic neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders) (specialist use only)
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Initially 5 micrograms/kg daily, adjusted according to response, can be given in single or divided doses, consult product literature and local protocol
  - Persistent neutropenia in HIV infection (specialist use only)
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Initially 1 microgram/kg daily, subsequent doses increased as necessary until neutrophil count in normal range, then adjusted to maintain neutrophil count in normal range—consult product literature; maximum 4 micrograms/kg per day
  - **CONTRA-INDICATIONS** Severe congenital neutropenia (Kostmann’s syndrome) with abnormal cytogenetics
  - **CAUTIONS** Osteoporotic bone disease (monitor bone density if given for more than 6 months) - secondary acute myeloid leukaemia
  - **SIDE-EFFECTS**
    - Common or very common: Anaemia - diarrhoea - dysuria - haemorrhage - hepatomegaly - hyperuricaemia - hypotension - osteoporosis - rash
**Lenograstim**

(Recombinant human granulocyte-colony stimulating factor; rHuG-CSF)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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<tbody>
<tr>
<td>Reduction in the duration of neutropenia and associated complications following bone-marrow transplantation for non-myeloid malignancy (specialist use only)</td>
</tr>
<tr>
<td>Reduction in the duration of neutropenia and associated complications following peripheral stem cell transplantation for non-myeloid malignancy (specialist use only)</td>
</tr>
<tr>
<td>BY INTRAVENOUS INFUSION, OR BY SUBCUTANEOUS INJECTION</td>
</tr>
<tr>
<td>Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range (max. 28 days), to be started the day after transplantation. Intravenous infusion to be given over 30 minutes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SIDE-EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common or very common Abdominal pain - asthenia</td>
</tr>
<tr>
<td>Rare or very rare Erythema nodosum - pyoderma gangrenosum - toxic epidermal necrolysis</td>
</tr>
</tbody>
</table>

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion (Neupogen®); (Nivestim®); (Zarzio®) give continuously or intermittently in Glucose 5%; for a filgrastim concentration of less than 1 500 000 units/mL (15 micrograms/mL) albumin solution (human albumin solution) is added to produce a final albumin concentration of 2 mg/mL; should not be diluted to a filgrastim concentration of less than 200 000 units/mL (2 micrograms/mL) and should not be diluted with sodium chloride solution.

**PRESCRIBING AND DISPENSING INFORMATION** Filgrastim is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

1 million units of filgrastim solution for injection contains 10 micrograms filgrastim.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Accofil (Accord Healthcare Ltd)**
  - Filgrastim 60 mega u per 1 ml Accofil 30million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £284.20
  - Filgrastim 96 mega u per 1 ml Accofil 48million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £455.70
- **Neupogen (Amgen Ltd)**
  - Filgrastim 30 mega u per 1 ml Neupogen 30million units/1ml solution for injection vials | 5 vial (Pf) £263.52
  - Neupogen Singleject (Amgen Ltd)
  - Filgrastim 60 mega u per 1 ml Neupogen Singleject 30million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pf) £52.70
  - Filgrastim 96 mega u per 1 ml Neupogen Singleject 48million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pf) £84.06
- **Nivestim (Pfizer Ltd)**
  - Filgrastim 60 mega u per 1 ml Nivestim 30million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £246.50
  - Nivestim 120 million units/0.2ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £153.00
  - Filgrastim 96 mega u per 1 ml Nivestim 48million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £395.25
- **Zarzio (Sanbo Ltd)**
  - Filgrastim 60 mega u per 1 ml Zarzio 30million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £250.75
  - Filgrastim 96 mega u per 1 ml Zarzio 48million units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pf) £399.50

**SIDE-EFFECTS**

- Common or very common Abdominal pain - asthenia
- Rare or very rare Erythema nodosum - pyoderma gangrenosum - toxic epidermal necrolysis

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

**EXCipients:** May contain Phenylalanine

<table>
<thead>
<tr>
<th>Granocyte (Chuigi Pharma UK Ltd)</th>
</tr>
</thead>
</table>
| Lenograstim 13.4 mega u Granocyte 13 million unit powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pf) £40.11 | 5 pre-filled disposable injection (Pf) £200.55
| Lenograstim 33.6 mega u Granocyte 34 million unit powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (Pf) £62.54 | 5 pre-filled disposable injection (Pf) £312.69

www.getintopharma.com
Lipegfilgrastim
(Glycopegylated recombinant methionyl human granulocyte-colony stimulating factor)

- **INDICATIONS AND DOSE**
  Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 6 mg, for each chemotherapy cycle, given approximately 24 hours after chemotherapy, dose expressed as filgrastim

- **CAUTIONS**
  - Myelosuppressive chemotherapy
  - Common or very common Chest pain • hypokalaemia • skin eruption

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - **Lonquex** (Teva UK Ltd)
      Lipegfilgrastim 10 mg per 1 ml
      Lonquex 6mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £652.06
  - **Pelmeg** (Napp Pharmaceuticals Ltd)
    Pelmeg 6mg/0.6ml solution for injection pre-filled syringes with Onpro kit | 1 pre-filled disposable injection £686.38 (Hospital only)
  - **Pelgraz** (Accord Healthcare Ltd)
    Pelgraz 6mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £686.37 (Hospital only)
  - **Ziextenzo** (Sanofizod Ltd)
    Ziextenzo 6mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £617.74

Pegfilgrastim
(Pegylated recombinant methionyl human granulocyte-colony stimulating factor)

- **INDICATIONS AND DOSE**
  Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 6 mg for each chemotherapy cycle, to be given at least 24 hours after chemotherapy, dose expressed as filgrastim

- **CAUTIONS**
  - Acute leukaemia • myelosuppressive chemotherapy
  - Common or very common Myalgia • nausea
  - Uncommon Glomerulonephritis

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - **Neulasta** (Amgen Ltd)
      Filgrastim (as Pegfilgrastim) 10 mg per 1 ml
      Neulasta 6mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £686.38
      Neulasta 6mg/0.6ml solution for injection pre-filled syringes with Onpro kit | 1 pre-filled disposable injection £686.38 (Hospital only)
    - **Plerixafor** (Sanofi)
      Plerixafor 20 mg per 1 ml
      Plerixafor 20mg/0.2ml solution for injection | 1 vial £882.77
  - **Filgrastim (as Pegfilgrastim)**
    Filgrastim (as Pegfilgrastim) 10 mg per 1 ml
    Filgrastim (as Pegfilgrastim) 10 mg per 1 ml
    Filgrastim (as Pegfilgrastim) 10 mg per 1 ml
    Filgrastim (as Pegfilgrastim) 10 mg per 1 ml
    Nominal 6mg/0.6ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £686.37 (Hospital only)
    Nominal 6mg/0.6ml solution for injection pre-filled syringes with Onpro kit | 1 pre-filled disposable injection £686.38 (Hospital only)

3.2 Stem cell mobilisation
IMMUNOSTIMULANTS > CHEMOKINE RECEPTOR ANTAGONISTS

Plerixafor
Plerixafor is a chemokine receptor antagonist.

- **INDICATIONS AND DOSE**
  Mobilise haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma (specialist use only)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult: 240 micrograms/kg daily usually for 2–4 days (max 7 days), to be administered 6–11 hours before initiation of apheresis, dose to be given following 4 days treatment with a granulocyte-colony stimulating factor

- **SIDE-EFFECTS**
  - Common or very common Arthralgia • constipation • diarrhoea • dizziness • dry mouth • erythema • fatigue • flatulence • gastrointestinal discomfort • headache • hyperhidrosis • malaise • muscle/skeletal pain • nausea • oral hypoesthesia • sleep disorders • vomiting
  - Uncommon Hypersensitivity

- **CONCEPTION AND CONTRACEPTION**
  Use effective contraception during treatment—teratogenic in animal studies.

- **PREGNANCY**
  Manufacturer advises avoid unless essential—teratogenic in animal studies.

- **BREAST FEEDING**
  Manufacturer advises avoid—no information available.

- **RENAI IMPAIRMENT**
  No information available if creatinine clearance less than 20 mL/minute.
  Dose adjustments Reduce dose to 150 micrograms/kg daily if creatinine clearance 20–50 mL/minute.

- **MONITORING REQUIREMENTS**
  Monitor platelets and white blood cell count.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.
  - Solution for injection
    - **Mozobil** (Sanofi)
      Mozobil 24mg/1.2ml solution for injection vials | 1 vial £4,882.77

4 Platelet disorders

Platelet disorders
Idiopathic thrombocytopenic purpura
Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. In adults, idiopathic thrombocytopenic purpura can be treated with a corticosteroid, e.g. prednisolone p. 678, gradually reducing the dose over several weeks. Splenectomy is considered if a satisfactory platelet count is not achieved or if there is a relapse on reducing the dose of corticosteroid or withdrawing it.

Immunoglobulin preparations, are also used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are also used for children often in preference to a corticosteroid. Anti-D (Rh) immunoglobulin p. 1289 is effective in raising the platelet count in about 80% of
unplasplenectomised rhesus-positive individuals; its effects may last longer than normal immunoglobulin p. 1290 for intravenous use, but further doses are usually required. Other therapies that have been tried in refractory idiopathic thrombocytopenic purpura include: azathioprine p. 836, cyclophosphamide p. 894, vincristine sulfate p. 929, ciclosporin p. 838, and danazol p. 742. Rituximab p. 882 [unlicensed indication] may also be effective and in some cases induces prolonged remission. For patients with chronic severe thrombocytopenia refractory to other therapy, tranexamic acid p. 110 may be given to reduce the severity of haemorrhage.

Eltrombopag below and romiplostim p. 1034 are thrombopoietin receptor agonists. They are licensed for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in patients refractory to other treatments, such as corticosteroids or immunoglobulins. Eltrombopag is an oral preparation and romiplostim is an injection which is made biosynthetically by recombinant DNA technology; they should both be used under the supervision of a specialist.

### Essential thrombocythaemia

Anagrelide below inhibits platelet formation. It is licensed for essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs. An at risk patient is defined by one or more of the following features: over 60 years of age, or a platelet count greater than 1000 x 10^9/L or history of thrombo-haemorrhagic events. Anagrelide should be initiated under specialist supervision.

### 4.1 Essential thrombocythaemia

**Other drugs used for Essential thrombocythaemia**

| Hydroxyurea, p. 935 |

### ANTITHROMBOTIC DRUGS > CYCLIC AMP PHOSPHODIESTERASE III INHIBITORS

#### Anagrelide

| 28-May-2018 |

**INDICATIONS AND DOSE**

Essential thrombocythaemia in patients who have not responded adequately to other drugs or who cannot tolerate other drugs (initiated under specialist supervision)

- **BY MOUTH**
  - Adult: Initially 500 micrograms twice daily, dose to be adjusted at weekly intervals according to response, increased in steps of 500 micrograms daily; usual dose 1–3 mg daily in divided doses (max. per dose 2.5 mg); maximum 10 mg per day

**CAUTIONS**
Cardiovascular disease—assess cardiac function before and regularly during treatment. concomitant use of drugs that prolong QT-interval—assess cardiac function before and regularly during treatment. risk factors for QT-interval prolongation—assess cardiac function before and regularly during treatment

**INTERACTIONS**
Appendix 1: anagrelide

**SIDE-EFFECTS**
- Common or very common Anaemia · arrhythmias · asthenia · diarrhoea · dizziness · fluid retention · gastrointestinal discomfort · gastrointestinal disorders · headaches · nausea · palpitations · skin reactions · vomiting
- Uncommon Alopecia · appetite decreased · arthralgia · chest pain · chills · confusion · congestive heart failure · constipation · depression · dry mouth · dysphonia · erectile function · fever · haemorrhage · hypertension · insomnia · malaise · memory loss · myalgia · nervousness · oedema · pain · pancreatitis · pancytopenia · pneumonia · pulmonary hypertension · respiratory disorders · sensation abnormal · syncope · thrombocytopenia · weight changes
- Rare or very rare Angina pectoris · cardiomyopathy · coordination abnormal · drowsiness · dysarthria · influenza like illness · myocardial infarction · nocturia · pericardial effusion · postural hypotension · renal failure · tinnitus · vasodilation · vision disorders
- Frequency not known Hepatitis · nephritis · tubulointerstitial

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

**PREGNANCY**
Manufacturer advises avoid (toxicity in animal studies).

**BREAST FEEDING**
Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
Manufacturer advises use with caution in mild impairment; avoid in moderate-to-severe impairment or if serum transaminases exceed 5 times the upper limit of normal.

**RENAL IMPAIRMENT**
Manufacturer advises avoid if eGFR less than 50 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**
- Monitor full blood count (monitor platelet count every 2 days for 1 week, then weekly until maintenance dose established).
- Monitor liver function.
- Monitor serum creatinine.
- Monitor urea.
- Monitor electrolytes (including potassium, magnesium and calcium) before and during treatment.

**PATIENT AND CARER ADVICE**
- Driving and skilled tasks Dizziness may affect performance of skilled tasks (e.g. cycling, driving).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

#### Capsule

- **Anagrelide (Non-proprietary)**
  - Anagrelide (as Anagrelide hydrochloride) 500 microgram Anagrelide 500microgram capsules | 100 capsule £404.57 DT + £336.62
  - Xagrid (Shire Pharmaceuticals Ltd) Anagrelide (as Anagrelide hydrochloride) 500 microgram Xagrid 500microgram capsules | 100 capsule £404.57 DT + £336.62

### 4.2 Immune thrombocytopenia

#### ANTIHAEMORRHAGICS > THROMBOPOIETIN RECEPTOR AGONISTS

| 17-Aug-2018 |

**INDICATIONS AND DOSE**
Chronic immune (idiopathic) thrombocytopenic purpura in patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision)

- **BY MOUTH**
  - Adult: Initially 50 mg once daily, dose to be adjusted to achieve a platelet count of 50x10^9/litre or more—consult product literature for dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day
  - Adult (patients of East Asian origin): Initially 25 mg once daily, dose to be adjusted to achieve a platelet count of 50x10^9/litre or more—consult product literature for
dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day.

Treatment of thrombocytopenia associated with chronic hepatitis C infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (under expert supervision)

▶ BY MOUTH

▶ Adult: Initially 25 mg once daily, dose to be adjusted to achieve a platelet count sufficient to initiate antiviral therapy then a platelet count of 50–75 × 10^9/litre during antiviral therapy—consult product literature for dose adjustments, discontinue if inadequate response after 2 weeks treatment at maximum dose; maximum 100 mg per day

Acquired severe aplastic anaemia in patients either refractory to or heavily pretreated with prior immunosuppressive therapy and are unsuitable for haematopoietic stem cell transplantation (under expert supervision)

▶ BY MOUTH

▶ Adult: Initially 50 mg once daily, dose to be adjusted to achieve a platelet count of 50 × 10^9/litre or more—consult product literature for dose adjustments, discontinue if no haematological response after 16 weeks treatment; maximum 150 mg per day

Adult (patients of East Asian origin): Initially 25 mg once daily, dose to be adjusted to achieve a platelet count of 50 × 10^9/litre or more—consult product literature for dose adjustments, discontinue if no haematological response after 16 weeks treatment; maximum 150 mg per day.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: ELTROMBOPAG (REVOLADE®): REPORTS OF INTERFERENCE WITH BILIRUBIN AND CREATININE TEST RESULTS (JULY 2018)

See Effect on laboratory tests.

● CAUTIONS Patients of East Asian origin • risk factors for thromboembolism

● INTERACTIONS ▶ Appendix 1: eltrombopag

● SIDE-EFFECTS

▶ Common or very common Abnormal loss of weight • alopecia • anaemia • anxiety • appetite abnormal • arthralgia • asthenia • catact • chest discomfort • chills • concentration impaired • confusion • constipation • cough • depression • diarrhoea • dizziness • drowsiness • dry eye • dry mouth • dysphagia • dyspnoea • eye discomfort • eye disorders • fever • gastrointestinal discomfort • gastrointestinal disorders • haemolytic anaemia • haemorrhage • headaches • hepatic disorders • hyperbilirubinaemia • hyperglycaemia • hypoglycaemia • increased risk of infection • influenza like illness • iron overload • lymphopenia • malaise • memory loss • menorrhagia • mood altered • muscle complaints • nasal complaints • nausea • neutropenia • oedema • oral disorders • oropharyngeal complaints • pain • palpitations • QT interval prolongation • sensation abnormal • skin reactions • sleep disorders • splenic infarction • sweat changes • syncope • taste altered • urine discolouration • vertigo • vision disorders • vomiting • weight decreased

▶ Uncommon Ainosocytosis • arhythmias • balance impaired • cardiovascular disorder • cyanosis • ear pain • electrolyte imbalance • embellishment and thrombosis • eosinophilia • eye inflammation • feeling hot • feeling jittery • food poisoning • gout • hemiparesis • increased leukocytes • lens opacity • muscle weakness • myocardial infarction • nephritis lupus • nerve disorders • rectosigmoid cancer • renal failure • retinal pigment epitheliopathy • sinus disorder • sleep apnoea • speech disorder • sunburn • thrombocytopenia • tremor • urinary disorders • urine abnormalities • vasodilation • wound inflammation

● CONCEPTION AND CONTRACEPTION Ensure effective contraception during treatment.

● PREGNANCY Avoid—toxicity in animal studies.

● BREAST FEEDING Manufacturer advises avoid.

● HEPATIC IMPAIRMENT

▶ When used for Idiopathic thrombocytopenic purpura Manufacturer advises consider avoiding.

▶ When used for Severe aplastic anaemia Manufacturer advises caution.

▶ When used for Thrombocytopenia associated with chronic hepatitis C infection Manufacturer advises caution (increased risk of hepatic decompensation and thromboembolic events).

Dose adjustments

▶ When used for Idiopathic thrombocytopenic purpura Manufacturer advises initial dose reduction to 25 mg once daily and wait at least 3 weeks before upward titration of dose.

▶ When used for Severe aplastic anaemia Manufacturer advises initial dose reduction to 25 mg once daily and wait at least 2 weeks before upward titration of dose.

● RENAL IMPAIRMENT Use with caution.

● PRE-TREATMENT SCREENING For severe aplastic anaemia, manufacturer advises do not initiate if patients have existing cytogenetic abnormalities of chromosome 7.

● MONITORING REQUIREMENTS

▶ Manufacturer advises monitor liver function before treatment, every two weeks when adjusting the dose, and monthly thereafter.

▶ Manufacturer advises regular ophthalmological examinations for cataract formation.

▶ Manufacturer advises peripheral blood smear prior to initiation to establish baseline level of cellular morphologic abnormalities; once stabilised, full blood count with white blood cell count differential should be performed monthly.

▶ For Idiopathic thrombocytopenic purpura, manufacturer advises monitor full blood count including platelet count and peripheral blood smears every week during treatment until a stable platelet count is reached (50 × 10^9/litre or more for at least 4 weeks), then monthly thereafter; monitor platelet count weekly for 4 weeks following treatment discontinuation.

▶ For Severe aplastic anaemia, manufacturer advises bone marrow examination with aspirations for cytogenetics prior to initiation, at 3 months of treatment and 6 months thereafter.

▶ For Thrombocytopenia associated with chronic hepatitis C infection, manufacturer advises monitor platelet count every week before and during antiviral treatment until a stable platelet count is reached (50–75 × 10^9/litre), then monitor full blood count including platelet count and peripheral blood smears monthly thereafter.

● EFFECT ON LABORATORY TESTS Eltrombopag is highly coloured and can cause serum discolouration and interference with total bilirubin and creatinine testing. If laboratory results are inconsistent with clinical observations, manufacturer advises re-testing using another method to help determine the validity of the result.

● DIRECTIONS FOR ADMINISTRATION Each dose should be taken at least 4 hours before or after any dairy products (or foods containing calcium), indigestion remedies, or medicines containing aluminium, calcium, iron,
magnesium, zinc, or selenium to reduce possible interference with absorption.

- **PATIENT AND CARER ADVICE** Patient counselling is advised on how to administer eltrombopag tablets.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - **Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (updated October 2018)**
      - **NICE TA293**
      - Eltrombopag (Revolade®) is recommended only if the manufacturer provides it with the discount agreed in the patient access scheme.

      Patients currently receiving eltrombopag whose disease does not meet these criteria should have the option to continue treatment until they and their NHS clinician consider it appropriate to stop.

      www.nice.org.uk/guidance/ta293

- **Scottish Medicines Consortium (SMC) decisions**
  - **SMC No. 625/10**
    - The Scottish Medicines Consortium has advised (August 2010) that eltrombopag (Revolade®) is accepted for restricted use within the NHS Scotland for the treatment of both splenectomised and non-splenectomised patients with severe symptomatic immune (idiopathic) thrombocytopenic purpura or a high risk of bleeding.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicinal forms containing the same drug.

  - **Tablet**
    - **Revolade** (Novartis Pharmaceuticals UK Ltd)
      - Eltrombopag (as Eltrombopag olamine) 25 mg Revolade 25mg tablets | 28 tablet | £77.00 DT + £77.00
      - Eltrombopag (as Eltrombopag olamine) 50 mg Revolade 50mg tablets | 28 tablet | £1,540.00 DT + £1,540.00
      - Eltrombopag (as Eltrombopag olamine) 75 mg Revolade 75mg tablets | 28 tablet | £2,310.00 DT + £2,310.00

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**Romiplostim**

- **DRUG ACTION** Romiplostim is an Fc–peptide fusion protein that binds to and activates the thrombopoietin (TPO) receptor, thereby increasing platelet production.

- **INDICATIONS AND DOSE** Chronic immune (idiopathic) thrombocytopenic purpura in patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision)

  - **BY SUBCUTANEOUS INJECTION**
    - **Adult:** Initially 1 microgram/kg once weekly, adjusted in steps of 1 microgram/kg once weekly (max. per dose 10 micrograms/kg once weekly) until a stable platelet count of 50x10⁹/litre or more is reached, consult product literature for further details of dose adjustments, discontinue treatment if inadequate response after 4 weeks at maximum dose

- **CAUTIONS** Risk factors for thromboembolism

- **SIDE-EFFECTS**
  - **Common or very common** Anaemia - angioedema - arthralgia - asthenia - bone marrow disorders - chills - constipation - diarrhoea - dizziness - embolism and thrombosis - fever - flushing - gastrointestinal discomfort - headaches - hypersensitivity - increased risk of infection - influenza like illness - muscle complaints - nausea - pain - palpitations - peripheral oedema - sensation abnormal - skin reactions - sleep disorders

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution; consider avoiding in moderate to severe impairment (risk of thromboembolic complications).

- **RENAL IMPAIRMENT** Manufacturer advises caution—no information available.

- **MONITORING REQUIREMENTS** Manufacturer advises monitor full blood count and peripheral blood smears for morphological abnormalities before and during treatment.

- **Driving and skilled tasks** Manufacturer advises that patients and their carers should be counselled on the effects on driving and the performance of skilled tasks—increased risk of dizziness.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - **Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (updated October 2018)**
      - **NICE TA221**
      - Romiplostim (Nplate®) is recommended as an option for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults, only if:

        - their condition is refractory to standard active treatments and rescue therapies, or
        - they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.

      Romiplostim is recommended only if the manufacturer makes it available with the discount agreed in the patient access scheme.

      Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

      www.nice.org.uk/guidance/ta221

- **Scottish Medicines Consortium (SMC) decisions**
  - **SMC No. 553/09**
    - The Scottish Medicines Consortium has advised (October 2009) that romiplostim (Nplate®) is accepted for restricted use within the NHS Scotland for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) and as second-line treatment for adult non-splenectomised patients where surgery is contra-indicated. Romiplostim is restricted use within NHS Scotland for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults, only if:
Fluid and electrolyte imbalances

Nutrition and metabolic disorders

1 Fluid and electrolyte imbalances

Fluids and electrolytes

Electrolyte replacement therapy

The electrolyte concentrations (intravenous fluid) table and the electrolyte content (gastro-intestinal secretions) table may be helpful in planning replacement electrolyte therapy; faeces, vomit, or aspiration should be saved and analysed where possible if abnormal losses are suspected.

Oral preparations for fluid and electrolyte imbalance

Sodium and potassium salts, may be given by mouth to prevent deficiencies or to treat established deficiencies of mild or moderate degree.

Oral potassium

Compensation for potassium loss is especially necessary:
- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias;
- in patients in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, cirrhosis of the liver, the nephrotic syndrome, and severe heart failure;
- in patients with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse.

Measures to compensate for potassium loss may also be required in the elderly since they frequently take inadequate amounts of potassium in the diet (but see warning on renal insufficiency). Measures may also be required during long-term administration of drugs known to induce potassium loss (e.g. corticosteroids). Potassium supplements are seldom required with the small doses of diuretics given to treat hypertension; potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide p. 227 or the thiazides when these are given to eliminate oedema.

If potassium salts are used for the prevention of hypokalaemia, then doses of potassium chloride daily (in divided doses) by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) to reduce the risk of hyperkalaemia.

Potassium salts cause nausea and vomiting and poor compliance is a major limitation to their effectiveness; when appropriate, potassium-sparing diuretics are preferable.

When there is established potassium depletion larger doses may be necessary, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma-potassium concentration and specialist advice would be required). Potassium depletion is frequently associated with chloride depletion and with metabolic alkalosis, and these disorders require correction.

Management of hyperkalaemia

Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes) calls for urgent treatment with calcium gluconate 10% p. 1045 by slow intravenous injection, titrated and adjusted to ECG improvement, to temporarily protect against myocardial excitability. An intravenous injection of soluble insulin (5–10 units) with 50 mL glucose 50% p. 1041 given over 5–15 minutes, reduces serum-potassium concentration; this is repeated if necessary or a continuous infusion instituted. Salbutamol p. 252 [unlicensed indication], by nebulisation or slow intravenous injection may also reduce plasma-potassium concentration; it should be used with caution in patients with cardiovascular disease. The correction of causal or compounding acidosis with sodium bicarbonate infusion p. 1038 should be considered (important: preparations of sodium bicarbonate and calcium salts should not be administered in the same line—risk of precipitation). Drugs exacerbating hyperkalaemia should be reviewed and stopped as appropriate; occasionally haemodialysis is needed.

Ion-exchange resins may be used to remove excess potassium in mild hyperkalaemia or in moderate hyperkalaemia when there are no ECG changes.

Oral sodium and water

Sodium chloride p. 1040 is indicated in states of sodium depletion and usually needs to be given intravenously. In chronic conditions associated with mild or moderate degrees of sodium depletion, e.g. in salt-losing bowel or renal disease, oral supplements of sodium chloride or sodium bicarbonate, according to the acid-base status of the patient, may be sufficient.

Oral rehydration therapy (ORT)

As a worldwide problem diarrhoea is by far the most important indication for fluid and electrolyte replacement. Intestinal absorption of sodium and water is enhanced by glucose (and other carbohydrates). Replacement of fluid and electrolytes lost through diarrhoea can therefore be achieved by giving solutions containing sodium, potassium, and glucose or another carbohydrate such as rice starch. Oral rehydration solutions should:
- enhance the absorption of water and electrolytes;
- replace the electrolyte deficit adequately and safely;
- contain an alkalinising agent to counter acidosis;
- be slightly hypo-osmolar (about 250 mmol/litre) to prevent the possible induction of osmotic diarrhoea;
- be simple to use in hospital and at home;
- be palatable and acceptable, especially to children;
- be readily available.

It is the policy of the World Health Organization (WHO) to promote a single oral rehydration solution but to use it flexibly (e.g. by giving extra water between drinks of oral rehydration solution to moderately dehydrated infants). The WHO oral rehydration solution contains sodium chloride 2.6 g, potassium chloride 1.5 g, sodium citrate 2.9 g, anhydrous glucose 13.5 g. It is dissolved in sufficient water to produce 1 litre (providing Na+ 75 mmol, K+ 20 mmol, Cl− 65 mmol, citrate 10 mmol, glucose 75 mmol/litre). This formulation is recommended by the WHO and the United Nations Children’s fund, but it is not commonly used in the UK.

Oral rehydration solutions used in the UK are lower in sodium (50–60 mmol/litre) than the WHO formulation since, in general, patients suffer less severe sodium loss.
### Fluids and electrolytes

#### Electrolyte concentrations—intravenous fluids

<table>
<thead>
<tr>
<th>Intra-venous infusion</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
<th>Cl⁻</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal plasma values</td>
<td>142</td>
<td>4.5</td>
<td>26</td>
<td>103</td>
<td>2.5</td>
</tr>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>Compound Sodium Lactate (Hartmann’s)</td>
<td>131</td>
<td>5</td>
<td>29</td>
<td>111</td>
<td>2</td>
</tr>
<tr>
<td>Sodium Chloride 0.18% and Glucose 4% (Adults only)</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Sodium Chloride 0.45% and Glucose 5% (Children only)</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Glucose 5% (Children only)</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Sodium Chloride 0.9% (Children only)</td>
<td>150</td>
<td>20</td>
<td>-</td>
<td>170</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Glucose 5%</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Sodium Chloride 0.9%</td>
<td>150</td>
<td>40</td>
<td>-</td>
<td>190</td>
<td>-</td>
</tr>
</tbody>
</table>

#### To correct metabolic acidosis

<table>
<thead>
<tr>
<th>Electrolyte content—in gastro-intestinal secretions</th>
<th>Millimoles per litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fluid</td>
<td>H⁺</td>
</tr>
<tr>
<td>Gastric</td>
<td>40-60</td>
</tr>
<tr>
<td>Biliary</td>
<td>-</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>-</td>
</tr>
<tr>
<td>Small bowel</td>
<td>-</td>
</tr>
</tbody>
</table>

Rehydration should be rapid over 3 to 4 hours (except in hypernatraemic dehydration in which case rehydration should occur more slowly over 12 hours). The patient should be reassessed after initial rehydration and if still dehydrated rapid fluid replacement should continue.

Once rehydration is complete further dehydration is prevented by encouraging the patient to drink normal volumes of an appropriate fluid and by replacing continuing losses with an oral rehydration solution; in infants, breast-feeding or formula feeds should be offered between oral rehydration drinks.

**Oral bicarbonate**

Sodium bicarbonate is given by mouth for chronic acidotic states such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe metabolic acidosis, sodium bicarbonate can be given intravenously.

Sodium bicarbonate may also be used to increase the pH of the urine; it is also used in dyspepsia.

Sodium supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated.

Where hyperchloremic acidosis is associated with potassium deficiency, as in some renal tubular and gastrointestinal disorders it may be appropriate to give oral potassium bicarbonate, although acute or severe deficiency should be managed by intravenous therapy.

**Parenteral preparations for fluid and electrolyte imbalance**

#### Electrolytes and water

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting and is unable to take adequate amounts by mouth. When intravenous administration is not possible, fluid (as sodium chloride 0.9% p. 1040 or glucose 5% p. 1041) can also be given by subcutaneous infusion (hypodermoclysis).

The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical investigations. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, e.g. 20% glucose, are best given through an indwelling catheter positioned in a large vein.

**Intravenous sodium**

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in sodium depletion, which can arise from such conditions as gastro-enteritis, diabetic ketoacidosis, ileus, and ascites. In a severe deficit of 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter the infusion can usually be at a slower rate.

Chronic hyponatraemia arising from inappropriate secretion of antidiuretic hormone should ideally be corrected...
by fluid restriction. However, if sodium chloride is required for acute or chronic hyponatraemia, regardless of the cause, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome and the rise in plasma-sodium concentration should not exceed 10 mmol/litre in 24 hours. In severe hyponatraemia, sodium chloride 1.8% may be used cautiously.

**Compound sodium lactate** (Hartmann’s solution) can be used instead of isotonic sodium chloride solution during or after surgery, or in the initial management of the injured or wounded; it may reduce the risk of hyperchloremic acidosis. Sodium chloride with glucose solutions p. 1041 are indicated when there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na⁺ remains extracellular.

Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

**Intravenous glucose**

Glucose solutions (5%) are used mainly to replace water deficit. Average water requirements in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as may occur in coma or dysphagia or in the elderly or apathetic who may not drink enough water on their own initiative.

Excessive loss of water without loss of electrolytes is uncommon, occurring in fevers, hyperthyroidism, and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres.

Glucose solutions are also used to correct and prevent hypoglycaemia and to provide a source of energy in those too ill to be fed adequately by mouth; glucose solutions are a key component of parenteral nutrition.

Glucose solutions are given in regimens with calcium and insulin for the emergency management of **hyperkalaemia**. They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion.

**Intravenous potassium**

Potassium chloride with sodium chloride intravenous infusion p. 1040 is the initial treatment for the correction of severe hypokalaemia and when sufficient potassium cannot be taken by mouth.

Repeated measurement of plasma-potassium concentration is necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia, which is especially likely in renal impairment.

Initial potassium replacement therapy should not involve glucose infusions, because glucose may cause a further decrease in the plasma-potassium concentration.

**Bicarbonate and lactate**

Sodium bicarbonate p. 1038 is used to control severe metabolic acidosis (pH<7.1) particularly that caused by loss of bicarbonate (as in renal tubular acidosis or from excessive gastro-intestinal losses). Mild metabolic acidosis associated with volume depletion should first be managed by appropriate fluid replacement because acidosis usually resolves as tissue and renal perfusion are restored. In more severe metabolic acidosis or when the acidosis remains unresponsive to correction of anoxia or hypovolaemia, sodium bicarbonate (L.26%) can be infused over 3–4 hours with plasma-pH and electrolyte monitoring. In severe shock, for example in cardiac arrest, metabolic acidosis can develop without sodium or volume depletion; in these circumstances sodium bicarbonate is best given as a small volume of hypertonic solution, such as 50 mL of 8.4% solution intravenously.

Sodium lactate intravenous infusion is no longer used in metabolic acidosis because of the risk of producing lactic acidosis, particularly in seriously ill patients with poor tissue perfusion or impaired hepatic function.

For **chronic acidotic states**, sodium bicarbonate can be given by mouth.

**Plasma and plasma substitutes**

Plasma and plasma substitutes (‘colloids’) contain large molecules that do not readily leave the intravascular space where they exert osmotic pressure to maintain circulatory volume. Compared to fluids containing electrolytes such as sodium chloride and glucose (‘crystalloids’), a smaller volume of colloid is required to produce the same expansion of blood volume, thereby shifting salt and water from the extravascular space. If resuscitation requires a volume of fluid that exceeds the maximum dose of the colloid then crystalloids can be given; packed red cells may also be required.

Albumin solution p. 1047, prepared from whole blood, contain soluble proteins and electrolytes but no clotting factors, blood group antibodies, or plasma cholinesterases; they may be given without regard to the recipient’s blood group.

Albumin is usually used after the acute phase of illness, to correct a plasma-volume deficit; hypoalbuminaemia itself is not an appropriate indication. The use of albumin solution in acute plasma or blood loss may be wasteful; plasma substitutes are more appropriate. Concentrated albumin solution (20%) can be used under specialist supervision in patients with an intravascular fluid deficit and oedema because of interstitial fluid overload, to restore intravascular plasma volume with less exacerbation of the salt and water overload than isotonic solutions. Concentrated albumin solution may also be used to obtain a diuresis in hypoalbuminaemic patients (e.g. in hepatic cirrhosis).

Recent evidence does not support the previous view that the use of albumin increases mortality.

**Plasma substitutes**

Dextran, gelatin p. 1048, and the hydroxyethyl starch, tetrasarch, are macromolecular substances which are metabolised slowly. Dextran and gelatin may be used at the outset to expand and maintain blood volume in shock arising from conditions such as burns or septicemia; they may also be used as an immediate short-term measure to treat haemorrhage until blood is available. Dextran and gelatin are rarely needed when shock is due to sodium and water depletion because, in these circumstances, the shock responds to water and electrolyte repletion.

Hydroxyethyl starches should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient; they should be used at the lowest effective dose for the first 24 hours of fluid resuscitation.

Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water, and electrolytes over periods of several days or weeks. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Large volumes of some plasma substitutes can increase the risk of bleeding through depletion of coagulation factors.
BICARBONATE

**Sodium bicarbonate**

- **INDICATIONS AND DOSE**
  - Alkalisation of urine | Relief of discomfort in mild urinary-tract infections
  - **BY MOUTH**
  - Adult: 3 g every 2 hours until urinary pH exceeds 7, to be dissolved in water

- **Maintenance of alkaline urine**
  - **BY MOUTH**
  - Adult: 5–10 g daily, to be dissolved in water

- **Chronic acidic states such as uraemic acidosis or renal tubular acidosis**
  - **BY SLOW INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
  - Adult: Administer an amount appropriate to the body base deficit, to be given by slow intravenous injection of a strong solution (up to 8.4%), or by continuous intravenous infusion of a weaker solution (usually 1.26%).

- **SIDE-EFFECTS**
  - With intravenous use | Skin exfoliation | soft tissue necrosis | ulcer
  - With oral use | Abdominal cramps | burping | flatulence | hypokalaemia | metabolic alkalosis

- **PREGNANCY**
  - With oral use | Use with caution in urinary conditions.

- **HEPATIC IMPAIRMENT**
  - With oral use | Manufacturer advises caution in cirrhosis. Salt restriction will be covered in the prelinis.

- **RENAL IMPAIRMENT**
  - With oral use | Avoid (except for specialised role in some forms of renal disease).

- **CONTRA-INDICATIONS**
  - With oral use | Salt restricted diet

- **CAUTIONS**
  - Avoid prolonged use in urinary conditions | cardiac disease | elderly | patients on sodium-restricted diet | respiratory acidosis

- **INTERACTIONS**
  - With intravenous use | Sodium bicarbonate
  - With oral use | Alkalinisation of urine | maintenance of alkaline urine

- **SIDE-EFFECTS**
  - With intravenous use | Skin exfoliation | soft tissue necrosis | ulcer
  - With oral use | Abdominal cramps | burping | flatulence | hypokalaemia | metabolic alkalosis

- **PREGNANCY**
  - With oral use | Use with caution in urinary conditions.

- **HEPATIC IMPAIRMENT**
  - With oral use | Manufacturer advises caution in cirrhosis. Salt restriction will be covered in the prelinis.

- **RENAL IMPAIRMENT**
  - With oral use | Avoid (except for specialised role in some forms of renal disease).

- **MONITORING REQUIREMENTS**
  - With intravenous use | Plasma-pH and electrolytes should be monitored.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use | For slow intravenous injection use a small volume of hypertonic solution (such as 50 mL of 8.4%). For continuous intravenous infusion a weaker solution of 1.26% solution can be infused over 3–4 hours.
  - With oral use | Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - With oral use | Sodium bicarbonate 500 mg capsules contain approximately 6 mmol each of Na⁺ and HCO₃⁻; Sodium bicarbonate 600 mg capsules contain approximately 7 mmol each of Na⁺ and HCO₃⁻. Oral solutions of sodium bicarbonate are required occasionally; these are available from 'special-order' manufacturers or specialist importing companies; the strength of sodium bicarbonate should be stated on the prescription.

  - With intravenous use | Usual strength Sodium bicarbonate 1.26% (12.6 g, 150 mmol each of Na⁺ and HCO₃⁻/litre), various other strengths available.

- **PATIENT AND CARER ADVICE**
  - With oral use | Patients or carers should be given advice on the administration of sodium bicarbonate oral medicines.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution, solution for injection, liquid

<table>
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<tr>
<th>Tablet</th>
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<tbody>
<tr>
<td><strong>Sodium bicarbonate (Non-proprietary)</strong></td>
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<td>Sodium bicarbonate 600 mg</td>
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</tr>
<tr>
<td>Sodium bicarbonate 84 mg per 1 ml</td>
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<tr>
<td>Sodium bicarbonate 84 mg per 1 ml solution for injection 250 ml bottles</td>
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<tr>
<td>Sodium bicarbonate 84 mg per 1 ml solution for injection 100 ml bottles</td>
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<tr>
<th>Oral solution</th>
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<tbody>
<tr>
<td><strong>Thamicarb (Thame Laboratories Ltd)</strong></td>
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<tr>
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<td>Sodium bicarbonate 84 mg per 1 ml</td>
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<table>
<thead>
<tr>
<th>Capsule</th>
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<tbody>
<tr>
<td><strong>Sodium bicarbonate (Non-proprietary)</strong></td>
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<td>Sodium bicarbonate 500 mg</td>
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<table>
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<tr>
<td><strong>Sodium bicarbonate (Non-proprietary)</strong></td>
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<tr>
<td>Sodium bicarbonate 12.6 mg per 1 ml Polyfusor sodium bicarbonate 1.26% solution for infusion 500 ml bottles</td>
</tr>
<tr>
<td>Sodium bicarbonate 14 mg per 1 ml Polyfusor sodium bicarbonate 1.4% solution for infusion 500 ml bottles</td>
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<tr>
<td>Sodium bicarbonate 27.4 mg per 1 ml Polyfusor sodium bicarbonate 2.74% solution for infusion 500 ml bottles</td>
</tr>
<tr>
<td>Sodium bicarbonate 42 mg per 1 ml Polyfusor sodium bicarbonate 4.2% solution for infusion 500 ml bottles</td>
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<tr>
<td>Sodium bicarbonate 84 mg per 1 ml Polyfusor sodium bicarbonate 8.4% solution for infusion 200 ml bottles</td>
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</tbody>
</table>

**ELECTROLYTES AND MINERALS**

> **POTASSIUM**

**Potassium chloride with calcium chloride and sodium chloride and sodium lactate**

*(Sodium Lactate Intravenous Infusion, Compound; Compound, Hartmann's Solution for Injection; Ringer-Lactate Solution for Injection)*

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057, sodium chloride p. 1040, calcium chloride p. 1045.

- **INDICATIONS AND DOSE**
  - For prophylaxis, and replacement therapy, requiring the use of sodium chloride and lactate, with minimal amounts of calcium and potassium
  - **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

- **INTERACTIONS**
  - Appendix 1: calcium salts | potassium chloride

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Compound sodium lactate intravenous infusion contains Na⁺
Potassium chloride with calcium chloride dihydrate and sodium chloride

(Ringer’s solution)
The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057, sodium chloride p. 1040.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**
- By Intravenous infusion
- Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

**INTERACTIONS** → Appendix 1: potassium chloride

**PRESCRIBING AND DISPENSING INFORMATION** Ringer’s solution for injection provides the following ions (in mmol/litre), Ca^{2+} 2.2, K^+ 4, Na^+ 147, CI^- 156.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Infusion**
- Potassium chloride with calcium chloride dihydrate and sodium chloride (Non-proprietary)
  - Potassium chloride 300 microgram per 1 ml, Calcium chloride 320 microgram per 1 ml, Sodium chloride 8.6 mg per 1 ml
    - Steriflex No.9 ringer infusion 500ml bags | 1 bag [POT] £1.96
    - Polyfurser Ringers solution for infusions 500ml bottles | 1 bottle [POT] £3.41

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Potassium chloride with glucose

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057, glucose p. 1041.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**
- By Intravenous infusion
- Adult: Dosed according to the deficit or daily maintenance requirements

**INTERACTIONS** → Appendix 1: potassium chloride

**PRESCRIBING AND DISPENSING INFORMATION**

Potassium chloride with glucose and sodium chloride

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057, sodium chloride p. 1040.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**
- BY INTRAVENOUS INFUSION
- Adult: Dosed according to the deficit or daily maintenance requirements

**INTERACTIONS** → Appendix 1: potassium chloride

**PRESCRIBING AND DISPENSING INFORMATION**

Concentration of potassium chloride to be specified by the prescriber (usually K^+ 10–40 mmol/litre).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Infusion**
- Potassium chloride with glucose and sodium chloride (Non-proprietary)
  - Sodium chloride 1.8 mg per 1 ml, Potassium chloride 3 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml
    - Potassium chloride 0.3% (potassium 20mmol/500ml) / Glucose 4% / Sodium chloride 0.18% infusion 500ml bags | 1 bag [POT] £2.22
    - Potassium chloride 0.3% (potassium 40mmol/1litre) / Glucose 4% / Sodium chloride 0.18% infusion 1litre bags | 1 bag [POT] £1.96
    - Potassium chloride 1.5 mg per 1 ml, Sodium chloride 1.8 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml
      - Potassium chloride 0.15% (potassium 10mmol/500ml) / Glucose 4% / Sodium chloride 0.18% infusion 500ml bags | 1 bag [POT] £2.0
    - Potassium chloride 1.8 mg per 1 ml, Potassium chloride 2 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml
      - Potassium chloride 0.15% (potassium 10mmol/500ml) / Glucose 5% / Sodium chloride 0.18% infusion 500ml bags | 1 bag [POT] £1.76

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Potassium chloride with potassium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057.
Potassium chloride with sodium chloride

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 1057, sodium chloride below.

**INDICATIONS AND DOSE**

**Electrolyte imbalance**
- **BY INTRAVENOUS INFUSION**
  - Adult: Depending on the deficit or the daily maintenance requirements (consult product literature)

**INTERACTIONS**

- Appendix 1: potassium chloride

**PRESCRIBING AND DISPENSING INFORMATION**

**Potassium chloride**
- **0.15% w/v solution for injection**
  - Each 1 ml contains 0.15 g potassium chloride.
  - Store in a cool dark place.

**Sodium chloride**
- **0.9% w/v solution for injection**
  - Each 1 ml contains 9 g sodium chloride.
  - Store in a cool dark place.

**MONITORING REQUIREMENTS**

- The jugular venous pressure should be assessed, the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

**SIDE-EFFECTS**

- With intravenous use: Chills, fever, hypervolaemia, hypotension, local reaction, localised pain, paraesthesia, skin reactions, tremor, vascular irritation, venous thrombosis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Effervescent tablets**
- Sando-K (HK Pharma Ltd)
  - Potassium bicarbonate 400 mg, Potassium chloride 600 mg
  - Each tablet contains potassium bicarbonate 400 mg, potassium chloride 600 mg and sodium chloride 285 mg (8 mmol Cl-).

**INTERACTIONS**

- Appendix 1: potassium chloride

**PRESCRIBING AND DISPENSING INFORMATION**

**Potassium chloride**
- **0.15% w/v solution for injection**
  - Each 1 ml contains 0.15 g potassium chloride.
  - Store in a cool dark place.

**Sodium chloride**
- **0.9% w/v solution for injection**
  - Each 1 ml contains 9 g sodium chloride.
  - Store in a cool dark place.

**MONITORING REQUIREMENTS**

- The jugular venous pressure should be assessed, the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

**SIDE-EFFECTS**

- With intravenous use: Chills, fever, hypervolaemia, hypotension, local reaction, localised pain, paraesthesia, skin reactions, tremor, vascular irritation, venous thrombosis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, solution for injection, injection, infusion, solution for infusion

Infusion
- **Potassium chloride with sodium chloride (Non-proprietary)**
  - Potassium chloride 3 mg per 1 ml, Sodium chloride 9 mg per 1 ml
  - Potassium chloride 0.3% (potassium 20 mmol/500 ml) / Sodium chloride 0.9% infusion 500 ml bags | 1 bag (PST) £0.95
  - Potassium chloride 0.3% (potassium 40 mmol/1 litre) / Sodium chloride 0.9% infusion 1 litre bags | 1 bag (PST) £0.95
  - Potassium chloride 1.5 mg per 1 ml, Sodium chloride 9 mg per 1 ml
  - Potassium chloride 0.15% (potassium 20 mmol/1 litre) / Sodium chloride 0.9% infusion 1 litre bags | 1 bag (PST) £0.95
  - Potassium chloride 0.1% (potassium 10 mmol/500 ml) / Sodium chloride 0.9% infusion 500 ml bags | 1 bag (PST) 81.30–81.67
  - Potassium chloride 2 mg per 1 ml, Sodium chloride 9 mg per 1 ml
  - Steriflex No. 28 potassium chloride 0.2% (potassium 27 mmol/litre) / sodium chloride 0.9% infusion 1 litre bags | 1 bag (PST) £2.20

**ELECTROLYTES AND MINERALS**

**SODIUM CHLORIDE**

**INDICATIONS AND DOSE**

**Prophylaxis of sodium chloride deficiency**
- **BY MOUTH**
  - Adult: 4–8 tablets daily, to be taken with water, up to maximum 20 tablets daily in severe depletion

**Chronic renal salt wasting**
- **BY MOUTH**
  - Adult: Up to 20 tablets daily, to be taken with appropriate fluid intake
Fluid and electrolyte imbalances

Sodium chloride 300 mg per 1 ml Sodium chloride 30% solution for injection 10ml ampolles | 10 ampolle (PO) £70.43 DT + £70.43

Solution for infusion

- Sodium chloride (Non-proprietary)
  - Sodium chloride 300 mg per 1 ml Sodium chloride 30% concentrate for solution for infusion 100ml vials | 10 vial (PO) £55.60 DT + £55.60
  - Sodium chloride 30% concentrate for solution for infusion 50ml vials | 1 vial (PO) £14.63 DT + £14.63 | 10 vial (PO) £77.50 DT + £77.50
  - Sodium chloride 30% concentrate for solution for infusion 10ml ampolles | 10 ampolle (PO) £70.40

Infusion

- Sodium chloride (Non-proprietary)
  - Sodium chloride 1.8 mg per 1 ml Polyfusor 0 sodium chloride 0.18% infusion 500ml bottles | 1 bottle (PO) £3.98
  - Sodium chloride 4.5 mg per 1 ml Sodium chloride 0.45% infusion 500ml bags | 1 bag (PO) £0.55
  - Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% infusion 100ml bags | 1 bag (PO) £1.00
  - Sodium chloride 0.9% infusion 250ml bags | 1 bag (PO) £0.95
  - Sodium chloride 0.9% infusion 1litre bags | 1 bag (PO) £0.95
  - Sodium chloride 0.9% infusion 500ml Viallo bags | 1 bag (PO) £0.95
  - Sodium chloride 0.9% infusion 2 litre bags | 1 bag (PO) £4.92
  - Sodium chloride 0.9% infusion 50ml bags | 1 bag (PO) £0.95
  - Sodium chloride 0.9% infusion 100ml polyethylene bottles | 1 bottle (PO) £0.55 | 20 bottles (PO) £11.00
  - Polyfusor S sodium chloride 0.9% infusion 500ml bottles | 1 bottle (PO) £2.70
  - Polyfusor S sodium chloride 0.9% infusion 1litre bottles | 1 bottle (PO) £3.59
  - Sodium chloride 18 mg per 1 ml Polyfusor SC sodium chloride 1.8% infusion 500ml bottles | 1 bottle (PO) £3.98
  - Sodium chloride 27 mg per 1 ml Polyfusor SD sodium chloride 2.7% infusion 500ml bottles | 1 bottle (PO) £3.98
  - Sodium chloride 50 mg per 1 ml Polyfusor SE sodium chloride 5% infusion 500ml bottles | 1 bottle (PO) £3.98

Combinations available: Potassium chloride with calcium chloride and sodium chloride, and sodium lactate, p. 1038 · Potassium chloride with calcium chloride dihydrate and sodium chloride, p. 1039 · Potassium chloride with glucose and sodium chloride, p. 1039 · Potassium chloride with sodium chloride, p. 1040

Sodium chloride with glucose

The properties listed below are those particular to the combination only. For the properties of the components please consider, sodium chloride p. 1040, glucose below.

- INDICATIONS AND DOSE
  - Combined water and sodium depletion
    - BY INTRAVENOUS INFUSION
    - Adults: (consult product literature)
  - MONITORING REQUIREMENTS
    - Maintenance fluid should accurately reflect daily requirements and close monitoring is required to avoid fluid and electrolyte imbalance.
  - MEDICINAL FORMS
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion
  - Infusion
    - Sodium chloride with glucose (Non-proprietary)
      - Sodium chloride 4.5 mg per 1 ml, Glucose anhydrous 25 mg per 1 ml Sodium chloride 0.45% / Glucose 2.5% infusion 500ml Viallo bags | 1 bag (PO) £0.95
      - Sodium chloride 1.8 mg per 1 ml, Glucose anhydrous 40 mg per 1 ml Polyfusor T glucose 4% / sodium chloride 0.18% infusion 500ml bottles | 1 bottle (PO) £2.40
      - Sodium chloride 0.18% / Glucose 4% infusion 500ml bags | 1 bag (PO) £0.95
      - Sodium chloride 0.18% / Glucose 4% infusion 1litre bags | 1 bag (PO) £0.95
      - Steriflex No.3 glucose 5% / sodium chloride 0.9% infusion 500ml bags | 1 bag (PO) £1.47

NUTRIENTS > SUGARS

Glucose

(Dextrose Monohydrate)

- INDICATIONS AND DOSE
  - Establish presence of gestational diabetes
    - BY MOUTH
      - Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid
  - Oral glucose tolerance test
    - BY MOUTH
      - Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid
  - Hypoglycaemia
    - BY INTRAVENOUS INFUSION
    - Child: 500 mg/kg, to be administered as Glucose 10% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs
    - Adult: 10 g, to be administered as Glucose 20% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs
  - Energy source
    - BY INTRAVENOUS INFUSION
    - Adult: 1–3 litres daily, solution concentration of 20–50% to be administered
  - Water replacement
    - BY INTRAVENOUS INFUSION
    - Adult: The volume of glucose solution needed to replace deficits may vary (consult product literature)
  - Persistent cyanosis (in combination with propranolol) when blood glucose less than 3 mmol/litre (followed by morphine)
    - BY INTRAVENOUS INFUSION
    - Child: 200 mg/kg, to be administered as Glucose 10% intravenous infusion over 10 minutes
  - Management of diabetic ketoacidosis
    - BY INTRAVENOUS INFUSION
    - Child: Glucose 5% or 10% should be added to replacement fluid once blood-glucose concentration falls below 14 mmol/litre
    - Adult: Glucose 10% should be given once blood-glucose concentration falls below 14 mmol/litre, to be administered into a large vein through a large-gauge needle at a rate of 125 ml/hour, in addition to the sodium chloride 0.9% infusion

DOSE EQUIVALENT AND CONVERSION

- 75 g anhydrous glucose is equivalent to Glucose BP 82.5 g.

- CAUTIONS
  - Do not give alone except when there is no significant loss of electrolyte prolonged administration of glucose solutions without electrolytes can lead to hyponatraemia and other electrolyte disturbances
**SID-EFFECTS** Chills · electrolyte imbalance · fever · fluid imbalance · hypersensitivity · local reaction · localised pain · polyuria · rash · venous thrombosis

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use in children: Injections containing more than 10% glucose can be irri tant and should be given into a central venous line; however, solutions containing up to 12.5% can be administered for a short period into a peripheral line.
- PRESCRIBING AND DISPENSING INFORMATION: Glucose BP is the mono hydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose.

**EXCEPTIONS TO LEGAL CATEGORY**
- With intravenous use: Prescription only medicine restriction does not apply to 50% solution where administration is for saving life in emergency.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, solution, solution for infusion for injection

**Solution for infusion**
- **Glucose** (Non-proprietary)
  - Glucose anhydrous 200 mg per 1 ml: Glucose 20% solution for infusion 100 ml vials | 1 vial (£): £6.00
  - Glucose anhydrous 500 mg per 1 ml: Glucose 50% solution for infusion 20 ml ampoules | 10 ampoules (£): £12.00–£14.00 DT = £12.00
  - Glucose 50% solution for infusion 50 ml vials | 25 vials (£): £50.00–£60.00 DT = £50.01

**Oral solution**
- **Rapilose OGGT** (Galen Ltd)
  - Glucose 250 mg per 1 ml: Rapilose OGGT solution | 300 ml £3.48

**Gel**
- **Dextrogel** (Nexeceuticals Ltd)
  - Glucose 400 mg per 1 gram: Dextrogel 40% gel | 75 gram £7.16 DT = £7.16 | 80 gram £6.84

**Glucose Boost** (Ennogen Healthcare Ltd)
- Glucose 400 mg per 1 gram: GlucoBoost 40% gel | 75 gram £5.72 DT = £7.16 | 80 gram £6.11

**Glucogel** (BBC Healthcare Ltd)
- Glucose 400 mg per 1 gram: Glucogel 40% gel original | 75 gram (£): £7.16 DT = £7.16 | 80 gram (£): £6.84

- **Rapilose** (Galen Ltd)
  - Glucose 400 mg per 1 gram: Rapilose 40% gel | 75 gram £5.49 DT = £7.16

**Infusion**
- **Glucose** (Non-proprietary)
  - Glucose anhydrous 50 mg per 1 ml: Glucose 5% infusion 1 litre bags | 1 bag (£): £3.50
  - Glucose 5% infusion 100 ml bags | 1 bag (£): £3.50
  - Glucose 5% infusion 250 ml bags | 1 bag (£): £3.50
  - Glucose 5% infusion 500 ml bags | 1 bag (£): £3.50
  - Polyvion D glucose 5% infusion 1 litre bottles | 1 bottle (£): £3.50
  - Polyvion F glucose 5% infusion 500 ml bottles | 1 bottle (£): £3.50
  - Glucose anhydrous 100 mg per 1 ml: Glucose 10% infusion 1 litre bags | 1 bag (£): £3.50
  - Glucose 10% infusion 500 ml bags | 1 bag (£): £3.50

**Glucose anhydrous 200 mg per 1 ml**
- Steriflex No.31 glucose 20% infusion 500 ml bags | 1 bag (£): £2.64

**Glucose** (as Glucose monohydrate) 300 mg per 1 ml: Glucose 30% infusion 500 ml polyethylene bottles | 10 bottle (£): £40.21

- **Glucose anhydrous 400 mg per 1 ml**
  - Steriflex No.33 glucose 40% infusion 500 ml bags | 1 bag (£): £2.81

**Glucose anhydrous 500 mg per 1 ml**
- Steriflex No.34 glucose 50% infusion 500 ml bags | 1 bag (£): £3.11

**Glucose anhydrous 700 mg per 1 ml**
- **Steriflex** 70% concentrate for solution for infusion 500 ml Viaflex bags | 1 bag (£): £3.84

**Combinations available:** Potassium chloride with glucose, p. 1039 · Potassium chloride with glucose and sodium chloride, p. 1039 · Sodium chloride with glucose, p. 1041

**ORAL REHYDRATION SALTS**

**Disodium hydrogen citrate with glucose, potassium chloride and sodium chloride**

(Formulated as oral rehydration salts)

**INDICATIONS AND DOSE**
- **Fluid and electrolyte loss in diarrhoea**
  - **BY MOUTH**
    - Child 1-11 months: 1–1½ times usual feed volume to be given
    - Child 1-11 years: 200 ml, to be given after every loose motion
    - Child 12-17 years: 200–400 ml, to be given after every loose motion, dose according to fluid loss
    - Adult: 200–400 ml, to be given after every loose motion, dose according to fluid loss

**DIRECTIONS FOR ADMINISTRATION**
- Reconstitute 1 sachet with 200 ml of water (freshly boiled and cooled for infants); 5 sachets reconstituted with 1 litre of water provide Na+ 60 mmol, K+ 20 mmol, Cl− 60 mmol, citrate 10 mmol, and glucose 90 mmol.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral powder formulations may include black currant, citrus, or natural.

**PATIENT AND CARER ADVICE**
- After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

Meditines for Children leaflet: Oral rehydration salts
www.medicinesforchildren.org.uk/oral-rehydration-salts

**Potassium chloride with rice powder, sodium chloride and sodium citrate**

(Formulated as oral rehydration salts)

**INDICATIONS AND DOSE**
- **Fluid and electrolyte loss in diarrhoea**
  - **BY MOUTH**
    - Adult: 200–400 ml, to be given after every loose motion, dose according to fluid loss

**DIRECTIONS FOR ADMINISTRATION**
- Reconstitute 1 sachet with 200 ml of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na+ 60 mmol, K+ 20 mmol, Cl− 50 mmol and citrate 10 mmol.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral powder formulations may include apricot, black currant, or raspberry.

**PATIENT AND CARER ADVICE**
- Patients and carers should be advised how to reconstitute Dioralyte® Relief oral powder.
- After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

www.getintopharma.com
**1.1 Calcium imbalance**

**Calcium imbalance**

**Calcium supplements**

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended amount reduces the rate of bone loss. If the actual dietary intake is less than the recommended amount, a supplement of as much as 40 mmol is appropriate.

In severe acute hypocalcaemia or hypocalcaemic tetany, an initial slow intravenous injection of calcium gluconate injection 10% p. 1045 should be given, with plasma-calcium and ECG monitoring (risk of arrhythmias if given too rapidly), and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence. Calcium chloride injection p. 1045 is also available, but is more irritant; care should be taken to prevent extravasation. Oral supplements of calcium and vitamin D may also be required in persistent hypocalcaemia. Concurrent hypomagnesaemia should be corrected with magnesium sulfate p. 1051.

See the role of calcium gluconate in temporarily reducing the toxic effects of hyperkalaemia.

**Severe hypercalcaemia**

Severe hypercalcaemia calls for urgent treatment before detailed investigation of the cause. Dehydration should be corrected first with intravenous infusion of sodium chloride 0.9% p. 1040. Drugs (such as thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium should be restricted.

If severe hypercalcaemia persists drugs which inhibit mobilisation of calcium from the skeleton may be required. The bisphosphonates are useful and pamidronate disodium p. 729 is probably the most effective.

Corticosteroids are widely given, but may only be useful where hypercalcaemia is due to sarcoidosis or vitamin D intoxication; they often take several days to achieve the desired effect.

Calcitonin (salmon) p. 733 can be used for the treatment of hypercalcaemia associated with malignancy; it is rarely effective where bisphosphonates have failed to reduce serum calcium adequately.

After treatment of severe hypercalcaemia the underlying cause must be established. Further treatment is governed by the same principles as for initial therapy. Salt and water depletion and drugs promoting hypercalcaemia should be avoided; oral administration of a bisphosphonate may be useful.

**Hyperparathyroidism**

Paricalcitol p. 1087 is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease.

Parathyroidectomy may be indicated for hyperparathyroidism.

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**Hypercalcaemia and hypercalciuria**

**CALCIUM REGULATING DRUGS > BONE RESORPTION INHIBITORS**

**Cinacalcet**

**DRUG ACTION** Cinacalcet reduces parathyroid hormone which leads to a decrease in serum calcium concentrations.

**INDICATIONS AND DOSE**

- **Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis**
  - **BY MOUTH**
    - Adult: Initially 30 mg once daily, dose to be adjusted every 2–4 weeks; maximum 180 mg per day

- **Treatment of hypercalcaemia in parathyroid carcinoma**
  - **BY MOUTH**
    - Adult: Initially 30 mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2–4 weeks according to response

**CAUTIONS** Treatment should not be initiated in patients with hypocalcaemia

**INTERACTIONS**

- **Appendix 1: cinacalcet**

**SIDE-EFFECTS**

- **Common or very common** Appetite decreased · asthenia · back pain · constipation · cough · diarrhoea · dizziness · dyspnoea · electrolyte imbalance · gastrointestinal discomfort · headache · hypersensitivity · hypotension · muscle complaints · nausea · paraesthesia · rash · seizure · upper respiratory tract infection · vomiting

- **Frequency not known** Heart failure aggravated · osteodystrophy · QT interval prolongation · tetany · ventricular arrhythmia

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment.

**MONITORING REQUIREMENTS**

- Measure serum-calcium concentration before initiation of treatment and within 1 week after starting treatment or adjusting dose, then monthly for secondary hyperparathyroidism, and every 2–3 months for primary hyperparathyroidism and parathyroid carcinoma.

- In secondary hyperparathyroidism measure parathyroid hormone concentration 1–4 weeks after starting treatment or adjusting dose, then every 1–3 months.
Etelcalcetide

26-Jul-2017

Etelcalcetide reduces parathyroid hormone secretion, which leads to a decrease in serum calcium concentrations.

INDICATIONS AND DOSE

Secondary hyperparathyroidism in patients with chronic kidney disease on haemodialysis

BY INTRAVENOUS INJECTION

Adult: Initially 5 mg 3 times a week, then increased in steps of 2.5–5 mg if required, dose to be increased at intervals of at least 4 weeks; usual maintenance 2.5–15 mg 3 times a week, max. dose 15 mg 3 times a week; consult product literature for information on missed doses, and for dose adjustment due to parathyroid hormone levels or serum-calcium concentrations

CAUTIONS

Conditions that may worsen with hypocalcaemia - hypocalcaemia (do not initiate if serum-calcium concentration is less than the lower limit of normal range) - switching from cinacalcet (do not initiate until 7 days after the last dose of cinacalcet)

CAUTIONS, FURTHER INFORMATION

Conditions that may worsen with hypocalcaemia. Manufacturer advises caution with use in patients with conditions that may worsen with hypocalcaemia, including predisposition to QT-interval prolongation, history of seizures, and history of congestive heart failure - serum-calcium concentration should be closely monitored.

INTERACTIONS

Appendix 1: etelcalcetide

SIDE-EFFECTS

Common or very common Diarrhoea; electrolyte imbalance - headache; heart failure aggravated; hypotension; muscle complaints; nausea; paraesthesia - QT interval prolongation; vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Manufacturer advises if formation of anti-etelcalcetide antibodies with a clinically significant effect is suspected, contact manufacturer to discuss antibody testing.

PREGNANCY

Manufacturer advises avoid — limited information available.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

MONITORING REQUIREMENTS

Manufacturer advises monitor parathyroid hormone level 4 weeks after treatment initiation or dose adjustment and approximately every 1–3 months during maintenance treatment; monitor serum-calcium concentration before treatment initiation, within 1 week of initiation or dose adjustment, and then approximately every 4 weeks during maintenance treatment.

HANDLING AND STORAGE

Manufacturer advises store in a refrigerator (2–8°C)—consult product literature for further information regarding storage outside refrigerator.

PATIENT AND CARER ADVICE

Manufacturer advises patients and their carers should be told to seek medical advice if symptoms of hypocalcaemia occur.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Etelcalcetide (as Etelcalcetide hydrochloride) 5 mg per 1 ml Parsabiv 2.5mg/0.5ml solution for injection vials | 6 vial £136.87 Parsabiv 10mg/2ml solution for injection vials | 6 vial £227.84 Parsabiv 5mg/1ml solution for injection vials | 6 vial £163.92

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2017) that etelcalcetide (Parsabiv) is not recommended for use within NHS Scotland for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on haemodialysis as the economic case was not demonstrated.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Parsabiv (Amgen Ltd) ▼

Etelcalcetide (as Etelcalcetide hydrochloride) 5 mg per 1 ml Parsabiv 2.5mg/0.5ml solution for injection vials | 6 vial £136.87 Parsabiv 10mg/2ml solution for injection vials | 6 vial £227.84 Parsabiv 5mg/1ml solution for injection vials | 6 vial £163.92

1.1b Hypocalcaemia

ELECTROLYTES AND MINERALS ▶ CALCULUM

Calcium salts

CONTRA-INDICATIONS

Conditions associated with hypocalcaemia (e.g. some forms of malignant disease) •

www.getintopharma.com
Calcium carbonate

- **INDICATIONS AND DOSE**
  - Phosphate binding in renal failure and hyperphosphataemia
    - **BY MOUTH**
      - Adult: (consult product literature)
        - *Calcium deficiency*
          - **BY MOUTH**
            - Adult: (consult product literature)

- **INTERACTIONS** → Appendix 1: calcium salts

- **SIDE-EFFECTS**
  - Uncommon Hypercalcaemia
  - Rare or very rare Flatulence; gastrointestinal discomfort; milk-alkali syndrome; skin reactions

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Each Sandocal® tablet contains 1 g calcium (Ca²⁺ 25 mmol); flavours of soluble tablet formulations may include orange.
  - There can be variation in the licensing of different medicines containing the same drug.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension
  - **Effervescent tablet**
    - CAUTIONARY AND ADVISORY LABELS 13 EXCIPIENTS: May contain Aspartame
      - Sandocal (GlaxoSmithKline Consumer Healthcare)
      - Calcium carbonate 1.75 gram, Calcium lactate gluconate 2.263 gram Sandocal 1000 effervescent tablets sugar-free | 30 tablet P £11.65 DT + £1.65

Calcium chloride

- **INDICATIONS AND DOSE**
  - Severe acute hypocalcaemia or hypocalcaemic tetany
    - **BY INTRAVENOUS INJECTION**
    - Adult: Dose according to requirements

- **CAUTIONS**
  - Avoid in respiratory acidosis · avoid in respiratory failure

- **INTERACTIONS** → Appendix 1: calcium salts

- **SIDE-EFFECTS**
  - Soft tissue calcification · taste unpleasant · vasodilation

- **DIRECTIONS FOR ADMINISTRATION**
  - Care should be taken to avoid extravasation.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Non-proprietary Calcium chloride dihydrogen 7.35% (calcium 20 mg or Ca²⁺ 500 micromol/mL); Calcium chloride dihydrogen 10% (calcium 27.3 mg or Ca²⁺ 680 micromol/mL); Calcium chloride dihydrogen 14.7% (calcium 40.1 mg or Ca²⁺ 1000 micromol/mL).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

- **Solution for infusion**
  - Calcium chloride (Non-proprietary)
    - Calcium chloride dihydrogen 100 mg per 1 ml Calcium chloride 10% solution for injection 10ml pre-filled syringes | 1 pre-filled disposable injection P £9.42 DT + £9.42
    - Calcium chloride dihydrogen 147 mg per 1 ml Calcium chloride 14.7% solution for injection 5ml ampoules | 10 ampoule P £120.98
      - Calcium chloride 14.7% solution for injection 10ml ampoules | 10 ampoule P £88.28 DT + £88.28

Calcium gluconate

- **INDICATIONS AND DOSE**
  - Severe acute hypocalcaemia or hypocalcaemic tetany
    - **INITIALLY BY SLOW INTRAVENOUS INJECTION**
      - Adult: Initially 10–20 mL, calcium gluconate injection 10% (providing approximately 2.25–4.5 mmol of calcium) should be administered with continued →
plasma-calcium and ECG monitoring, and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence, alternatively (by continuous intravenous infusion), initially 50 mL/hour, adjusted according to response, infusion to be administered using 100 mL of calcium gluconate 10% diluted in 1 litre of glucose 5% or sodium chloride 0.9%

Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes)
- **BY SLOW INTRAVENOUS INJECTION**
- Adult: 10–20 mL, calcium gluconate 10% should be administered, dose titrated and adjusted to ECG improvement

**Calcium deficiency** | Mild asymptomatic hypocacalaemia
- **BY MOUTH**
- Adult: Dose according to requirements

**DOSE EQUIVALENCE AND CONVERSION**
- 0.11 mmol/kg is equivalent to 0.5 mL/kg of calcium gluconate 10%.

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**Calcium lactate**

**INDICATIONS AND DOSE**

- **Calcium deficiency**
  - Adult: Dose according to requirements

**INTERACTIONS** → Appendix 1: calcium salts

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Calcium lactate (Non-proprietary)
      - Calcium lactate 300 mg | Calcium lactate 300mg tablets | 84 tablet [DT = £4.57] | 84 tablet [GSS] £4.57 DT = £4.57

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**Calcium phosphate**

**INDICATIONS AND DOSE**

- **Indications listed in combination monographs (available in the UK only in combination with other drugs)**
  - **BY MOUTH**
  - Adult: Doses listed in combination monographs

**INTERACTIONS** → Appendix 1: calcium salts

**SIDE-EFFECTS**
- Epigastric pain · gastrointestinal disorder · hypercalcaemia

**MEDICINAL FORMS**
- No licensed medicines listed.

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**Parathyroid hormones and analogues**

**Parathyroid hormone**  
(Human recombinant parathyroid hormone)

**DRUG ACTION**
- Parathyroid hormone is produced by recombinant DNA technology; endogenous parathyroid hormone is involved in modulating serum calcium and phosphate levels, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover.

**INDICATIONS AND DOSE**

- **Chronic hypoparathyroidism (specialist use only)**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS**
- Bone metastases · current or previous radiation therapy to skeleton · increased risk factors for osteosarcoma (including Paget’s disease or hereditary disorders) · pseudohypoparathyroidism · skeletal malignancy · unexplained raised levels of bone-specific alkaline phosphatase

**CAUTIONS**
- Concomitant use of cardiac glycosides (hypercacalaemia may predispose to digitalis toxicity)—monitor cardiac glycoside levels and check for signs and symptoms of digitalis toxicity · concomitant use of drugs that affect calcium levels · young adults with open epiphyses—increased risk of osteosarcoma

**INTERACTIONS** → Appendix 1: parathyroid hormone

**SIDE-EFFECTS**
- Common or very common Electrolyte imbalance · fatigue · pain in extremity

**SIDE-EFFECTS, FURTHER INFORMATION**
- Hypercalcaemia is more likely during initial dose titration; if severe hypercalcaemia develops, hydrate and consider suspending treatment (including calcium supplement and active vitamin D).

**PREGNANCY**
- Manufacturer advises use only if potential benefit outweighs risk—no information available.
1.2 Low blood volume

BLOOD AND RELATED PRODUCTS > PLASMA PRODUCTS

### Albumin solution

**(Human Albumin Solution)**

- **INDICATIONS AND DOSE**
  - Acute or sub-acute loss of plasma volume e.g. in burns, pancreatitis, trauma, and complications of surgery (with isotonic solutions)
  - Plasma exchange (with isotonic solutions)
  - Severe hypoaalbuminaemia associated with low plasma volume and generalised oedema where salt and water restriction with plasma volume expansion are required (with concentrated solutions 20%)
  - Paracentesis of large volume ascites associated with portal hypertension (with concentrated solutions 20%)

- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  - Cardiac failure · severe anaemia

- **CAUTIONS**
  - Correct dehydration when administering concentrated solution · history of cardiac disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) · history of circulatory disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) · increased capillary permeability

- **SIDE-EFFECTS**
  - Rare or very rare
    - Fever · flushing · nausea · shock · urticaria

- **MONITORING REQUIREMENTS**
  - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - A solution containing protein derived from plasma, serum, or normal placentas; at least 95% of the protein is albumin. The solution may be isotonic (containing 3.5–5% protein) or concentrated (containing 15–25% protein).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Infusion**
    - Flexbumin (Baxalta UK Ltd)
      - Albumin solution human 200 gram per 1 litre Flexbumin 20% infusion 100ml bags | 1 bag [P01 00]
      - Flexbumin 20% infusion 50ml bags | 1 bag [P01 00]
    - Solution for infusion
      - Albunorm (Octapharma Ltd)
        - Albumin solution human 50 mg per 1 ml Albunorm 5% solution for infusion 250ml bottles | 1 bottle [P01 00 £33.75]
        - Albunorm 5% solution for infusion 100ml bottles | 1 bottle [P01 00 £13.50]
        - Albunorm 5% solution for infusion 500ml bottles | 1 bottle [P01 00 £67.50]
      - Albumin solution human 200 mg per 1 ml Albunorm 20% solution for infusion 100ml bottles | 1 bottle [P01 00 £44.00]
      - Albunorm 20% solution for infusion 500ml bottles | 1 bottle [P01 00 £27.00]
    - Alburex (CSL Behring UK Ltd)
      - Albumin solution human 50 mg per 1 ml Alburex 5% solution for infusion 500ml vials | 1 vial [P01 00 £50.00]
    - Albumin solution human 200 mg per 1 ml Alburex 20% solution for infusion 100ml vials | 1 vial [P01 00 £40.00]
    - Albutein (Grifols UK Ltd)
      - Albumin solution human 50 mg per 1 ml Albutein 5% solution for infusion 500ml vials | 1 vial [P01 00]
      - Albutein 5% solution for infusion 250ml vials | 1 vial [P01 00]
Fluid and electrolyte imbalances

Gelatin

- **INDICATIONS AND DOSE**
  - Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 500–1000 ml, use 3.5–4% solution

- **CAUTIONS**
  - Cardiac disease · severe liver disease

- **SIDE-EFFECTS**
  - Rare or very rare: Chills · dyspnoea · fever · hyperhidrosis · hypersensitivity · hypertension · hypotension · hypoxia · tachycardia · tremor · urticaria · wheezing

- **PREGNANCY**
  - Manufacturer of Geloplasma® advises avoid at the end of pregnancy.

- **HEPATIC IMPAIRMENT**
  - Manufacturers advise avoid preparations that contain lactate (risk of impaired lactate metabolism).

- **RENAL IMPAIRMENT**
  - Use with caution in renal impairment.

- **MONITORING REQUIREMENTS**
  - Urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.
  - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The gelatin is partially degraded.
  - Gelaspan® contains succinylated gelatin (modified fluid gelatin, average molecular weight 26 500) 40 g, Na⁺ 151 mmol, K⁺ 4 mmol, Mg²⁺ 1 mmol, Cl⁻ 103 mmol, Ca²⁺ 1 mmol, acetate 24 mmol/litre; Gelofusine® contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 124 mmol/litre; Geloplasma® contains partially hydrolysed and succinylated gelatin (modified liquid gelatin) (as anhydrous gelatin) 30 g (3%), Na⁺ 150 mmol, K⁺ 5 mmol, Mg²⁺ 1.5 mmol, Cl⁻ 100 mmol, lactate 30 mmol/litre; Isoplex® contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 145 mmol, K⁺ 4 mmol, Mg²⁺ 0.9 mmol, Cl⁻ 105 mmol, lactate 25 mmol/litre; Volplex® contains succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 125 mmol/litre.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Infusion

- Gelaspan® (B.Braun Medical Ltd)
  - Gelatin 40 mg per 1 ml Gelaspan 4% infusion 500ml Ecobags | 1 bag (P) £5.55 (Hospital only)
  - Gelofusine® (B.Braun Medical Ltd)
  - Gelatin 40 mg per 1 ml Gelofusine 4% infusion 1 litre Ecobags | 1 bag (P) £9.31
  - Geloplasma® (Fresenius Kabi Ltd)
  - Gelatin 30 mg per 1 ml Geloplasma 3% infusion 500ml Freeflex bags | 20 bag (P) £5.15
  - Isoplex® (Kent Pharmaceuticals Ltd)
  - Gelatin 40 mg per 1 ml Isoplex 4% infusion 500ml bags | 10 bag (P) £75.00 (Hospital only)
  - Volplex® (Kent Pharmaceuticals Ltd)
  - Gelatin 40 mg per 1 ml Volplex 4% infusion 500ml bags | 10 bag (P) £47.00 (Hospital only)

**PLASMA SUBSTITUTES**

Dextran 70 with sodium chloride

- **INDICATIONS AND DOSE**
  - Initial treatment of hypovolaemia with hypotension induced by traumatic injury

  - **BY INTRAVENOUS INFUSION**
    - Adult: 250 ml, to be given over 2–5 minutes using RescueFlow®, followed immediately by administration of isotonic fluids.

- **CAUTIONS**
  - Cardiac disease · hyperosmolality · severe hypoglycaemia · severe liver disease

- **SIDE-EFFECTS**
  - Anaphylactic reaction

- **PREGNANCY**
  - Avoid—reports of anaphylaxis in mother causing fetal anoxia, neurological damage and death.

- **RENAL IMPAIRMENT**
  - Use with caution.

- **MONITORING REQUIREMENTS**
  - Where possible, monitor central venous pressure.
  - Urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.
  - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

- **EFFECT ON LABORATORY TESTS**
  - Can interfere with some laboratory tests—dextran may interfere with blood group cross-matching or biochemical measurements, and these should be carried out before infusion is begun.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Dextran 70 is dextran with an average molecular weight of about ‘70 000’.

- **MEDICINAL FORMS**
  - No licensed medicines listed.

Albinum solution human 200 mg per 1 ml Albutein 20% solution for infusion 100ml vials | 1 vial (P) £9
  - Albutein 20% solution for infusion 50ml vials | 1 vial (P) £8
  - Biotest (Biotest UK Ltd)
  - Albinum solution human 50 mg per 1 ml Human Albinum Biotest 5% solution for infusion 250ml vials | 1 vial (P) £5
  - Albinum solution human 200 mg per 1 ml Human Albinum Biotest 20% solution for infusion 50ml vials | 1 vial (P) £8
  - Human Albinum Biotest 20% solution for infusion 100ml vials | 1 vial (P) £9
  - Grifols (Grifols UK Ltd)
    - Albinum solution human 50 mg per 1 ml Human albinum Grifols 5% solution for infusion 500ml bottles | 1 bottle (P) £42.75
    - Human albinum Grifols 5% solution for infusion 250ml bottles | 1 bottle (P) £21.38
    - Human albinum Grifols 5% solution for infusion 100ml bottles | 1 bottle (P) £9.30
  - Zenalb (Bio Products Laboratory Ltd)
    - Albinum solution human 45 mg per 1 ml Zenalb 4.5% solution for infusion 250ml bottles | 1 bottle (P) £46.80
    - Zenalb 4.5% solution for infusion 500ml bottles | 1 bottle (P) £55.02
    - Albinum solution human 200 mg per 1 ml Zenalb 20% solution for infusion 100ml bottles | 1 bottle (P) £54.00
    - Zenalb 20% solution for infusion 50ml bottles | 1 bottle (P) £27.00

Notes:

- **cross-matching or biochemical measurements, and these**
  - is dextran with an average molecular weight of about

- **PLASMA SUBSTITUTES**

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 500–1000 ml, use 3.5–4% solution
Magnesium imbalance 1049

1.3 Magnesium imbalance

Magnesium imbalance

Overview
Magnesium is an essential constituent of many enzyme systems, particularly those involved in energy generation; the largest stores are in the skeleton.

Magnesium salts are not well absorbed from the gastrointestinal tract, which explains the use of magnesium sulfate p. 1051 as an osmotic laxative. Magnesium is excreted mainly by the kidneys and is therefore retained in renal failure, but significant hypermagnesaemia (causing muscle weakness and arrhythmias) is rare.

Hypomagnesaemia
Since magnesium is secreted in large amounts in the gastrointestinal fluid, excessive losses in diarrhoea, stoma or fistula are the most common causes of hypomagnesaemia; deficiency may also occur in alcoholism or as a result of treatment with certain drugs. Hypomagnesaemia often causes secondary hypocalcaemia, and also hypokalaemia and hyponatraemia.

Symptomatic hypomagnesaemia is associated with a deficit of 0.5–1 mmol/l; up to 160 mmol Mg2+ over up to 5 days may be required to replace the deficit (allowing for urinary losses). Magnesium is given initially by intravenous infusion or by intramuscular injection of magnesium sulfate; the intramuscular injection is painful. Plasma magnesium concentration should be measured to determine the rate and duration of infusion and the dose should be reduced in renal impairment. To prevent recurrence of the deficit, magnesium may be given by mouth, but there is limited evidence of benefit. Magnesium aspartate powder for oral solution p. 1050 is available as a licensed preparation and, magnesium glycerophosphate tablets and liquid p. 1050 [unlicensed] are available from ‘special-order’ manufacturers or specialist importing companies.

Arrhythmias
Magnesium sulfate injection has also been recommended for the emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia (when hypomagnesaemia may also be present) and when salves of rapid ventricular tachycardia show the characteristic twisting wave front known as torsade de pointes.

Myocardial infarction
Limited evidence that magnesium sulfate prevents arrhythmias and reperfusion injury in patients with suspected myocardial infarction has not been confirmed by large studies. Routine use of magnesium sulfate for this purpose is not recommended.

Eclampsia and pre-eclampsia
Magnesium sulfate injection is the drug of choice for the treatment of seizures and the prevention of recurrent...
seizures in women with eclampsia. Regimens may vary between hospitals. Calcium gluconate injection p. 1045 is used for the management of magnesium toxicity.

Magnesium sulfate injection is also of benefit in women with pre-eclampsia in whom there is concern about developing eclampsia. The patient should be monitored carefully.

1.3a Hypomagnesaemia

**ELECTROLYTES AND MINERALS > MAGNESIUM**

**Magnesium aspartate**

- **INDICATIONS AND DOSE**
  - Treatment and prevention of magnesium deficiency
  - **BY MOUTH**
  - Adult: 10–20 mmol daily, taken as 1–2 sachets of Magnaspartate® powder.

- **CONTRA-INDICATIONS** Disorders of cardiac conduction
- **INTERACTIONS** → Appendix 1: magnesium

- **SIDE-EFFECTS**
  - Uncommon: Diarrhoea, faeces soft
  - Rare or very rare: Fatigue, hypermagnesaemia
  - Frequency not known: Gastrointestinal irritation

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Side-effects generally occur at higher doses; if side-effects (such as diarrhoea) occur, consider interrupting treatment and restarting at a reduced dose.

- **OVERDOSE**
  - Symptoms of hypermagnesaemia may include nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, reflexes absent (due to neuromuscular blockade), respiratory depression, speech slurred, diplopia, muscle weakness, arrhythmias, coma, and cardiac arrest.

- **RENAL IMPAIRMENT** Avoid in severe impairment (eGFR less than 30 mL/minute/1.73²).
- **DIRECTIONS FOR ADMINISTRATION** Dissolve sachet contents in 50–200 mL water, tea or orange juice and take immediately.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Magnaspartate® contains magnesium aspartate 6.5 g (10 mmol Mg²⁺)/sachet.

- **PATIENT AND CARER ADVICE** Patients and carers should be given advice on how to administer magnesium aspartate powder.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder

  - **Powder**
    - Magnescoid (Imported (Germany))
    - Magnesium (as Magnesium aspartate hydrochloride) 121.5 mg Magnescoid (magnesium 5mmol) oral powder 5 sachets
    - Magnaspartate (KoRa Healthcare)
    - Magnesium (as Magnesium aspartate) 243 mg Magnaspartate 243mg/magnesium 10mmol oral powder sachets | 10 sachet (£33.35)

- **DOSE EQUIVALENCE AND CONVERSION**
  - Magnesium glycerocephosphate 1 g is approximately equivalent to Mg²⁺ 4 mmol or magnesium 97 mg.

**NEOMAG® CHEWABLE TABLETS**

- **Hypomagnesaemia**
  - **BY MOUTH**
  - Adult: Initially 1–2 tablets 3 times a day, dose to be adjusted according to the serum total magnesium level.

- **DOSE EQUIVALENCE AND CONVERSION**
  - Each Neomag® chewable tablet contains Mg²⁺ 4 mmol or magnesium 97 mg.

- **UNLICENSED USE** Preparations other than Neomag® are not licensed for use.

- **INTERACTIONS** → Appendix 1: magnesium

- **SIDE-EFFECTS** Diarrhoea, hypermagnesaemia

- **OVERDOSE** Symptoms of hypermagnesaemia may include nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, reflexes absent (due to neuromuscular blockade), respiratory depression, speech slurred, diplopia, muscle weakness, arrhythmias, coma, and cardiac arrest.

- **RENAL IMPAIRMENT** Increased risk of toxicity.

- **Dose adjustments** Avoid or reduce dose.

- **NEOMAG® CHEWABLE TABLETS** Manufacturer advises to avoid in severe impairment.

- **MONITORING REQUIREMENTS** Manufacturer advises to monitor serum magnesium levels every 3–6 months.

- **DIRECTIONS FOR ADMINISTRATION** Neomag® chewable tablets Manufacturer advises that tablets may be broken into quarters and chewed or swallowed with water.

**SCOTTISH MEDICINES CONSORTIUM (SMC) DECISIONS**

The Scottish Medicines Consortium (SMC) has advised (September 2017) that magnesium glycerocephosphate (Neomag®) is accepted for use within NHS Scotland as an oral magnesium supplement for the treatment of patients with chronic magnesium loss, hypomagnesaemia or drug-induced hypomagnesaemia.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, powder

  - **Tablet**
    - Mag-4 (Ennogen Healthcare Ltd)
    - Magnesium (as Magnesium glycerocephosphate) 9.72 mg Mag-4 (magnesium 9.72mg (4mmol)) tablets | 30 tablet (£84.50)

  - **Oral solution**
    - LiquiMag GP (Fontus Health Ltd)
    - Magnesium (as Magnesium glycerocephosphate) 24.25 mg per 1 mL LiquiMag GP (magnesium 121.25mg/5ml (5mmol/5ml)) oral solution sugar-free | 200 mL £49.99
    - MagnaPhos (TriOn Pharma Ltd)
    - Magnesium (as Magnesium glycerocephosphate) 19.44 mg per 1 mL MagnaPhos (magnesium 97.2mg/5ml (4mmol/5ml)) oral solution | 200 mL £37.87 DT = £37.84
    - Magnesium (as Magnesium glycerocephosphate) 24.25 mg per 1 mL MagnaPhos (magnesium 121.25mg/5ml (5mmol/5ml)) oral solution | 200 mL £37.87 DT = £37.87

  - **Chewable tablet**
    - EXCIPENTS: May contain Aspartame
    - MagnEss Gly (Essential-Healthcare Ltd)
    - Magnesium (as Magnesium glycerocephosphate) 9.72 mg MagnEss Gly 9.72mg (4mmol) chewable tablets sugar-free | 50 tablet £13.89 DT = £22.77
    - MagnaPhate (Arjun Products Ltd)
    - Magnesium (as Magnesium glycerocephosphate) 9.72 mg MagnaPhate (magnesium 9.72mg (4mmol)) chewable tablets sugar-free | 50 tablet £22.64 DT = £22.77
Magnesium sulfate

**INDICATIONS AND DOSE**

Severe acute asthma | Continuing respiratory deterioration in anaphylaxis

- **BY INTRAVENOUS INFUSION**
  - Child 2-17 years: 40 mg/kg (max. per dose 2 g), to be given over 20 minutes
  - Adult: 1.2–2 g, to be given over 20 minutes

Prevention of seizures in pre-eclampsia

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 4 g, to be given over 5–15 minutes, followed by (by intravenous infusion) 1 gram/hour for 24 hours, if seizure occurs, additional dose of 2 g by intravenous injection to be administered

Treatment of seizures and prevention of seizure recurrence in eclampsia

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Up to 40 g, given over a period of up to 5 days, dose given depends on the amount required to replace the deficit (allowing for urinary losses)

**Hypomagnesaemia**

- **BY INTRAVENOUS INFUSION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: Up to 40 g, given over a period of up to 5 days, dose given depends on the amount required to replace the deficit (allowing for urinary losses)

**Hypomagnesaemia maintenance (e.g. in intravenous nutrition)**

- **BY INTRAVENOUS INFUSION, OR BY INTRAMUSCULAR INJECTION**
  - Adult: 2.5–5 g daily, usual dose 3 g daily

Emergency treatment of serious arrhythmias

- **BY INTRAVENOUS INJECTION**
  - Adult: 2 g, to be given over 10–15 minutes, dose may be repeated once if necessary

Rapid bowel evacuation (acts in 2–4 hours)

- **BY MOUTH**
  - Adult: 5–10 g, dose to be mixed in a glass of water, taken preferably before breakfast

**DOSE EQUIVALENCE AND CONVERSION**

- Magnesium sulfate heptahydrate 1 g equivalent to Mg²⁺ approx. 4 mmol.

**UNLICENSED USE**

- Unlicensed indication in severe acute asthma and continuing respiratory deterioration in anaphylaxis.

**CONTRA-INDICATIONS**

- With oral use in rapid bowel evacuation—acute gastrointestinal conditions (in adults)

**CAUTIONS**

- With oral use in rapid bowel evacuation—elderly and debilitated patients (in adults)

**INTERACTIONS**

- Appendix 1: magnesium

**SIDE-EFFECTS**

- Rare or very rare

- With oral use in Paralytic ileus (in adults)

- Frequency not known

- With intravenous use Electrolyte imbalance

- With oral use Diarrhoea (in adults) - gastrointestinal discomfort (in adults) - hypermagnesaemia (in adults)

**Overdose**

- Symptoms of hypermagnesaemia may include nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, reflexes absent (due to neuromuscular blockade), respiratory depression, speech slurred, diplopia, muscle weakness, arrhythmias, coma, and cardiac arrest.

**PREGNANCY**

- When used for Hypomagnesaemia or Arrhythmias or Prevention of seizures in pre-eclampsia or Treatment of seizures and prevention of seizure recurrence in eclampsia or Severe acute asthma or Continuing respiratory deterioration in anaphylaxis Not known to be harmful for short-term intravenous administration in eclampsia, but excessive doses in third trimester cause neonatal respiratory depression. Sufficient amount may cross the placenta in mothers treated with high doses e.g. in pre-eclampsia, causing hypotonia and respiratory depression in newborns.

**HEPATIC IMPAIRMENT**

- Avoid in hepatic coma if risk of renal failure.

**RENAL IMPAIRMENT**

- Increased risk of toxicity.
  - Dose adjustments: Avoid or reduce dose.

**MONITORING REQUIREMENTS**

- Monitor blood pressure, respiratory rate, urinary output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech).

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use In severe hypomagnesaemia administer initially via controlled infusion device (preferably syringe pump). For intravenous injection, in arrhythmias, hypomagnesaemia, eclampsia, and pre-eclampsia, give continuously in Glucose 5% or Sodium chloride 0.9%. Concentration of magnesium sulfate heptahydrate should not exceed 20% (200 mg/mL or 0.8 mmol/mL Mg²⁺); dilute 1 part of magnesium sulfate injection 50% with at least 1.5 parts of water for injections. Max. rate 150 mg/minute (0.6 mmol/minute Mg²⁺).

**PRESCRIBING AND DISPENSING INFORMATION**

- With intramuscular use or intravenous use The BP directs that the label states the strength as the % w/v of magnesium sulfate heptahydrate and as the approximate concentration of magnesium ions (Mg²⁺) in mmol/mL. Magnesium Sulfate Injection BP is a sterile solution of Magnesium Sulfate Heptahydrate.

**EXCEPTIONS TO LEGAL CATEGORY**

- With oral use in adults Magnesium sulfate is on sale to the public as Epsom Salts.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, solution for injection, infusion, solution for infusion

**Solution for injection**

- **Magnesium sulfate (Non-properitary)**
  - Magnesium sulfate heptahydrate 500 mg per 1 ml
  - Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 10ml ampoules | 10 ampoule (Pfizer) £21.70–£21.71 DT = £21.71 | 50 ampoule (Pfizer) £21.71
  - Magnesium sulfate 50% (magnesium 2mmol/ml) solution for injection 20ml vials | 10 vial (Pfizer) £57.40
Blood and nutrition
regimens, see Intravenous nutrition p.
parenteral nutrition dehypophosphataemic vitamin D-resistant rickets. addition to vitamin D in a small minority of patients with analogue or calcimimetics.
concomitant use of a calcium supplement, a vitamin D development of renal bone disease; this could include the part of a multiple therapeutic approach to control the disease on haemodialysis or peritoneal dialysis. It is used as treatment of patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 4 mmol/litre or more that cannot be controlled by a phosphate supplements; efficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis.
For phosphate requirements in total parenteral nutrition regimens, see Intravenous nutrition p. 1071.

Phosphate-binding agents
Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used as phosphate binding agents and can cause aluminium accumulation.
Sevelamer p. 1054 is licensed for the treatment of hyperphosphataemia in patients on haemodialysis or peritoneal dialysis. Sevelamer carbonate is also licensed for the treatment of patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more.
Lanthanum p. 1053 is licensed for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), and in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet.
Sucroferric oxyhydroxide p. 1054 is licensed for the control of hyperphosphataemia in patients with chronic kidney disease on haemodialysis or peritoneal dialysis. It is used as part of a multiple therapeutic approach to control the development of renal bone disease; this could include the concomitant use of a calcium supplement, a vitamin D analogue or calcimimetics.

1.4 Phosphate imbalance

Phosphate imbalance

Phosphate supplements
Oral phosphate supplements p. 1055 may be required in addition to vitamin D in a small minority of patients with hyperphosphataemic vitamin D-resistant rickets.
Phosphate infusion is occasionally needed in alcohol dependence or in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis.

Phosphate-binding agents
Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used as phosphate binding agents and can cause aluminium accumulation.

Sevelamer p. 1054 is licensed for the treatment of hyperphosphataemia in patients on haemodialysis or peritoneal dialysis. Sevelamer carbonate is also licensed for the treatment of patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more.
Lanthanum p. 1053 is licensed for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), and in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet.
Sucroferric oxyhydroxide p. 1054 is licensed for the control of hyperphosphataemia in patients with chronic kidney disease on haemodialysis or peritoneal dialysis. It is used as part of a multiple therapeutic approach to control the development of renal bone disease; this could include the concomitant use of a calcium supplement, a vitamin D analogue or calcimimetics.
**Hyperphosphataemia**

**INDICATIONS AND DOSE**

Hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) | Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet

- **BY MOUTH**
  - Adult: 1.5–3 g daily in divided doses, dose to be adjusted according to serum-phosphate concentration every 2–3 weeks, to be taken with or immediately after meals

**CAUTIONS**

Acute peptic ulcer - bowel obstruction - Crohn’s disease - ulcerative colitis

**INTERACTIONS** → Appendix 1: lanthanum

**SIDE-EFFECTS**

- **Common or very common** Constipation - diarrhoea - electrolyte imbalance - gastrointestinal discomfort - gastrointestinal disorders - headache - nausea - vomiting
- **Uncommon** Alopecia - appetite abnormal - arthralgia - asthenia - burping - chest pain - dizziness - dry mouth - eosinophilia - hyperglycaemia - hyperhidrosis - hyperparathyroidism - increased risk of infection - irritable bowel syndrome - malaise - myalgia - oral disorders - osteoporosis - pain - peripheral oedema - taste altered - thirst - vertigo - weight decreased

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises caution—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution (may be excreted in bile—possible risk of slower elimination and increased plasma concentrations in patients with reduced bile flow)—monitor liver function tests.

**DIRECTIONS FOR ADMINISTRATION**

Tablets are to be chewed. Each sachet of powder to be mixed with soft food and consumed within 15 minutes.

**PATIENT AND CARER ADVICE**

Patient and carers should be given advice on how to administer lanthanum tablets and powder.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. 286/06

The Scottish Medicines Consortium has advised (May 2007) that lanthanum chewable tablets (Fosrenol®) are accepted for restricted use within NHS Scotland for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis, as a second-line agent, where a non-aluminium, non-calcium phosphate binder is required.

SMC No. 640/10

The Scottish Medicines Consortium has advised (October 2010) that lanthanum (Fosrenol®) is not recommended for use within NHS Scotland for the control of hyperphosphataemia in patients with chronic renal failure not on dialysis with serum phosphate levels >1.78 mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels, as the clinical and economic analysis presented was not demonstrated.

SMC No. 821/12

The Scottish Medicines Consortium has advised (December 2012) that lanthanum oral powder (Fosrenol®) is accepted for restricted use within NHS Scotland as a second-line agent in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or CAPD.
Sevelamer  

**INDICATIONS AND DOSE**

RENAGEL®  
Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis  
- **BY MOUTH**  
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be given with meals and adjusted according to serum-phosphate concentration; usual dose 2.4–12 g daily in 3 divided doses

RENAVELA® 2.4G ORAL POWDER SACHETS  
Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis: Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more  
- **BY MOUTH**  
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be taken with meals and adjusted according to serum-phosphate concentration every 2–4 weeks—consult product literature; usual dose 6 g daily in 3 divided doses

RENAVELA® 800MG TABLETS  
Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis: Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more  
- **BY MOUTH**  
  - Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be taken with meals and adjusted according to serum-phosphate concentration every 2–4 weeks; usual dose 6 g daily in 3 divided doses

**CONTRA-INDICATIONS**  
Bowel obstruction

**CAUTIONS**  
Gastro-intestinal disorders

**SIDE-EFFECTS**  
- Common or very common: Constipation, diarrhoea, gastrointestinal discomfort, gastrointestinal disorders, nausea, vomiting
- Frequency not known: Skin reactions

**PREGNANCY**  
Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**  
RENAVELA® 2.4G ORAL POWDER SACHETS  
Unlikely to be present in milk (however, manufacturer advises avoid).

Sucroferric oxyhydroxide  

**INDICATIONS AND DOSE**

Hyperphosphataemia in patients with chronic kidney disease on haemodialysis or peritoneal dialysis  
- **BY MOUTH**  
  - Adult: Initially 1.5 g daily in 3 divided doses, dose to be taken with meals, then adjusted in steps of 500 mg every 2–4 weeks, dose adjusted according to serum-phosphate concentration; maintenance 1.5–2 g daily in divided doses; maximum 3 g per day

**CONTRA-INDICATIONS**  
Haemochromatosis, iron accumulation disorders

**CAUTIONS**  
Gastrointestinal disorders, hepatic disorders, major gastrointestinal surgery, peritonitis in the last 3 months

**SIDE-EFFECTS**  
- Common or very common: Constipation, diarrhoea, gastrointestinal discomfort, gastrointestinal disorders, nausea, product taste abnormal, tooth discolouration, vomiting
- Uncommon: Dysphagia, dyspnoea, electrolyte imbalance, fatigue, headache, skin reactions, tongue discolouration

www.getintopharma.com
1.4b Hypophosphataemia

LAXATIVES  OSMOTIC LAXATIVES

Phosphate

- INDICATIONS AND DOSE
  - Treatment of moderate to severe hypophosphatemia
    - BY INTRAVENOUS INFUSION
      - Adult: (consult product literature)
  - Established hypophosphataemia (with monobasic potassium phosphate)
    - BY INTRAVENOUS INFUSION
      - Adult: 9 mmol every 12 hours, increased if necessary up to 0.5 mmol/kg (max. per dose 50 mmol), increased dose to be used in critically ill patients; dose to be infused over 6–12 hours, according to severity
  - Vitamin D-resistant hypophosphatemic osteomalacia
    - BY MOUTH USING EFFERVESCENT TABLETS
      - Adult: 4–6 tablets daily, using Phosphate Sandoz®.

- SIDE-EFFECTS
  - COMMON SIDE-EFFECTS
    - Diarrhoea
  - SPECIFIC SIDE-EFFECTS
    - With intravenous use: Acute kidney injury · extravasation necrosis · hypocalcaemia · hypotension · metastatic calcification · oedema
    - With oral use: Abdominal distress
  - SIDE-EFFECTS, FURTHER INFORMATION
    - Diarrhoea is a common side-effect and should prompt a reduction in dosage.
  - RENAL IMPAIRMENT
    - Dose adjustments: Reduce dose.
    - Monitoring: Monitor closely in renal impairment.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Chewable tablet
    - Phosphate Sandoz (HK Pharma Ltd) ▼
    - Iron (as Sucroferric oxyhydroxide) 500 mg
  - Solution for infusion
    - Sodium dihydrogen phosphate anhydrous 1.936 gram
      - 100 tablet £19.39 DT = £19.39
  - Infusion
    - Phosphate (Non-proprietary)
      - Potassium dihydrogen phosphate 136 mg per 1 ml
      - Potassium dihydrogen phosphate 13.6% (potassium 10mmol/10ml) solution for infusion 10ml ampoules: 10 ampoule £101.96 DT = £101.96

1.5 Potassium imbalance

1.5a Hyperkalaemia

Calcium polystyrene sulfonate

- INDICATIONS AND DOSE
  - Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
    - BY MOUTH
      - Adult: 15 g 3–4 times a day
    - BY RECTUM
      - Adult: 30 g, retained for 9 hours followed by irrigation to remove resin from colon

- CONTRA-INDICATIONS
  - Hyperparathyroidism · metastatic carcinoma · multiple myeloma · obstructive bowel disease · sarcoidosis

- INTERACTIONS
  - Appendix 1: polystyrene sulfonate

- SIDE-EFFECTS
  - Appetite decreased · constipation (discontinue—avoid magnesium-containing laxatives) · diarrhoea · electrolyte imbalance · epigastric discomfort · gastrointestinal disorders · gastrointestinal necrosis (in combination with sorbitol) · hypercalcaemia (in dialysed patients and occasionally in those with renal impairment) · increased risk of infection · nausea · vomiting

- PREGNANCY
  - Manufacturers advise use only if potential benefit outweighs risk—no information available.

- BREAST FEEDING
  - Manufacturers advise use only if potential benefit outweighs risk—no information available.

- MONITORING REQUIREMENTS
  - Monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre).

- DIRECTIONS FOR ADMINISTRATION
  - With rectal use: Mix each 30 g of resin with 150 mL of water or 10% glucose.
Patiromer calcium 13-Sep-2018

**INDICATIONS AND DOSE**

**Hyperkalaemia**
- **BY MOUTH**
  - Adult: Initially 8.4 g once daily; adjusted in steps of 8.4 g as required, dose adjustments should be made at intervals of at least one week; maximum 25.2 g per day

**PHARMACOKINETICS**
- Onset of action 4–7 hours.

**CAUTIONS** Risk factors for hyperkalaemia (calcium partially released from counterion complex) - severe gastrointestinal disorders (ischaemia, necrosis, and intestinal perforation reported with other potassium binders)

**INTERACTIONS** → Appendix 1: patiromer calcium

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - constipation - diarrhoea - flatulence - hypomagnesaemia
- **Uncommon** Nausea - vomiting

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available (although no effects on the infant are anticipated).

**MONITORING REQUIREMENTS** Manufacturer advises monitor for electrolyte disturbances, particularly plasma-potassium (as clinically indicated) and plasma-magnesium (continue to monitor for at least 1 month after initiation of treatment).

**DIRECTIONS FOR ADMINISTRATION**
- Manufacturer advises Veltassa® should be mixed with approx. 40 mL of water, then stirred and mixed with a further approx. 40 mL of water; the powder will not dissolve. More water may be added as needed. The mixture should be taken within 1 hour of preparation. Apple juice or cranberry juice may be used instead of water, other liquids should be avoided as they may contain high amounts of potassium.
- **HANDLING AND STORAGE** Store in a refrigerator (2–8°C) prior to dispensing; once dispensed, patient may store below 25°C for up to 6 months.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

SMC No. SMC2084

The Scottish Medicines Consortium (SMC) has advised (August 2018) that patiromer calcium (Veltassa®) is not recommended for use within NHS Scotland for the treatment of hyperkalaemia in adults as the economic case was not demonstrated.

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**Sodium polystyrene sulfonate**

**INDICATIONS AND DOSE**

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
- **BY MOUTH**
  - Adult: 15 g 3–4 times a day
  - **BY RECTUM**
  - Adult: 30 g, retain for 9 hours followed by irrigation to remove resin from colon

**CONTRA-INDICATIONS** Obstructive bowel disease

**CAUTIONS** Congestive heart failure - hypertension - oedema

**INTERACTIONS** → Appendix 1: polystyrene sulfonate

**SIDE-EFFECTS** Appetite decreased - bezoar - constipation (discontinue - avoid magnesium-containing laxatives) - diarrhoea - electrolyte imbalance - epigastric discomfort - gastrointestinal disorders - increased risk of infection - nausea - necrosis (in combination with sorbitol) - vomiting

**PREGNANCY** Manufacturers advise use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Manufacturers advise use only if potential benefit outweighs risk—no information available.

**RENAL IMPAIRMENT** Use with caution.

**MONITORING REQUIREMENTS** Monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre).

**DIRECTIONS FOR ADMINISTRATION**
- With rectal use Mix each 30 g of resin with 150 mL of water or 10% glucose.
- With oral use Administer dose (powder) in a small amount of water or honey—do not give with fruit juice or squash, which have a high potassium content.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Powder**

**CAUTIONARY AND ADVISORY LABELS** 13
- Veltassa® (Vifor Fresenius Medical Care Renal Pharma UK Ltd)
- Patiromer calcium (as Patiromer sorbitex calcium)
- Patiromer calcium (as Patiromer sorbitex calcium)

**Sodium polystyrene sulfonate 999.34 mg per 1 gram** Resonium A powder sugar-free | 454 gram (P) £81.11 DT = £81.11

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www.getintopharma.com
1.5b Hypokalaemia

**ELECTROLYTES AND MINERALS** > **POTASSIUM**

### Potassium bicarbonate with potassium acid tartrate

#### INDICATIONS AND DOSE

**Hyperkalaemic acidosis associated with potassium deficiency (as in some renal tubular and gastrointestinal disorders)**
- **BY MOUTH**
- **Adults:** (consult product literature)

#### CONTRA-INDICATIONS

- Hypochloraemia · plasma-potassium concentration above 5 mmol/litre

#### CAUTIONS

- Cardiac disease · elderly

#### SIDE-EFFECTS

- Abdominal pain · diarrhoea · flatulence · nausea · vomiting

#### RENAL IMPAIRMENT

- Avoid in severe impairment.

#### DIRECTIONS FOR ADMINISTRATION

- **Prevention of hypokalaemia (patients with normal diet)**
- **BY INTRAVENOUS INFUSION**
  - **Potassium bicarbonate** 500 mg Potassium bicarbonate 300 mg, Potassium acid tartrate 300 mg
  - Potassium acid tartrate 300 mg, Potassium bicarbonate 500 mg

#### PRESCRIBING AND DISPENSING INFORMATION

- These tablets do not contain chloride.

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

**Effervescent tablet**

- **CAUTIONARY AND ADVISORY LABELS** 13, 21
- **Potassium bicarbonate with potassium acid tartrate (Non-proprietary)**
- **Potassium acid tartrate 300 mg, Potassium bicarbonate 500 mg** Potassium (potassium 6.5mmol) effervescent tablets BPC 1968 | 56 tablet \( \text{MRP} \) £81.27 DT + £90.99

### Potassium chloride

#### INDICATIONS AND DOSE

**Prevention of hypokalaemia (patients with normal diet)**
- **BY MOUTH**
- **Adults:** 2–4 g daily in divided doses

**Electrolyte imbalance**
- **BY INTRAVENOUS INFUSION**
- **Adults:** Dose dependent on deficit or the daily maintenance requirements

#### CONTRA-INDICATIONS

- Plasma-potassium concentration above 5 mmol/litre

#### CAUTIONS

- With intravenous use seek specialist advice in very severe potassium depletion or difficult cases
- With oral use Cardiac disease · elderly · hiatus hernia (with modified-release preparations) · history of peptic ulcer (with modified-release preparations) · intestinal stricture (with modified-release preparations)

#### INTERACTIONS

- **Appendix 1: potassium chloride**

#### SIDE-EFFECTS

**GENERAL SIDE-EFFECTS**

- Hyperkalaemia

**SPECIFIC SIDE-EFFECTS**

- **With oral use** Abdominal cramps · diarrhoea · gastrointestinal disorders · nausea · vomiting

#### RENAL IMPAIRMENT

- Avoid in severe impairment.

**Dose adjustments** Smaller doses must be used in the prevention of hypokalaemia, to reduce the risk of hyperkalaemia.

**Monitoring**

- Close monitoring required in renal impairment—high risk of hyperkalaemia.

#### MONITORING REQUIREMENTS

- **Regular monitoring of plasma-potassium concentration is essential in those taking potassium supplements.**
- **With intravenous use** ECG monitoring should be performed in difficult cases.

#### DIRECTIONS FOR ADMINISTRATION

- **With oral use** Potassium salts are preferably given as a liquid (or effervescent) preparation, rather than modified-release tablets; they should be given as the chloride (the use of effervescent potassium tablets BPC 1968 should be restricted to hyperkalaemic states).
- **With intravenous use** Potassium chloride concentrate must be diluted with not less than 50 times its volume of sodium chloride intravenous infusion 0.9% or other suitable diluent and mixed well. Ready-mixed infusion solutions should be used where possible; alternatively, potassium chloride concentrate as ampoules containing 1.5 g (K 20 mmol) in 10 mL, is thoroughly mixed with 500 mL of sodium chloride 0.9% intravenous infusion and given slowly over 2 to 3 hours with specialist advice and ECG monitoring in difficult cases. For peripheral intravenous infusions, the concentration of potassium should not usually exceed 40 mmol/L. Higher concentrations of potassium chloride may be given in very severe depletion, but require specialist advice.

#### PRESCRIBING AND DISPENSING INFORMATION

**Kay-Cee-L®** contains 1 mmol/mL each of K+ and Cl-.

**Potassium Tablets**

- **With oral use** Do not confuse Effervescent Potassium Tablets BPC 1968 with effervescent potassium chloride tablets. Effervescent Potassium Tablets BPC 1968 do not contain chloride ions and their use should be restricted to hyperkalaemic states.

**PATIENT AND CARER ADVICE**

- Patient or carers should be given advice on how to administer potassium chloride modified-release tablets.
- **Salt substitutes** A number of salt substitutes which contain significant amounts of potassium chloride are readily available as health food products (e.g. LoSalt® and Ruthmol®). These should not be used by patients with renal failure as potassium intoxication may result.

#### LESS SUITABLE FOR PRESCRIBING

- Modified-release tablets are less suitable for prescribing. Modified-release preparations should be avoided unless effervescent tablets or liquid preparations inappropriate.

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release tablet, oral solution, solution for injection, infusion, solution for infusion

**Modified-release tablet**

- **CAUTIONARY AND ADVISORY LABELS** 25, 27
- **Potassium chloride (Imported)**
- **Potassium chloride 600 mg** Kaleorid LP 600mg tablets | 30 tablet \( \text{MRP} \) £N0.30 600mg tablets | 100 tablet \( \text{MRP} \) £N0.85

www.getintopharma.com
Solution for infusion
- Potassium chloride (Non-proprietary)
  - Potassium chloride 150 mg per 1 ml Potassium chloride 15% (potassium 20mmol/10ml) solution for infusion 10ml ampoules | 10 ampoule [PDF] £10.00 | 20 ampoule [PDF] £6.50–£10.70
  - Potassium chloride 200 mg per 1 ml Potassium chloride 20% (potassium 13.3mmol/5ml) solution for infusion 5ml ampoules | 10 ampoule [PDF] £8.00
  - Potassium chloride 20% (potassium 27mmol/10ml) solution for infusion 10ml ampoules | 10 ampoule [PDF] £133.38

Oral solution
- Potassium chloride 75 mg per 1 ml Kay-Cee-L syrup sugar-free | 500 ml £8.77 DT + £8.77

Infusion
- Potassium chloride (Non-proprietary)
  - Potassium chloride 30 mg per 1 ml Potassium chloride 3% (potassium 40mmol/100ml) infusion 100ml bags | 1 bag [PDF] £14.40
  - Potassium chloride 3% (potassium 20mmol/50ml) infusion 50ml bags | 1 bag [PDF] £13.38

CAUTIONARY AND ADVISORY LABELS 21
- Kay-Cee-L (Geistlich Sons Ltd)

Potassium chloride 30 mg per 1 ml Kay-Cee-L syrup sugar-free | 500 ml £8.77 DT + £8.77

1058 Metabolic disorders

2 Metabolic disorders

2.1 Acute porphyrías

Acute porphyrías

Overview

The acute porphyrías (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolevulinic acid dehydratase deficiency porphyria) are hereditary disorders of haem biosynthesis; they have a prevalence of about 1 in 75 000 of the population.

Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute porphyric crises. Since acute porphyrías are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs.

Where there is no safe alternative, drug treatment for serious or life-threatening conditions should not be withheld from patients with acute porphyria. Where possible, the clinical situation should be discussed with a porphyria specialist for advice on how to proceed and monitor the patient. In the UK clinical advice can be obtained from the National Acute Porphyria Service or from the UK Porphyria Medicines Information Service (UKPMIS)—see details below.

Haem arginate p. 1059 is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyric crises.

In the United Kingdom the National Acute Porphyria Service (NAPS) provides clinical support and treatment with haem arginate from two centres (University Hospital of Wales and King’s College Hospital). To access the service telephone (029) 2074 7747 and ask for the Acute Porphyria Service.

Drugs unsafe for use in acute porphyrías

The following list contains drugs on the UK market that have been classified as ‘unsafe’ in porphyria because they have been shown to be porphyrinogenic in animals or in vitro, or have been associated with acute attacks in patients. Absence of a drug from the following lists does not necessarily imply that the drug is safe. For many drugs no information about porphyria is available.

An up-to-date list of drugs considered safe in acute porphyrías is available from the UKPMIS, see Useful resources below.

Further information may be obtained from: porphyria.eu/ and also from:

- The UK Porphyria Medicines Information Service (UKPMIS)
- University Hospital of Wales
- CF14 4XW
- Cardiff
- (029) 2074 2979/3877

Quite modest changes in chemical structure can lead to changes in porphyrinogenicity but where possible general statements have been made about groups of drugs; these should be checked first.

Unsafe Drug Groups (check first)

- Anabolic steroids
- Antidepressants, MAOIs (contact UKPMIS for advice)
- Antidepressants, Tricylic and related (contact UKPMIS for advice)
- Barbiturates (includes primidone and thiopental)
- Contraceptives, hormonal (for detailed advice contact UKPMIS or a porphyria specialist)
- Hormone replacement therapy (for detailed advice contact UKPMIS or a porphyria specialist)
- Imidazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)
- Non-nucleoside reverse transcriptase inhibitors (contact UKPMIS for advice)
- Progestogens (for detailed advice contact UKPMIS or a porphyria specialist)
- Protease inhibitors (contact UKPMIS for advice)
- Sulfonamides (includes co-trimoxazole and sulfasalazine)
- Sulfonylureas (glipizide and glimepiride are thought to be safe)
- Taxanes (contact UKPMIS for advice)
- Triazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)

Unsafe Drugs (check groups above first)

- Aceclofenac
- Alcohol
- Amiodarone
- Aprepitant
- Artemether with lumefantrine
- Bexarotene
- Bosentan
- Busulfan
- Carbamazepine
- Chloral hydrate (although evidence of hazard is uncertain, manufacturer advises avoid)
- Chloramphenicol
- Chloroform (small amounts in medicines probably safe)
- Clemastine
- Clindamycin
- Cocaine
- Danazol
- Dapsone
- Diltiazem
- Disopyramide
- Disulfiram
- Ergometrine
- Ergotamine
- Erythromycin
- Etamsylate
- Ethosuximide
- Etomidate
- Flutamide
- Fosaprepitant
- Fosphenytoin
- Griseofulvin
- Hydralazine
- Iosfamide
- Indapamide
- Indomethacin
- Indinavir
- Indomethacin
- Indinavir
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- Indomethacin
- Indinavir
2.2 Carnitine deficiency

AMINO ACIDS AND DERIVATIVES

Levcarnitin (Carnitine)

- **INDICATIONS AND DOSE**
  - **Primary carnitine deficiency due to inborn errors of metabolism**
    - **BY MOUTH**
      - Adult: Up to 200 mg/kg daily in 2-4 divided doses; maximum 3 g per day
    - **BY SLOW INTRAVENOUS INJECTION**
      - Adult: Up to 100 mg/kg daily in 2-4 divided doses, to be administered over 2-3 minutes
  - **Secondary carnitine deficiency in haemodialysis patients**
    - **INITIALLY BY SLOW INTRAVENOUS INJECTION**
      - Adult: 20 mg/kg, to be administered over 2-3 minutes, after each dialysis session, dosage adjusted according to plasma-carnitine concentration, then (by mouth) maintenance 1 g daily, administered if benefit is gained from first intravenous course

- **CAUTIONS**
  - Diabetes mellitus

- **SIDE-EFFECTS**
  - Rare or very rare Abdominal cramps · diarrhoea · nausea · skin odour abnormal · vomiting

SIDE-EFFECTS, FURTHER INFORMATION Side-effects may be dose-related—monitor tolerance during first week and after any dose increase.

- **PREGNANCY**
  - Appropriate to use; no evidence of teratogenicity in animal studies.

- **RENAL IMPAIRMENT**
  - Accumulation of metabolites may occur with chronic oral administration in severe impairment.

- **MONITORING REQUIREMENTS**
  - Monitoring of free and acyl carnitine in blood and urine recommended.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

  **Solution for injection**
  - **Levcarnitin (Non-proprietary)**
    - L-Carnitine 200 mg per 1 ml Carnitor 1g/5ml solution for injection ampoules | 5 ampoule (50) £59.50
  - **Oral solution**
    - Carnitor (Logixx Pharma Solutions Ltd)
      - L-Carnitine 300 mg per 1 ml L-Carnitine 1.5g/5ml (30%) oral solution paediatric [20 ml (50) £71.40 DT + £71.40 | 40 ml (50) £118.00]
      - Carnitor oral single dose 1g solution sugar-free [10 unit dose (50) £35.00 DT + £35.00]
Chewable tablet
- Carnitor (Logix Pharma Solutions Ltd)
  L-Carnitine 1 gram  Carnitor 1g chewable tablets  | 10 tablet POM £35.00
Capsule
- Levcarnitine (Non-proprietary)
  L-Carnitine 250 mg  Bio-Carnitine 250mg capsules  | 125 capsule £11.06

2.3 Cystinosis

2.3a Nephropathic cystinosis

AMINO ACIDS AND DERIVATIVES

Mercaptamine
(Cysteamine)

- **INDICATIONS AND DOSE**
  Nephropathic cystinosis (specialist use only)
  - **BY MOUTH**
    - Adult (body-weight 50 kg and above): Initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks to avoid intolerance, maintenance 2 g daily in 4 divided doses
  - **TO THE EYE**
    - Adult: Apply 1 drop 4 times a day, to be applied to both eyes (minimum 4 hours between doses); dose may be reduced according to response (minimum daily dose 1 drop in each eye)

- **DOSE EQUIVALENCE AND CONVERSION**
  - With oral use
    - 1.3 g/m² is approximately equivalent to 50 mg/kg.

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**
Mercaptamine has been confused with mercaptopurine; care must be taken to ensure the correct drug is prescribed and dispensed.

**CAUTIONS**
- When used by eye  Contact lens wearers
- With oral use  dose of phosphate supplement may need to be adjusted if transferring from phosphocysteamine to mercaptamine

**SIDE-EFFECTS**
- Common or very common
  - When used by eye (topical)  Dry eye  eye discomfort  eye disorders  - vision blurred
  - With oral use  Appetite decreased  asthenia  breath odour  diarrhoea  drowsiness  encephalopathy  fever  gastrointestinal discomfort  headache  nausea  skin reactions  vomiting
  - Uncommon
    - With oral use  Compression fracture  gastrointestinal ulcer  - hair colour changes  hallucination  - joint hyperextension  leg pain  leucopenia  musculoskeletal disorders  nephrotic syndrome  nervousness  osteopenia  seizure
  - Frequency not known
    - With oral use  Depression  intracranial pressure increased  - papilloedema
  - **ALLERGY AND CROSS-SENSITIVITY**  Contra-indicated if history of hypersensitivity to penicillamine.

**PREGNANCY**
- With oral use  Manufacturer advises avoid—teratogenic and toxic in animal studies.

- **BREAST FEEDING**
  - With oral use  Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - With oral use  Leucocyte-cystine concentration and haematological monitoring required—consult product literature.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Mercaptamine has a very unpleasant taste and smell, which can affect compliance.

- **HANDLING AND STORAGE**
  - When used by eye  Manufacturer advises store in a refrigerator (2–8°C)—after opening store at room temperature up to 25°C for up to 7 days; protect from light.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - Scottish Medicines Consortium (SMC) decisions
    - With oral use  The Scottish Medicines Consortium has advised (November 2017) that mercaptamine (Procysbi®) is not recommended for use within NHS Scotland for the treatment of proven nephropathic cystinosis.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops
    - Gastro-resistant capsule
      - Procysbi (Chiesi Ltd)
      - Mercaptamine (as Mercaptamine bitartrate) 25 mg  Procysbi 25mg gastro-resistant capsules  | 60 capsule POM £335.97
      - Mercaptamine (as Mercaptamine bitartrate) 75 mg  Procysbi 75mg gastro-resistant capsules  | 250 capsule POM £4,199.65
    - Eye drops
      - EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
      - Cystaran (Imported (United States))
        - Mercaptamine (as Mercaptamine hydrochloride) 4.4 mg per 1 ml  Cystaran 0.44% eye drops  | 15 ml POM £8
      - Cystadrops (Recordati Rare Diseases UK Ltd)
        - Mercaptamine (as Mercaptamine hydrochloride) 3.8 mg per 1 ml  Cystadrops 3.8mg/ml eye drops  | 5 ml POM £86.60
  - Capsule

- **CAUTIONARY AND ADVISORY LABELS 21**
  - Cystagon (Recordati Rare Diseases UK Ltd)
    - Mercaptamine (as Mercaptamine bitartrate) 50 mg  Cystagon 50mg capsules  | 100 capsule POM £70.00 DT + £70.00
    - Mercaptamine (as Mercaptamine bitartrate) 150 mg  Cystagon 150mg capsules  | 100 capsule POM £190.00 DT + £190.00

- **2.4 Fabry’s disease**

ENZYMES

Agalsidase alfa

- **DRUG ACTION**
  - Agalsidase alfa, an enzyme produced by recombinant DNA technology are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

- **INDICATIONS AND DOSE**
  - Fabry’s disease (specialist use only)
    - **BY INTRAVENOUS INFUSION**
    - Adult: 200 micrograms/kg every 2 weeks

- **INTERACTIONS**
  - → Appendix 1: agalsidase

- **SIDE-EFFECTS**
  - Common or very common
    - Arrhythmias  - asthenia  chest discomfort  - chills  cough  diarrhoea  dizziness  dyspnœa  excessive tearing  fever  flushing  gastrointestinal discomfort  headache  hoarseness  hypersonia  hypertension  increased risk of infection  influenza like illness  joint disorders  malaise  musculoskeletal discomfort  myalgia  nausea  otoxicity  pain  -
palpitations • peripheral oedema • peripheral swelling • rhinorhoea • sensation abnormal • skin reactions • taste altered • temperature sensation altered • throat complaints • tremor • vomiting

▶ Uncommon Altered smell sensation • angioedema • hypersensitivity • sensation of pressure

▶ Frequency not known Heart failure • hypodipsia • hypotension • myocardial ischaemia

SIDE-EFFECTS, FURTHER INFORMATION Infusion-related reactions; manage by slowing the infusion rate, or minimise by pre-treatment with an antihistamine or corticosteroid — consult product literature.

PREGNANCY Use with caution.

BREAST FEEDING Use with caution — no information available.

DIRECTIONS FOR ADMINISTRATION Administration for intravenous infusion, give intermittently in sodium chloride 0.9%; dilute requisite dose with 100 mL infusion fluid and give over 40 minutes using an in-line filter; use within 3 hours of dilution.

MEDIKLJN FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

▶ Replagal (Shire Pharmaceuticals Ltd)
Agalsidase beta 1 mg per 1 ml Replagal 1.5mg/3.5ml solution for infusion vials | 1 vial (£20.18)

PAEDIATRIC USE

Adult: 35 mg 1061 dilute with at least 50 mL; doses 35–70 mg dilute with at least 100 mL; doses 70–100 mg dilute with at least 250 mL; doses greater than 100 mg dilute with 500 mL and give through an in-line low protein-binding 0.2 micron filter at an initial rate of no more than 15 mg/hour; for subsequent infusions, infusion rate may be increased gradually once tolerance has been established.

MIGALASTAT (Migalastat HCL)

Drug action Migalastat is a pharmacological chaperone that binds to the active sites of certain mutant forms of alpha-galactosidase A, thereby stabilising these mutant forms in the endoplasmic reticulum, and facilitating normal trafficking to lysosomes.

INDICATIONS AND DOSE

Fabry's disease (specialist use only)

▶ BY MOUTH
Adult: 123 mg once daily on alternate days, take at the same time of day, at least 2 hours before or after food

SIDE-EFFECTS

Common or very common Constipation • defaecation urgency • depression • diarrhoea • dizziness • dry mouth • dyspnoea • epistaxis • fatigue • gastrointestinal discomfort • headache • muscle complaints • nausea • pain in extremity • palpitations • proteinuria • sensation abnormal • skin reactions • torture • vertigo

PREGNANCY Manufacturer advises avoid — toxicity in animal studies.

BREAST FEEDING Manufacturer advises avoid — present in milk in animal studies.

RENAL IMPAIRMENT Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS Manufacture advises monitor renal function, echocardiographic parameters and biochemical markers every 6 months.

PATIENT AND CARER ADVICE
Missed doses Manufacturer advises if a dose is missed entirely for the day, the missed dose should not be taken and the next dose should be taken on the normal day and at the normal time (not to be taken on 2 consecutive days).

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
Migalastat for treating Fabry disease (February 2017)
NICE HST4
Migalastat is recommended, within its marketing authorisation, as an option for treating Fabry disease in people over 16 years of age with an amenable mutation, only if migalastat is provided with the discount agreed in the patient access scheme, and only if enzyme replacement therapy would otherwise be offered.

www.nice.org.uk/guidance/hst4

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium (November 2016) has advised that migalastat (Galafold®) is accepted for restricted use within NHS Scotland for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (x-
2.5 Gaucher’s disease

Other drugs used for Gaucher’s disease Miglustat, p. 1066

Eliglustat

BY MOUTH

Adult: 84 mg once daily

Type 1 Gaucher disease (CYP2D6 poor metabolisers) (under expert supervision)

BY MOUTH

Adult: 84 mg twice daily

CONTRA-INDICATIONS Cardiac disease (no information available) - concurrent use of Class IA and Class III antiarrhythmics - long QT syndrome (no information available)

INDICATIONS AND DOSE

Type 1 Gaucher disease (CYP2D6 poor metabolisers) (under expert supervision)

BY MOUTH

Adult: 84 mg once daily

Eliglustat (as Eliglustat tartrate) 84.4 mg Cerdelga 84mg capsules £19,164.96

IMIGLUCERASE

BY INTRAVENOUS INFUSION

Adult: Initially 60 units/kg every 2 weeks; maintenance, adjusted according to response, doses as low as 15 units/kg once every 2 weeks may improve haematological parameters and organomegaly

SIDE-EFFECTS

Common or very common Angioedema - cough - dyspnoea - hypersensitivity - skin reactions


PREGNANCY Manufacturer advises use with caution - limited information available.

BREAST FEEDING No information available.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Eliglustat for treating type 1 Gaucher disease (June 2017)

Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers. Eliglustat is only recommended when the manufacturer provides it with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2017) that eliglustat (Cerdelga (Amicus Therapeutics UK Ltd) ▼) is accepted for use within NHS Scotland for the long-term treatment of adult patients with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Eliglustat is only recommended when the manufacturer advises use with caution for patients with type 1 Gaucher disease who are CYP2D6 poor, intermediate or extensive metabolisers. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

CONTRA-INDICATIONS Cardiac disease (no information available) - concurrent use of Class IA and Class III antiarrhythmics - long QT syndrome (no information available)

INTERACTIONS

Common or very common Arthralgia - constipation - dyspepsia - fatigue - gastrointestinal disorders - nausea - palpitations

Frequency not known Syncpe

PREGNANCY Manufacturer advises avoid—limited information available.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

PRE-TREATMENT SCREENING Manufacturer advises CYP2D6 metaboliser status should be determined before initiation of treatment.

MONITORING REQUIREMENTS

For treatment-naive patients showing less than 20% spleen volume reduction after 9 months of treatment, manufacturer advises monitor for further improvement or consider an alternative treatment.

For patients with stable disease who have switched from enzyme replacement therapy, manufacturer advises monitor for disease progression—consider reinstiution of enzyme replacement therapy or an alternative treatment if response sub-optimal.

PRESCRIBING AND DISPENSING INFORMATION The manufacturer of Cerdelga ® has provided a Prescriber Guide, which includes a prescriber checklist.

PATIENT AND CARER ADVICE A patient alert card should be provided.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Eliglustat for treating type 1 Gaucher disease (June 2017)

Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers. Eliglustat is only recommended when the manufacturer provides it with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (December 2017) that eliglustat (Cerdelga (Amicus Therapeutics UK Ltd) ▼) is accepted for use within NHS Scotland for the long-term treatment of adult patients with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Eliglustat is only recommended when the manufacturer advises use with caution for patients with type 1 Gaucher disease who are CYP2D6 poor, intermediate or extensive metabolisers. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

CONTRA-INDICATIONS Cardiac disease (no information available) - concurrent use of Class IA and Class III antiarrhythmics - long QT syndrome (no information available)

INTERACTIONS

Common or very common Arthralgia - constipation - dyspepsia - fatigue - gastrointestinal disorders - nausea - palpitations

Frequency not known Syncpe

PREGNANCY Manufacturer advises avoid—limited information available.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

PRE-TREATMENT SCREENING Manufacturer advises CYP2D6 metaboliser status should be determined before initiation of treatment.

MONITORING REQUIREMENTS

For treatment-naive patients showing less than 20% spleen volume reduction after 9 months of treatment, manufacturer advises monitor for further improvement or consider an alternative treatment.

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PRESCRIBING AND DISPENSING INFORMATION The manufacturer of Cerdelga ® has provided a Prescriber Guide, which includes a prescriber checklist.

PATIENT AND CARER ADVICE A patient alert card should be provided.
Velaglucerase alfa

**Drug Action** Velaglucerase alfa is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for the treatment of type I Gaucher’s disease.

**Indications and Dose**

**Type I Gaucher’s disease (specialist use only)**
- By intravenous infusion
  - Adult: Initially 60 units/kg every 2 weeks; adjusted according to response to 15–60 units/kg every 2 weeks

**Side-effects**
- Common or very common Arthralgia · asthenia · chest discomfort · dizziness · dyspnoea · fever · flushing · gastrointestinal discomfort · headache · hypersensitivity · hypertension · hypotension · infusion related reaction · nausea · pain · skin reactions · tachycardia
- Electrolytes: May contain sodium chloride

**Further Information** Infusion-related reactions are very common; manage by slowing the infusion rate, or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature. 

**Pregnancy**
- Manufacturer advises use with caution—limited information available.

**Breast Feeding**
- Manufacturer advises caution—no information available.

**Monitoring Requirements**
- Monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur.

**Directions for Administration**
- Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of Cystadane® powder.

**Prescribing and Dispensing Information**
- Betaine should be used in conjunction with dietary restrictions and may be given with supplements of vitamin B12, pyridoxine, and folate under specialist advice.

**National Funding/Access Decisions**
- Scottish Medicines Consortium (SMC) decisions

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<th>Adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism (specialist use only)</th>
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**By MOUTH**
- Adult: 3 g twice daily (max. per dose 10 g), adjusted according to response; maximum 20 g per day

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- Electrolytes: May contain sodium chloride
- Velaglucerase alfa 400 unit
  - VPRIV 400 units powder for solution for infusion vials [1 vial](£1,400.20)

**Methyl Donors**

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**By MOUTH**
- Adult: 3 g twice daily (max. per dose 10 g), adjusted according to response; maximum 20 g per day

**Medicinal Forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Powder**
- Cystadane
  - Recordati Rare Diseases UK Ltd
  - Betaine 1 gram per 1 gram

| Cystadane oral powder | 180 gram | £347.00 DT – £347.00 |

www.getintopharma.com
2.7 Hypophosphatasia

ENZYMES

Asfotase alfa

- **DRUG ACTION** Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase that promotes mineralisation of the skeleton.

- **INDICATIONS AND DOSE**
  - Paediatric-onset hypophosphatasia (initiated by a specialist)
  - Adult: 2 mg/kg 3 times a week, alternatively 1 mg/kg 6 times a week, dosing frequency depends on body-weight—consult product literature for further information

- **CAUTIONS** Hypersensitivity reactions

- **SIDE-EFFECTS**
  - Common or very common: Bruising tendency - chills - cutis laxa - fever - headache - hypersensitivity - irritability - lipohypertrophy - myalgia - nausea - oral hypoesthesia - pain - skin reactions - vasodilatation

- **CAUTIONS, FURTHER INFORMATION**
  - Hypersensitivity reactions. Reactions, including signs and symptoms consistent with anaphylaxis, have occurred within minutes of administration and can occur in patients on treatment for more than one year; if these reactions occur, manufacturer advises immediate discontinuation of treatment and initiation of appropriate medical treatment. For information on re-administration, consult product literature.

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor serum parathyroid hormone and calcium concentrations—supplements of calcium and oral vitamin D may be required.
  - Manufacturer advises periodic ophthalmological examination and renal ultrasounds.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises max. 1 mL per injection site; administer multiple injections if more than 1 mL is required—consult product literature.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8 °C).

- **PATIENT AND CARER ADVICE**
  - Injection guides. The manufacturer has produced injection guides for patients and carers to support training given by health care professionals.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE decisions**
    - Asfotase alfa for treating paediatric-onset hypophosphatasia (August 2017) NICE HST6
    - Asfotase alfa is recommended as an option for treating paediatric-onset hypophosphatasia only:
      - for people who meet the criteria for treatment within the managed access arrangement (see section 4.18 of the guidance), and
      - for the duration of this arrangement and in line with the other conditions it specifies, and
    - when the manufacturer provides asfotase alfa with the confidential commercial terms agreed with NHS England.
    - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
    - [www.nice.org.uk/guidance/HST6](www.nice.org.uk/guidance/HST6)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**
    - Strensiq (Alexion Pharma UK Ltd)
    - Asfotase alfa 40 mg per 1 mL
    - Strensiq 18 mg/0.45 mL solution for injection vials | 12 vial (£50) £12,700.80 (Hospital only)
    - Strensiq 28 mg/0.7 mL solution for injection vials | 12 vial (£50) £15,756.80 (Hospital only)
    - Strensiq 40 mg/mL solution for injection vials | 12 vial (£50) £28,224.00 (Hospital only)
    - Asfotase alfa 100 mg per 1 mL
    - Strensiq 80 mg/0.8 mL solution for injection vials | 12 vial (£50) £56,448.00 (Hospital only)

2.8 Mucopolysaccharidosis

ENZYMES

Elosulfase alfa

- **DRUG ACTION** Elosulfase alfa is an enzyme produced by recombinant DNA technology that provides replacement therapy in conditions caused by N-acetylgalactosamine-6-sulfatase (GALNS) deficiency.

- **INDICATIONS AND DOSE**
  - **Mucopolysaccharidosis IVA (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
    - Adult: 2 mg/kg once weekly

- **CAUTIONS**
  - Elderly—no information available
  - Infusion-related reactions

  - **CAUTIONS, FURTHER INFORMATION**
    - Infusion-related reactions. Infusion-related reactions can occur; manufacturer advises these may be minimised by pre-treatment with an antihistamine and antipyretic, given 30–60 minutes before treatment. If reaction is severe, stop infusion and start appropriate treatment. Caution and close monitoring is advised during re-administration following a severe reaction.

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain - chills - diarrhoea - dizziness - dysphagia - fever - headache - hypersensitivity - infusion related reaction - myalgia - nausea - ophthalmological pain - vomiting

  - **PREGNANCY** Manufacturer advises avoid unless essential—limited information available.

  - **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies.

  - **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Vimizim®), give intermittently in Sodium chloride 0.9%; body-weight under 25 kg, dilute requisite dose to final volume of 100 mL infusion fluid and mix gently, give over 4 hours through in-line filter (0.2 micron) initially at a rate of 3 mL/hour, then increase to a rate of 6 mL/hour after 15 minutes, then increase gradually if tolerated every 15 minutes by 6 mL/hour to max. 36 mL/hour; body-weight...
25 kg or over, dilute requisite dose to final volume of 250 mL and mix gently, give over 4 hours through in-line filter (0.2 micron) initially at a rate of 6 mL/hour, then increase to a rate of 12 mL/hour after 15 minutes, then increase gradually if tolerated every 15 minutes by 12 mL/hour to max. 72 mL/hour.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator at 2–8°C. After dilution use immediately or, if necessary, store at 2–8°C for max. 24 hours, followed by up to 24 hours at 23–27°C.
- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Manufacturer advises patients and carers should be counselled about the effects on driving and performance of skilled tasks—increased risk of dizziness.
- **NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE decisions**
  - Elosulfase alfa for treating mucopolysaccharidosis type IVa (December 2015) NICE HST2
  - Elosulfase alfa, within its marketing authorisation, is recommended for funding for treating mucopolysaccharidosis type IVa (MPS IVa) according to the conditions in the managed access agreement for elosulfase alfa.
  - www.nice.org.uk/guidance/HST2

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

**EXCIPIENTS:** May contain Polysorbates, sorbitol

- **Vimizim** (Biogen Idec Ltd) ▼
- **Elosulfase alfa 1 mg per 1 ml** Vimizim 5mg/5ml concentrate for solution for infusion vials | 1 vial (1065) £522.00

### Galsulfase

- **DRUG ACTION** Galsulfase is a recombinant form of human N-acetylgalactosamine-4-sulfatase.

### Indications and dose

- **Mucopolysaccharidosis VI (specialist use only)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: 1 mg/kg once weekly

- **CAUTIONS** Acute febrile illness (consider delaying treatment) - acute respiratory illness (consider delaying treatment) - infusion-related reactions can occur - respiratory disease

- **SIDE-EFFECTS** Abdominal pain - anemia - chest pain - chills - conjunctivitis - corneal opacity - dysphonia - ear pain - face oedema - hypertension - increased risk of infection - infusion related reaction - malaise - nasal congestion - reflexes absent - umbilical hernia

### Side-effects, further information

Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

- **CONCEPTION AND CONTRACEPTION** Contra-indicated in women of child-bearing potential.
- **PREGNANCY** Manufacturer advises avoid.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Elaprase®), give intermittently in Sodium chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and mix gently; infuse through a 0.2 micron in-line filter; give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours; if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL infusion fluid and give over at least 4 hours.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

- **Naglazyme** (BioMarin Europe Ltd) ▼
- **Galsulfase 1 mg per 1 ml** Naglazyme 5mg/5ml solution for infusion vials | 1 vial (582) £982.00

### Idursulfase

- **DRUG ACTION** Idursulfase is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase.

### Indications and dose

- **Mucopolysaccharidosis II (specialist use only)**
  - **BY INTRAVENOUS INFUSION**
    - Adult: 500 micrograms/kg once weekly

- **CAUTIONS** Acute febrile respiratory illness (consider delaying treatment) - infusion-related reactions can occur - severe respiratory disease

- **SIDE-EFFECTS**
  - **Common or very common** Arthralgia - chest pain - cough - dyspnea - face oedema - hypertension - hypotension - nausea - oedema - respiratory disorders - skin reactions - tongue swelling - tremor - vomiting

- **Frequency not known** Hypersensitivity

### Side-effects, further information

Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

- **CONCEPTION AND CONTRACEPTION** Contra-indicated in women of child-bearing potential.
- **PREGNANCY** Manufacturer advises avoid.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

### Directions for administration

For intravenous infusion (Naglazyme®), give intermittently in Sodium chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and mix gently; infuse through a 0.2 micron in-line filter; give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours; if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL infusion fluid and give over at least 4 hours.

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

### Solution for infusion

- **Elaprase** (Shire Pharmaceuticals Ltd) ▼
- **Idursulfase 2 mg per 1 ml** Elaprase 6mg/3ml concentrate for solution for infusion vials | 1 vial (985) £1,985.00

www.getintopharma.com
Laronidase

- **DRUG ACTION** Laronidase is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in the treatment of non-neurological manifestations of mucopolysaccharidosis I, a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase.

- **INDICATIONS AND DOSE**
  - Non-neurological manifestations of mucopolysaccharidosis I (specialist use only)
    - **BY INTRAVENOUS INFUSION**
      - Adult: 100 units/kg once weekly

- **CAUTIONS** Infusion-related reactions can occur

- **INTERACTIONS** → Appendix 1: laronidase

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain · alopecia · anaphylactic reaction · angioedema · chills · cough · diarrhea · dizziness · dyspnoea · fatigue · fever · flushing · headache · hypotension · influenza like illness · joint disorders · nausea · pain · pallor · paraesthesia · peripheral coldness · respiratory disorders · restlessness · skin reactions · sweat changes · tachycardia · temperature sensation altered · vomiting
  - Frequency not known Cyanosis · hypoxia · oedema

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

- **PREGNANCY** Manufacturer advises avoid unless essential—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor immunoglobulin G (IgG) antibody concentration.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Aldurazyme 
  
  ), give intermittently in Sodium chloride 0.9%; body-weight under 20 kg, use 100 mL infusion fluid; body-weight over 20 kg use 250 mL infusion fluid; withdraw volume of infusion fluid equivalent to volume of laronidase concentrate being added; give through in-line filter (0.22 micron) initially at a rate of 2 units/kg/hour then increase gradually every 15 minutes to max. 43 units/kg/hour.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for infusion**
    - ELECTROLYTES: May contain Sodium
      - Aldurazyme (Genzyme Therapeutics Ltd)
        - Laronidase 100 unit per 1 ml Aldurazyme 500units/5ml solution for infusion vials | 1 vial | £444.70

  - **Medication**
    - There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - Zavesca (Actelion Pharmaceuticals UK Ltd)
    - Miglustat 100 mg | Zavesca 100mg capsules | 84 capsule | £3,934.17 (Hospital only)

2.9 Niemann-Pick type C disease

- **ENZYME INHIBITORS** > GLUCOSYLCERAMIDE SYNTHASE INHIBITORS

Miglustat

- **DRUG ACTION** Miglustat is an inhibitor of glucosylceramide synthase.

- **INDICATIONS AND DOSE**
  - Mild to moderate type I Gaucher’s disease for whom enzyme replacement therapy is unsuitable (under expert supervision)
    - **BY MOUTH**
      - Adult: 100 mg 3 times a day, reduced if not tolerated to 100 mg 1–2 times a day

- **TREATMENT OF PROGRESSIVE NEUROLOGICAL MANIFESTATIONS OF NIEMANN-PICK TYPE C DISEASE (UNDER EXPERT SUPERVISION)**
  - **BY MOUTH**
    - Adult: 200 mg 3 times a day

- **SIDE-EFFECTS**
  - Common or very common Appetite decreased · asthenia · chills · constipation · depression · diarrhoea · dizziness · flatulence · gastrointestinal discomfort · headache · insomnia · libido decreased · malaise · muscle spasms · muscle weakness · nausea · peripheral neuropathy · sensation abnormal · thrombocytopenia · tremor · vomiting · weight decreased

- **CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment. Men should avoid fathering a child during and for 3 months after treatment.

- **PREGNANCY**
  - Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution (no information available).

- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m²

  - **Dose adjustments**
    - For Gaucher’s disease initially 100 mg twice daily if eGFR 50–70 mL/minute/1.73 m².
    - Initially 100 mg once daily if eGFR 30–50 mL/minute/1.73 m².
    - For Niemann-Pick type C disease, initially 200 mg twice daily if eGFR 50–70 mL/minute/1.73 m².
    - Initially 100 mg twice daily if eGFR 30–50 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Monitor cognitive and neurological function.
  - Monitor growth and platelet count in Niemann-Pick type C disease.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
2.10 Pompe disease

ENZYMES

Alglucosidase alfa

- **DRUG ACTION** Alglucosidase alfa is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in Pompe disease, a lysosomal storage disorder caused by deficiency of acid alpha-glucosidase.

- **INDICATIONS AND DOSE**
  - **Pompe disease (specialist use only)**
    - **BY INTRAVENOUS INFUSION**
      - Adult: 20 mg/kg every 2 weeks
  - **CAUTIONS**
    Cardiac dysfunction • infusion-related reactions—consult product literature • respiratory dysfunction

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain • angioedema • arthralgia • chest discomfort • chills • cough • cyanosis • diarrhoea • dizziness • fatigue • feeling hot • fever • flushing • hypotension • irritable • local swelling • muscle complaints • nausea • oedema • pallor • paraesthesia • respiratory disorders • skin reactions • thrombosis • tremor • vomiting
  - **Frequency not known** Abdominal pain • angioedema • apnoea • arthralgia • cardiac arrest • dyspnoea • excessive tearing • eye inflammation • headache • hypotension • nephrotic syndrome • peripheral coldness • proteinuria • vasoconstriction

- **SIDE-EFFECTS, FURTHER INFORMATION** Infusion-related reactions are very common, calling for use of antihistamine, antipyretic, or corticosteroid; consult product literature for details.

- **PREGNANCY** Toxicity in animal studies, but treatment should not be withheld.

- **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor closely if cardiac dysfunction.
  - Monitor closely if respiratory dysfunction.
  - Monitor immunoglobulin G (IgG) antibody concentration.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (**Myozyme®**), give intermittently in Sodium chloride 0.9%; reconstitute 50 mg with 10.3 mL water for injections to produce 5 mg/mL solution; gently rotate vial without shaking; dilute requisite dose with infusion fluid to give a final concentration of 0.5–4 mg/mL; give through a low protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **Myozyme (Genzyme Therapeutics Ltd)**
    - Alglucosidase alfa 50 mg Myozyme 50mg powder for concentrate for solution for infusion vials | 1 vial (£356.06) (Hospital only)

2.11 Tyrosinaemia type I

ENZYME INHIBITORS

4- HYDROXYPHENYLPYRUVATE DIOXYGENASE INHIBITORS

Nitisinone

**(NTBC)**

- **INDICATIONS AND DOSE**
  - Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)
    - **BY MOUTH**
      - Adult: Initially 500 micrograms/kg twice daily, adjusted according to response; maximum 2 mg/kg per day

- **INTERACTIONS**
  - **Appendix 1: nitisinone**

- **SIDE-EFFECTS**
  - **Common or very common**
    - Corneal opacity • eye inflammation • eye pain • granulocytopenia • leucopenia • photophobia • thrombocytopenia
  - **Uncommon**
    - Leucocytosis • skin reactions

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid—adverse effects in animal studies.

- **PRE-TREATMENT SCREENING**
  - Slit-lamp examination of eyes recommended before treatment.

- **MONITORING REQUIREMENTS**
  - Monitor liver function regularly.
  - Monitor platelet and white blood cell count every 6 months.

- **DIRECTIONS FOR ADMINISTRATION**
  - Capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Oral suspension**
  - **Orfadin (Swedish Orphan Biovitrum Ltd)**
    - Nitisinone 4 mg per 1 ml Orfadin 4mg/1ml oral suspension sugar-free | 90 ml (£1,692.00 DT + £1,692.00)
    - Nitisinone 5 mg Nitisinone 5mg capsules | 60 capsule (£845.25)
    - Nitisinone 10 mg Nitisinone 10mg capsules | 60 capsule (£1,546.50)
  - **Orfadin (Swedish Orphan Biovitrum Ltd)**
    - Nitisinone 2 mg Nitisinone 2mg capsules | 60 capsule (£423.00)
    - Nitisinone 5 mg Nitisinone 5mg capsules | 60 capsule (£1,127.00)
    - Nitisinone 10 mg Nitisinone 10mg capsules | 60 capsule (£2,062.00)

- **Capsule**
  - **Nitisinone (Non-proprietary)**
    - Nitisinone 2 mg Nitisinone 2mg capsules | 60 capsule (£564.00)
    - Nitisinone 5 mg Nitisinone 5mg capsules | 60 capsule (£1,000.00)
    - Nitisinone 10 mg Nitisinone 10mg capsules | 60 capsule (£2,062.00)

- **Powder for solution for infusion**
  - **Myozyme (Genzyme Therapeutics Ltd)**
    - Alglucosidase alfa 50 mg Myozyme 50mg powder for concentrate for solution for infusion vials | 1 vial (£356.06) (Hospital only)
2.12 Urea cycle disorders

AMINO ACIDS AND DERIVATIVES

Carglumic acid

- **INDICATIONS AND DOSE**
  - Hyperammonaemia due to N-acetylglutamate synthase deficiency (under expert supervision)
    - By mouth
      - Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma–ammonia concentration; maintenance 5–50 mg/kg twice daily, the total daily dose may alternatively be given in 3–4 divided doses
  - Hyperammonaemia due to organic acidaemia (under expert supervision)
    - By mouth
      - Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma-ammonia concentration, the total daily dose may alternatively be given in 3–4 divided doses

**IMPORTANT SAFETY INFORMATION**

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS
For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

- **SIDE-EFFECTS**
  - Common or very common Hyperhidrosis
  - Uncommon Bradycardia; diarrhoea; fever; vomiting
  - Frequency not known Rash

- **PREGNANCY** Manufacturer advises avoid unless essential—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **DIRECTIONS FOR ADMINISTRATION** Dispersible tablets must be dispersed in at least 5–10 mL of water and taken orally immediately, or administered via a nasogastric tube.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Dispensible tablet**

**CAUTIONARY AND ADVISORY LABELS** 13

- Carglumic acid (Non-proprietary)
  - Carglumic acid 200 mg: Carglumic acid 200mg dispersible tablets sugar-free sugar-free | 5 tablet (POD) £21.69 sugar-free | 60 tablet (POD) £2,624.30
  - Carbaglu (Recordati Rare Diseases UK Ltd)
    - Carbaglu 200 mg: Carbaglu 200mg dispersible tablets sugar-free | 5 tablet (POD) £299.00 sugar-free | 15 tablet (POD) £897.00 sugar-free | 60 tablet (POD) £3,499.00
  - Ucedane (Lucane Pharma Ltd)
    - Ucedane 200 mg: Ucedane 200mg dispersible tablets sugar-free | 60 tablet (POD) £3,300.00

**DRUGS FOR METABOLIC DISORDERS**

AMMONIA LOWERING DRUGS

Glycerol phenylbutyrate

- **DRUG ACTION** Glycerol phenylbutyrate is a nitrogen-binding agent that provides an alternative vehicle for waste nitrogen excretion.

- **INDICATIONS AND DOSE**
  - Urea cycle disorders (specialist use only)
    - By mouth, or by gastrostomy tube, or by nasogastric tube
    - Adult (body surface area up to 1.3 m²): Initially 9.4 g/m² daily in divided doses, usual maintenance 5.3–12.4 g/m² daily in divided doses, each dose should be rounded up to the nearest 0.5 mL and given with each meal. For dose adjustments based on individual requirements—consult product literature
    - Adult (body surface area 1.3 m² and above): Initially 8 g/m² daily in divided doses, usual maintenance 5.3–12.4 g/m² daily in divided doses, each dose should be rounded up to the nearest 0.5 mL and given with each meal. For dose adjustments based on individual requirements—consult product literature

**IMPORTANT SAFETY INFORMATION**

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS
For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

- **CONTRA-INDICATIONS** Treatment of acute hyperammonaemia

- **CAUTIONS** Elderly—limited information available - intestinal malabsorption - pancreatic insufficiency

- **INTERACTIONS** Appendix 1: glycerol phenylbutyrate

- **SIDE-EFFECTS**
  - Common or very common Appetite abnormal - constipation - diarrhoea - dizziness - fatigue - food aversion - gastrointestinal discomfort - gastrointestinal disorders - headache - menstrual cycle irregularities - nausea - oral disorders - peripheral oedema - skin reactions - tremor - vomiting

- **PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure).

- **Dose adjustments** Manufacturer advises use lowest possible dose—consult product literature.

- **RENAL IMPAIRMENT** Manufacturer advises use with caution in severe impairment—no information available.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises may be added to a small amount of apple sauce, ketchup,
or squash puree and used within 2 hours. For administration advice via nasogastric or gastrostomy tube—consult product literature.

- **HANDLING AND STORAGE**  Manufacturer advises discard contents of bottle 14 days after opening.
- **PATIENT AND CARER ADVICE**  Driving and skilled tasks  Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.
- **NATIONAL FUNDING/ACCESS DECISIONS**

### Scottish Medicines Consortium (SMC) decisions

**SNC No. 1342/18**

The Scottish Medicines Consortium (SMC) has advised (August 2018) that glycerol phenylbutyrate (Ravicti<sup>®</sup>) is accepted for use within NHS Scotland as an adjunctive therapy for chronic management of adult and paediatric patients aged 2 months and older with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Glycerol phenylbutyrate must be used with dietary protein restriction and, in some cases, dietary supplements. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

- **MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.
- **SIDE-EFFECTS**

#### Sodium phenylbutyrate

- **INDICATIONS AND DOSE**

  **Long-term treatment of urea cycle disorders**

  (as adjunctive therapy in all patients with neonatal-onset disease and in those with late-onset disease who have a history of hyperammonaemic encephalopathy) (under expert supervision)

  - **BY MOUTH**
  - **Adult:** 9.9–13 g/m<sup>2</sup> daily in divided doses, with meals; maximum 20 g per day

- **INTERACTIONS**

  - **Common or very common**  Abdominal pain · anaemia · appetite decreased · constipation · depression · headache · irritability · leucocytosis · leucopenia · menstrual cycle irregularities · metabolic acidosis · metabolic alkalosis · nausea · oedema · renal tubular acidosis · skin reactions · syncope · taste altered · thrombocytopenia · thrombocytosis · vomiting · weight increased
  - **Uncommon**  Anorectal haemorrhage · aplastic anaemia · arrhythmia · gastrointestinal disorders · pancreatitis

- **CONCEPTION AND CONTRACEPTION**  Manufacturer advises adequate contraception during administration in women of child-bearing potential.

- **PREGNANCY**  Avoid—toxicity in animal studies.

- **BREAST FEEDING**  Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT**  Manufacturer advises caution.

- **RENAL IMPAIRMENT**  Manufacturer advises use with caution (preparations contain significant amounts of sodium).

- **DIRECTIONS FOR ADMINISTRATION**  Granules should be mixed with food before taking. *Ravicti*<sup>®</sup> granules must not be administered by nasogastric or gastrostomy tubes.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution.

#### Granules

- **Ammonaps (Swedish Orphan Biovitrum Ltd)**
  - Sodium phenylbutyrate 940 mg per 1 gram Ammonaps 940mg/g granules sugar-free | 266 gram (POD) £860.00 DT = £860.00
  - **Pheburane** (Lucane Pharma Ltd)
  - Sodium phenylbutyrate 483 mg per 1 gram Pheburane 483mg/g granules | 174 gram (POD) £131.00

#### Tablet

- **Ammonaps (Swedish Orphan Biovitrum Ltd)**
  - Sodium phenylbutyrate 500 mg Ammonaps 500mg tablets | 250 tablet (POD) £493.00 DT = £493.00

### 2.13 Wilson’s disease

#### Other drugs used for Wilson’s disease

Penicillamine, p. 1097

#### ANTIDOTES AND CHELATORS

##### COPPER ABSORPTION INHIBITORS

#### Zinc acetate

- **INDICATIONS AND DOSE**

  **Wilson’s disease (initiated under specialist supervision)**

  - **BY MOUTH**
  - **Adult:** 50 mg 3 times a day (max. per dose 50 mg 5 times a day) adjusted according to response

- **DOSE EQUIVALENT AND CONVERSION**

  Doses expressed as elemental zinc.

- **PHARMACOKINETICS**

  - Symptomatic Wilson’s disease patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect.

- **CAUTIONS**  Portal hypertension (risk of hepatic decompensation when switching from chelating agent)

- **INTERACTIONS**  → Appendix 1: zinc

- **SIDE-EFFECTS**

  - **Common or very common**  Epigastric discomfort (usually transient)
  - **Uncommon**  Leucopenia · sideroblastic anaemia
  - **Frequency not known**  Condition aggravated

- **SIDE-EFFECTS, FURTHER INFORMATION**

  Transient gastric irritation may be reduced if first dose is taken mid-morning or with a little protein.

- **PREGNANCY**

  **Dose adjustments**  Reduce dose to 25 mg 3 times daily adjusted according to plasma-copper concentration and urinary copper excretion.

- **BREAST FEEDING**  Manufacturer advises avoid; present in milk—may cause zinc-induced copper deficiency in infant.
BLOOD AND NUTRITION

Selenium deficiency

Overview
Selenium deficiency can occur as a result of inadequate diet or prolonged parenteral nutrition. A selenium supplement should not be given unless there is good evidence of deficiency.

INDICATIONS AND DOSE
Selenium deficiency
- BY MOUTH, OR BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION
- Adult: 100–500 micrograms daily

3.2 Zinc deficiency

Zinc deficiency

Overview
Zinc supplements should not be given unless there is good evidence of deficiency (hypoproteinaemia sparsely lowers plasma–zinc concentration) or in zinc-losing conditions. Zinc deficiency can occur as a result of inadequate diet or malabsorption; excessive loss of zinc can occur in trauma, burns, and protein-losing conditions. A zinc supplement is given until clinical improvement occurs, but it may need to be continued in severe malabsorption, metabolic disorders, or in zinc-losing states.

Zinc is used in the treatment of Wilson’s disease and acrodermatitis enteropathica, a rare inherited abnormality of zinc absorption. Parenteral nutrition regimens usually include trace amounts of zinc. If necessary, further zinc can be added to intravenous feeding regimens.

ELECTROLYTES AND MINERALS > ZINC

Zinc sulfate

INDICATIONS AND DOSE
Zinc deficiency or supplementation in zinc-losing conditions
- BY MOUTH USING EFFERVESCENT TABLETS
- Child (body-weight up to 10 kg): 22.5 mg daily, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
- Child (body-weight 10–30 kg): 22.5 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in

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Water and taken after food, dose expressed as elemental zinc
- Child (body-weight 31 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
- Adult (body-weight 31 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc

Additional elemental zinc for intravenous nutrition
- By intravenous injection
  - Adults: 6.5 mg daily (Zn + 100 micromol)

Unlicensed use Solvazine® is not licensed for use in acrodermatitis enteropathica.

Interactions → Appendix 1: zinc

Side-effects Diarrhoea - gastritis - gastrointestinal discomfort - nausea - vomiting

Pregnancy Crosses placenta; risk theoretically minimal, but no information available.

Breast feeding Present in milk; risk theoretically minimal, but no information available.

Renal impairment Accumulation may occur in acute renal failure.

Prescribing and dispensing information Each Solvazine® tablet contains zinc sulfate monohydrate 125 mg (45 mg zinc).

Medicinal forms There can be variation in the licensing of different medicines containing the same drug.

Effervescent tablet Cautionary and advisory labels 13, 21
  - Solvazine (Galen Ltd) Zinc sulfate monohydrate 125 mg. Solvazine 125mg effervescent tablets sugar-free | 90 tablet [P] £17.20 DT + £17.20

4 Nutrition (intravenous)

Intravenous nutrition

Overview
When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to ordinary oral or tube feeding—supplemental parenteral nutrition, or may be the sole source of nutrition—total parenteral nutrition (TPN). Indications for this method include preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; severe or prolonged disorders of the gastro-intestinal tract; major surgery, trauma, or burns; prolonged coma or refusal to eat; and some patients with renal or hepatic failure. The composition of proprietary preparations available is given under Proprietary Infusion Fluids for Parenteral Feeding p. 1072.

Parenteral nutrition requires the use of a solution containing amino acids, glucose, fat, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of a 3-litre bag. A single dose of vitamin B₁₂ as hydroxocobalamin p. 1026, is given by intramuscular injection; regular vitamin B₁₂ injections are not usually required unless total parenteral nutrition continues for many months. Folic acid p. 1025 is given in a dose of 15 mg once or twice each week, usually in the nutrition solution. Other vitamins are usually given daily; they are generally introduced in the parenteral nutrition solution. Alternatively, if the patient is able to take small amounts by mouth, vitamins may be given orally.

The nutrition solution is infused through a central venous catheter inserted under full surgical precautions. Alternatively, infusion through a peripheral vein may be used for supplementary as well as total parenteral nutrition for periods of up to a month, depending on the availability of peripheral veins; factors prolonging cannula life and preventing thrombophlebitis include the use of soft polyurethane paediatric cannulas and use of feeds of low osmolality and neutral pH. Only nutritional fluids should be given by the dedicated intravenous line.

Before starting, the patient should be well oxygenated with a near normal circulating blood volume and attention should be given to renal function and acid-base status. Appropriate biochemical tests should have been carried out beforehand and serious deficits corrected. Nutritional and electrolyte status must be monitored throughout treatment.

Complications of long-term parenteral nutrition include gall bladder sludging, gall stones, cholestasis and abnormal liver function tests. For details of the prevention and management of parenteral nutrition complications, specialist literature should be consulted.

Protein is given as mixtures of essential and non-essential synthetic L-amino acids. Ideally, all essential amino acids should be included with a wide variety of nonessential ones to provide sufficient nitrogen together with electrolytes. Solutions vary in their composition of amino acids; they often contain an energy source (usually glucose p. 1041) and electrolytes.

Energy is provided in a ratio of 0.6 to 1.1 megajoules (150–250 kcals) per gram of protein nitrogen. Energy requirements must be met if amino acids are to be utilised for tissue maintenance. A mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.

Glucose is the preferred source of carbohydrate, but if more than 180 g is given per day frequent monitoring of blood glucose is required, and insulin may be necessary. Glucose in various strengths from 10 to 50% must be infused through a central venous catheter to avoid thrombosis.

In parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of glucose and to prevent hypophosphataemia; between 20 and 30 mol of phosphate is required daily.

Fructose and sorbitol have been used in an attempt to avoid the problem of hyperosmolar hyperglycaemic non-ketotic acidosis but other metabolic problems may occur, as with xylitol and ethanol which are now rarely used.

Fat emulsions have the advantages of a high energy to fluid volume ratio, neutral pH, and iso-osmolality with plasma, and provide essential fatty acids. Several days of adaptation may be required to attain maximal utilisation. Reactions include occasional febrile episodes (usually only with 20% emulsions) and rare anaphylactic responses. Interference with biochemical measurements such as those for blood gases and calcium may occur if samples are taken before fat has been cleared. Daily checks are necessary to ensure complete clearance from the plasma in conditions where fat metabolism may be disturbed. Additives should not be mixed with fat emulsions unless compatibility is known.

Administration
Because of the complex requirements relating to parenteral nutrition full details relating to administration have been omitted. In all cases product literature and other specialist literature should be consulted.

BNF 78
## Proprietary Infusion Fluids for Parenteral Feeding

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1.2 Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoven 25 (Fresenius Kabi Ltd) Net price 500 ml = £19.72</td>
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<td>Clinimix N9G20E (Baxter Healthcare Ltd) Net price (dual compartment bag of amino acids with electrolytes 1000 mL and glucose 20% with calcium 1000 mL) 2 litre: no price available</td>
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<td>Intralipid 20% (Fresenius Kabi Ltd) Net price 100 ml = £6.21; Net price 250 ml = £10.16; Net price 500 ml = £13.52</td>
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<tr>
<td>Kabiven (Fresenius Kabi Ltd) Net price (triple compartment bag of amino acids and electrolytes 300 mL, 450 mL, 600 mL, or 750 mL; glucose 526 mL, 790 mL, 1053 mL, or 1316 mL; lipid emulsion 200 mL, 300 mL, 400 mL, or 500 mL) 1.026 litre: no price available; Net price 1.54 litre = £44.09; Net price 2.053 litre = £57.42; Net price 2.566 litre = £59.92</td>
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<td>Kabiven peripheral (Fresenius Kabi Ltd) Net price (triple compartment bag of amino acids and electrolytes 300 mL, 400 mL, or 500 mL; glucose 885 mL, 1180 mL, or 1475 mL; lipid emulsion 255 mL, 340 mL, or 425 mL) 1.44 litre = £30.77; Net price 1.92 litre = £44.09; Net price 2.4 litre = £55.72</td>
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</tbody>
</table>

1 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2 Excludes protein- or amino acid-derived energy

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## Nutrition (intravenous)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1 kcal energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
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<tr>
<td><strong>Nutriflex basal (B.Braun Medical Ltd)</strong></td>
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<td>4.6</td>
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<td><strong>Nutriflex peri (B.Braun Medical Ltd)</strong></td>
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<td>5.7</td>
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<td><strong>Nutriflex plus (B.Braun Medical Ltd)</strong></td>
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<td><strong>NuTRIflex Lipid plus without Electrolytes (B.Braun Medical Ltd)</strong></td>
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<td>5.44</td>
<td>3600</td>
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<tr>
<td><strong>NuTRIflex Lipid special without Electrolytes (B.Braun Medical Ltd)</strong></td>
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<td>8.0</td>
<td>4004</td>
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</tbody>
</table>

1 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2 Excludes protein- or amino acid-derived energy
### Blood and nutrition

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1,2-Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
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</thead>
<tbody>
<tr>
<td>NuTRIflex Omega plus (B.Braun Medical Ltd)</td>
<td>5.4</td>
<td>3600</td>
<td>K⁺ 28.0, Mg²⁺ 3.2, Na⁺ 40.0, Acet 36.0, Cl⁻ 36.0</td>
<td>Ca⁺⁺ 3.2 mmol, Zn⁺⁺ 24 micromol, phosphate 12 mmol, anhydrous glucose 120 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3 acid triglycerides 4 g</td>
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<tr>
<td>NuTRIflex Omega special (B.Braun Medical Ltd)</td>
<td>8.0</td>
<td>4004</td>
<td>K⁺ 37.6, Mg²⁺ 4.24, Na⁺ 53.6, Cl⁻ 48.0</td>
<td>Ca⁺⁺ 4.24 mmol, Zn⁺⁺ 30 micromol, phosphate 16 mmol, anhydrous glucose 144 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3 acid triglycerides 4 g</td>
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<tr>
<td>OliClinomel N4-550E (Baxter Healthcare Ltd)</td>
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<td>2184</td>
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<td>Ca⁺⁺ 2 mmol, phosphate 8.5 mmol, refined olive and soya oil 20 g, anhydrous glucose 80 g</td>
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<td>OliClinomel N4-720E (Baxter Healthcare Ltd)</td>
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<td>3024</td>
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<td>Ca⁺⁺ 1.8 mmol, phosphate 8 mmol, refined olive and soya oil 40 g, anhydrous glucose 80 g</td>
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<td>Ca⁺⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 100 g</td>
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<td>Ca⁺⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 120 g</td>
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<td>OliClinomel N7-1000 (Baxter Healthcare Ltd)</td>
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<tr>
<td>OliClinomel N7-1000E (Baxter Healthcare Ltd)</td>
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<td>4368</td>
<td>K⁺ 24.0, Mg²⁺ 2.2, Na⁺ 32.0, Cl⁻ 57.0</td>
<td>Ca⁺⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g</td>
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<td>OliClinomel N8-800 (Baxter Healthcare Ltd)</td>
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<td>3360</td>
<td>- - - -</td>
<td>phosphate 2.25 mmol, refined olive and soya oil 30 g, anhydrous glucose 125 g</td>
</tr>
</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy
## Nutrition (intravenous)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>Energy 1kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omegaven (Fresenius Kabi Ltd) Net price 100 ml: no price available</td>
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<td>4700</td>
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<td>highly refined fish oil 100 g, glycerol 25 g, egg phosphatide 12 g</td>
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<td>Plasma-Lyte 148 (water) (Baxter Healthcare Ltd) Net price 1 litre: no price available</td>
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<td>5.0 1.5 140.0 27.0 98.0</td>
<td>gluconate 23 mmol</td>
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<td>Plasma-Lyte 148 (dextrose 5%) (Baxter Healthcare Ltd) Net price 1 litre: no price available</td>
<td>-</td>
<td>840</td>
<td>5.0 1.5 140.0 27.0 98.0</td>
<td>gluconate 23 mmol, anhydrous glucose 50 g</td>
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<tr>
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<td>16.0 1.5 40.0 12.0 40.0</td>
<td>Ca(^{2+}) 2.5 mmol, lactate 12 mmol, anhydrous glucose 50 g</td>
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<td>Synthamin 9 (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>9.1</td>
<td>-</td>
<td>60.0 5.0 70.0 100.0 70.0</td>
<td>acid phosphate 30 mmol</td>
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<td>Synthamin 9 EF (electrolyte-free) (Baxter Healthcare Ltd) Net price 500 ml: no price available; Net price 1 litre: no price available</td>
<td>9.1</td>
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<td>- - - -</td>
<td>44.0 22.0</td>
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<td>-</td>
<td>60.0 5.0 70.0 140.0 70.0</td>
<td>acid phosphate 30 mmol</td>
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<td>- - - -</td>
<td>68.0 34.0</td>
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<td>-</td>
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<td>acid phosphate 30 mmol</td>
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<tr>
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<td>82.0 40.0</td>
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<tr>
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<td>1700</td>
<td>20.0 1.5 50.0 -</td>
<td>Ca(^{2+}) 2.5 mmol, anhydrous glucose 100 g</td>
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<td>Vamin 14 (Fresenius Kabi Ltd) Net price 500 ml: no price available; Net price 1 litre = £16.02</td>
<td>13.5</td>
<td>-</td>
<td>50.0 8.0 100.0 135.0 100.0</td>
<td>Ca(^{2+}) 5 mmol, SO(_4)(^{2-}) 8 mmol</td>
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<td>Vamin 14 (electrolyte-free) (Fresenius Kabi Ltd) Net price 500 ml = £9.48; Net price 1 litre = £16.02</td>
<td>13.5</td>
<td>-</td>
<td>- - - -</td>
<td>90.0 -</td>
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<td>Vamin 18 (electrolyte-free) (Fresenius Kabi Ltd) Net price 500 ml = £11.99; Net price 1 litre = £23.38</td>
<td>18.0</td>
<td>-</td>
<td>- - - -</td>
<td>110.0 -</td>
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</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
NUTRIENTS > PARENTERAL NUTRITION

Parenteral nutrition supplements

- **INDICATIONS AND DOSE**
  - **Supplement in intravenous nutrition**
    - **BY INTRAVENOUS INFUSION, OR BY SLOW INTRAVENOUS INJECTION**
    - Adult: (consult product literature)

**Dipeptiven 20g/100ml Concentrate for Solution for Infusion Bottles**

Amino acid supplement for hypercatabolic or hypermetabolic states

- **BY INTRAVENOUS INFUSION**
- Adult: 300–400 mg/kg daily, dose not to exceed 20% of total amino acid intake

- **CAUTIONS**
- **Pedtrac® Solution for Infusion 10ml Vials** Reduced biliary excretion - reduced biliary excretion in cholestatic liver disease - reduced biliary excretion in markedly reduced urinary excretion (careful biochemical monitoring required) - total parenteral nutrition exceeding one month

- **Directions for Administration** Because of the complex requirements relating to parenteral nutrition, full details relating to administration have been omitted. In all cases specialist pharmacy advice, product literature, and other specialist literature should be consulted. Compatibility with the infusion solution must be ascertained before adding supplementary preparations. Additives should not be mixed with fat emulsions unless compatibility is known.

**Cernevit Solution for Injection Vials and Diluent** Dissolve in 5 mL water for injections.

**Pedtrac® Solution for Infusion 10ml Vials** For addition to Vaminolact®, Vamin® 14 Electrolyte-Free solutions, and glucose intravenous infusions.

**Additrace Solution for Infusion 10ml Ampoules** For addition to Vamin® solutions and glucose intravenous infusions.

**Dipeptiven 20g/100ml Concentrate for Solution for Infusion Bottles** For addition to infusion solutions containing amino acids.

**Addiphos® Vials** For addition to Vamin® solutions and glucose intravenous infusions.

**Decan Concentrate for Solution for Infusion 40ml Bottles** For addition to infusion solutions.

**Tracutil® Ampoules** For addition to infusion solutions.

**Solivito N Powder for Solution for Infusion Vials** Solvito N® powder for reconstitution contains biotin 60 micrograms, cyanocobalamin 5 micrograms, folic acid 400 micrograms, glycine 300 micrograms, nicotinamide 40 mg, pyridoxine hydrochloride 4.9 mg, riboflavin sodium phosphate 4.9 mg, sodium ascorbate 113 mg, sodium pantethenate 16.5 mg, thiamine mononitrate 3.1 mg.

**Vitlipid N Adult Emulsion for Infusion 10ml Ampoules** Vitlipid N® adult emulsion contains vitamin A 330 units, ergocalciferol 20 units, dl-alpha tocopherol 1 unit, phytomenadione 15 micrograms/mL.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for injection**

- **Cernevit (Baxter Healthcare Ltd)**
  - Cyanocobalamin 6 microgram, Biotin 69 microgram, Folic acid 414 microgram, Thiamine 3.51 mg, Riboflavin (as Riboflavin sodium phosphate) 4.14 mg, Pyridoxine (as Pyridoxine hydrochloride) 4.53 mg, Pantothenic acid (as Dexamethasone) 17.25 mg, Nicotinamide 4.6 mg, Ascorbic acid 125 mg, Alpha tocopherol 11.2 unit, Colecalciferol 220 unit, Retinol 3500 unit

- **Decan (Baxter Healthcare Ltd)**
  - Calcium gluconate 3500 unit, Magnesium 125 mg, Sodium chloride 989 microgram, Magnesium chloride 99 microgram per 1 mL, Sodium fluoride 210 microgram per 1 mL, Copper chloride 340 microgram per 1 mL, Ferric chloride 544 microgram per 1 mL, Zinc chloride 1.36 mg per 1 mL

- **Additrace (Fresenius Kabi Ltd)**
  - Sodium glycerophosphate 216 mg per 1 mL, Sodium carbonate 4.32g/20ml concentration for solution for infusion 1 mL vial £5.60

- **Dipeptiven (Fresenius Kabi Ltd)**
  - Sodium molybdate 4.85 microgram per 1 mL, Chromic chloride 5.33 microgram per 1 mL, Sodium selenite 10.5 microgram per 1 mL, Potassium iodide 16.6 microgram per 1 mL, Manganese chloride 99 microgram per 1 mL, Sodium fluoride 210 microgram per 1 mL, Copper chloride 340 microgram per 1 mL, Ferric chloride 544 microgram per 1 mL, Zinc chloride 1.36 mg per 1 mL

- **Pedtrac® (Fresenius Kabi Ltd)**
  - Manganese (as Manganese chloride) 1 microgram per 1 mL, Iodine (as Potassium iodide) 1 microgram per 1 mL, Selenium (as Sodium selenite) 2 microgram per 1 mL, Copper (as Copper chloride) 20 microgram per 1 mL, Fluoride (as Sodium fluoride)
Enteral nutrition

Overview

The body’s reserves of protein rapidly become exhausted in severely ill patients, especially during chronic illness or in those with severe burns, extensive trauma, pancreatitis, or intestinal fistula. Much can be achieved by frequent meals and by persuading the patient to take supplementary snacks of ordinary food between the meals.

However, extra calories, protein, other nutrients, and vitamins are often best given by supplementing ordinary food with extra calorie sources and by persuading the patient to take supplementary snacks of ordinary food between the meals.

In patients who cannot tolerate or cannot metabolise certain common constituents of food. In certain clinical conditions, some food preparations are regarded as drugs and can be prescribed within the NHS if they have been approved by the Advisory Committee on Borderline Substances (ACBS).

Coeliac disease

Coeliac disease is caused by an abnormal immune response to gluten. For management and further information, see Coeliac disease p. 37.

Phenylketonuria

Phenylketonuria (hyperphenylalaninaemia, PKU), which results from the inability to metabolise phenylalanine, is managed by restricting dietary intake of phenylalanine to a small amount sufficient for tissue building and repair.

Sapropterin dihydrochloride below, a synthetic form of tetrahydrobiopterin, is licensed as an adjunct to dietary restriction of phenylalanine in the management of patients with phenylketonuria and tetrahydrobiopterin deficiency.

Aspartame (used as a sweetener in some foods and medicines) contributes to the phenylalanine intake and may affect control of phenylketonuria. Where the presence of aspartame is specified in the product literature this is indicated in the BNF against the preparation; the patient should be informed of this.

5.1a Phenylketonuria

**DRUGS FOR METABOLIC DISORDERS ▶ TETRAHYDROBIOPTERIN AND DERIVATIVES**

**Sapropterin dihydrochloride**

*Phenylketonuria (adjunct to dietary restriction of phenylalanine) (specialist use only)*

- **INDICATIONS AND DOSE**
  - **Phenylketonuria** (adjunct to dietary restriction of phenylalanine) (specialist use only)
    - **BY MOUTH**
      - Adult: Initially 10 mg/kg once daily, adjusted according to response; usual dose 5–20 mg/kg once daily, dose to be taken preferably in the morning, the total daily dose may alternatively be given in 2–3 divided doses; maximum 20 mg/kg per day

- **CAUTIONS** History of convulsions
- **INTERACTIONS** → Appendix 1: sapropterin
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · cough · diarrhoea · headache · laryngeal pain · nasal congestion · vomiting
  - **Frequency not known** Hypersensitivity
- **PREGNANCY** Manufacturer advises caution—consider only if strict dietary management inadequate.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.

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**Vitlipid N Adult** Emulsion for injection

<table>
<thead>
<tr>
<th>Constituent</th>
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</thead>
<tbody>
<tr>
<td>Alpha tocopherol</td>
<td>640 microgram per 1 ml</td>
</tr>
<tr>
<td>Retinol palmitate</td>
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<tr>
<td>Ergocalciferol</td>
<td>69 microgram per 1 ml</td>
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<tr>
<td>Phytomenadione</td>
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<tr>
<td>Alpha tocopherol</td>
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<tr>
<td>Ergocalciferol</td>
<td>500 nanogram per 1 ml</td>
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<td>Phytomenadione</td>
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<tr>
<td>Thiamine</td>
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<tr>
<td>Pyridoxine</td>
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<tr>
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</tr>
<tr>
<td>Folic acid</td>
<td>0.5 microgram</td>
</tr>
<tr>
<td>B complex</td>
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<tr>
<td>Ferric chloride</td>
<td>204.6 microgram per 1 ml</td>
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<td>197.9 microgram per 1 ml</td>
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<tr>
<td>Manganese chloride</td>
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<tr>
<td>Sodium molybdate dihydrate</td>
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<tr>
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**Vitlipid N Infant** Emulsion for injection

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<tr>
<td>Water</td>
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6 Vitamin deficiency

Vitamins

Overview
Vitamins are used for the prevention and treatment of specific deficiency states or where the diet is known to be inadequate; they may be prescribed in the NHS to prevent or treat deficiency but not as dietary supplements.

Their use as general 'pick-me-ups' is of unproven value and, in the case of preparations containing vitamin A or D, may actually be harmful if patients take more than the prescribed dose. The 'fad' for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid p. 1082 and pyridoxine hydrochloride p. 1080, is unscientific and can be harmful.


Dental patients
It is unjustifiable to treat stomatitis or glossitis with mixtures of vitamin preparations; this delays diagnosis and correct treatment.

Most patients who develop a nutritional deficiency despite an adequate intake of vitamins have malabsorption and if this is suspected the patient should be referred to a medical practitioner.

Vitamin A
Deficiency of vitamin A p. 1079 (retinol) is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption).

Vitamin B group
Deficiency of the B vitamins, other than vitamin B$_6$, is rare in the UK and is usually treated by preparations containing thiamine p. 1080 (B$_1$), riboflavin (B$_2$), and nicotinamide p. 1272, which is used in preference to nicotinic acid p. 201, as it does not cause vasodilatation. Other members (or substances traditionally classified as members) of the vitamin B complex such as aminobenzoic acid, biotin, choline, inositol nicotinate p. 233, and pantothetic acid or pantothenol may be included in vitamin B preparations but there is no evidence of their value.

The severe deficiency states Wernicke’s encephalopathy and Korsakoff’s psychosis, especially as seen in chronic alcoholism, are best treated initially by the parenteral administration of B vitamins (Pabrinex®), followed by oral administration of thiamine in the longer term. Anaphylaxis has been reported with parenteral B vitamins.

As with other vitamins of the B group, pyridoxine hydrochloride (B$_6$) deficiency is rare, but it may occur during isoniazid p. 587 therapy or penicillamine p. 1097 treatment in Wilson’s disease and is characterised by peripheral neuritis. High doses of pyridoxine hydrochloride are given in some metabolic disorders, such as hyperoxaluria, and it is also used in sideroblastic anaemia. There is evidence to suggest that pyridoxine hydrochloride may provide some benefit in premenstrual syndrome. It has been tried for a wide variety of other disorders, but there is little sound evidence to support the claims of efficacy.

Nicotinic acid inhibits the synthesis of cholesterol and triglyceride. Folic acid p. 1025 and vitamin B$_12$ are used in the treatment of megaloblastic anaemia. Folic acid p. 941 (available as calcium folinate) is used in association with cytotoxic therapy.

Vitamin C
Vitamin C (ascorbic acid) therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency are commonly found, especially in the elderly. Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a patient with these signs is more likely to have leukaemia. Investigation should not be delayed by a trial period of vitamin treatment.

Claims that vitamin C ameliorates colds or promotes wound healing have not been proven.

Vitamin D
The term Vitamin D is used for a range of compounds which possess the property of preventing or curing rickets. They include ergocalciferol p. 1086 (calciferol, vitamin D$_2$), colecalciferol p. 1084 (vitamin D$_3$), dihydrotachysterol p. 1086, alfalcaldip p. 1083 (1α-hydroxycholecalciferol), and calcitrol p. 1083 (1,25-dihydroxycholecalciferol). Simple vitamin D deficiency can be prevented by taking an oral supplement of ergocalciferol (calciferol, vitamin D$_2$) or colecalciferol (vitamin D$_3$) daily. Vitamin D deficiency can occur in people whose exposure to sunlight is limited and in those whose diet is deficient in vitamin D. In these individuals, ergocalciferol or colecalciferol daily by mouth may be given to treat vitamin D deficiency; higher doses may be necessary for severe deficiency. Patients who do not respond should be referred to a specialist.
Preparations containing colecalciferol with calcium carbonate p. 1085 are available for the management of combined calcium and vitamin D deficiency, or for those at high risk of deficiency.

Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses.

Vitamin D requires hydroxylation by the kidney to its active form, therefore the hydroxylated derivatives alfalcacidol or calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of postmenopausal osteoporosis.

Paricalcitol p. 1087, a synthetic vitamin D analogue, is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease.

Vitamin E

The daily requirement of vitamin E (tocopherol) has not been well defined but is probably 3 to 15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestasis. In young children with congenital cholestasis, abnormally low vitamin E concentrations may be found in association with neuromuscular abnormalities, which usually respond only to the parenteral administration of vitamin E.

Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

Vitamin K

Vitamin K is necessary for the production of blood clotting factors and proteins necessary for the normal calcification of bone.

Because vitamin K is fat soluble, patients with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient. Menadione sodium phosphate p. 1089 is a water-soluble synthetic vitamin K derivative that can be given orally to prevent vitamin K deficiency in malabsorption syndromes.

Oral coumarin anticoagulants act by interfering with vitamin K metabolism in the hepatic cells and their effects can be antagonised by giving vitamin K.

Other compounds

Potassium aminobenzoate p. 1080 has been used in the treatment of various disorders associated with excessive fibrosis such as scleroderma and Peyronie’s disease. In Peyronie’s disease there is some evidence to support efficacy in reducing progression when given early in the disease; however, there is no evidence for reversal of the condition. The therapeutic value of potassium aminobenzoate in scleroderma is doubtful.

**VITAMINS AND TRACE ELEMENTS**

**MUTIVITAMINS**

### Vitamin A and D

**INDICATIONS AND DOSE**

Prevention of vitamin A and D deficiency

- **BY MOUTH**
  - Child: 1 capsule daily, 1 capsule contains 4000 units vitamin A and 400 units (10 micrograms) vitamin D
  - Adult: (consult product literature)

**UNLICENSED USE**

- In children Not licensed in children under 6 months of age.

**SIDE-EFFECTS**

- **Overdose** Prolonged excessive ingestion of vitamins A and D can lead to hypervitaminosis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **Vitamins A and D (Non-proprietary)**
    - **Vitamin D 400 unit, Vitamin A 4000 unit**
    - **Capsules BPC 1973** 28 capsule £2.81 84 capsule £6.73-£8.42 DT = £8.42

### Vitamins A, C, and D

The properties listed below are those particular to the combination only. For the properties of the components please consider, vitamin A below, ascorbic acid p. 1082.

**INDICATIONS AND DOSE**

Prevention of vitamin deficiency

- **BY MOUTH**
  - Child 1 month–4 years: 5 drops daily, 5 drops contain vitamin A approx. 700 units, vitamin D approx. 300 units (7.5 micrograms), ascorbic acid approx. 20 mg

**INTERACTIONS** → Appendix 1: ascorbic acid · vitamin A

**PRESCRIBING AND DISPENSING INFORMATION**

This drug contains vitamin D; consult individual vitamin D monographs.

Available free of charge to children under 4 years in families on the Healthy Start Scheme, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

*Healthy Start Vitamins for women* (containing ascorbic acid, vitamin D, and folic acid) are also available free of charge to women on the Healthy Start Scheme during pregnancy and until their baby is one year old, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Oral drops**
  - **Healthy Start Children’s Vitamin** (Secretary of State for Health)
    - **Vitamin A and D3 concentrate.55 mg per 1 ml, Sodium ascorbate 18.58 mg per 1 ml, Ascorbic acid 150 mg per 1 ml, Vitamin D 2000 iu per 1 ml, Vitamin A 5000 iu per 1 ml** Healthy Start Children’s Vitamin drops | 10 ml

### Vitamin A

(Retinol)

**INDICATIONS AND DOSE**

Vitamin A deficiency

- **BY MOUTH**
  - Child 1-11 months: 5000 units daily, to be taken with or after food, higher doses may be used initially for treatment of severe deficiency
  - Child 1-17 years: 10 000 units daily, to be taken with or after food, higher doses may be used initially for treatment of severe deficiency

**UNLICENSED USE**

Preparations containing only vitamin A are not licensed.
1080 Vitamin deficiency

**Potassium aminobenzoate**

- **INDICATIONS AND DOSE**
  - Peyronie’s disease | Scleroderma
    - **BY MOUTH**
      - Adult: 12 g daily in divided doses, to be taken after food
  
- **CONTRA-INDICATIONS** Hyperkalaemia | severe liver damage

- **CAUTIONS** Interrupt treatment during periods of low food intake (such as fasting, anorexia and nausea)—increased risk of hypoglycaemia

- **INTERACTIONS** → Appendix 1: potassium aminobenzoate

- **SIDE-EFFECTS** Hepatitis | hypoglycaemia

- **PREGNANCY** Manufacturer advises avoid—limited information available.

- **BREAST FEEDING** Manufacturer advises unknown if excreted in milk—risk to infant cannot be excluded.

- **RENAL IMPAIRMENT** Manufacturer advises use with caution—increased risk of hyperkalaemia; avoid if GFR less than 45 mL/minute.

- **MONITORING REQUIREMENTS** Manufacturer advises liver function tests should be performed monthly—discontinue immediately if elevated.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Powder**
    - **CAUTIONARY AND ADVISORY LABELS** 13, 21
      - **Potaba** (Cheplapharm Arzneimittel GmbH)
        - Potassium aminobenzoate 3 gram
          - Potaba 3g sachets
            - 40 sachets £34.31 DT = £34.31

**Pyridoxine hydrochloride**

(Vitamin B₆)

- **INDICATIONS AND DOSE**
  
  - **Deficiency states**
    - **BY MOUTH**
      - Adult: 20–50 mg 1–3 times a day
  
  - **Isoniazid-induced neuropathy (prophylaxis)**
    - **BY MOUTH**
      - Adult: 10–20 mg daily
  
  - **Isoniazid-induced neuropathy (treatment)**
    - **BY MOUTH**
      - Adult: 50 mg 3 times a day
  
  - **Idiopathic sideroblastic anaemia**
    - **BY MOUTH**
      - Adult: 100–400 mg daily in divided doses
  
  - **Prevention of penicillamine-induced neuropathy in Wilson’s disease**
    - **BY MOUTH**
      - Adult: 20 mg daily
  
  - **Premenstrual syndrome**
    - **BY MOUTH**
      - Adult: 50–100 mg daily

- **UNLICENSED USE** Not licensed for prophylaxis of penicillamine-induced neuropathy in Wilson’s disease.
  
  - Not licensed for treatment of premenstrual syndrome.

**IMPORTANT SAFETY INFORMATION**

Prolonged use of pyridoxine in a dose of 10 mg daily is considered safe but the long-term use of pyridoxine in a dose of 200 mg or more daily has been associated with neuropathy. The safety of long-term pyridoxine supplementation with doses above 10 mg daily has not been established.

- **SIDE-EFFECTS** Peripheral neuritis
  - **Overdose** Overdosage induces toxic effects.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - Pyridoxine hydrochloride (Non-proprietary)
      - Pyridoxine hydrochloride 10 mg
        - 28 tablet £16.31 DT = £16.31
      - Pyridoxine hydrochloride 20 mg
        - 500 tablet £35.00 DT = £35.00
      - Pyridoxine hydrochloride 50 mg
        - 28 tablet £16.31 DT = £15.75
  
  - **Oral solution**
    - **Pyridose** (TriOn Pharma Ltd)
      - Pyridoxine hydrochloride 20 mg per 1 ml
        - 100 ml £29.86 DT = £36.79
  
  - **Capsule**
    - Pyridoxine hydrochloride (Non-proprietary)
      - Pyridoxine hydrochloride 100 mg
        - Vitamin B6 100mg capsules
          - 100 capsule £5.50
          - 120 capsule £11.00

**Thiamine**

(Vitamin B₁)

- **INDICATIONS AND DOSE**
  
  - **Mild deficiency**
    - **BY MOUTH**
      - Adult: 25–100 mg daily
Severe deficiency
▶ BY MOUTH
▶ Adult: 200–300 mg daily in divided doses

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVISE (SEPTEMBER 2007)**

Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:

- This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
- Intravenous administration should be by infusion over 30 minutes;
- Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

- **CAUTIONS** Anaphylaxis may occasionally follow injection.
- **BREAST FEEDING** Severely thiamine-deficient mothers should avoid breast-feeding as toxic methyl-glyoxal present in milk.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, modified-release tablets, vitamin B compound tablets, and vitamin B compound strong tablets.

- **modified-release tablet**
  ▶ Thiamine (Non-proprietary)
  Thiamine hydrochloride 100 mg Vitamin B1 100mg modified-release tablets | 90 tablet £4.46

- **tablet**
  ▶ Thiamine (Non-proprietary)
  Thiamine hydrochloride 25 mg Vitamin B1 25mg tablets | 100 tablet £
  Thiamine hydrochloride 50 mg Thiamine 50mg tablets | 28 tablet £1.67–1.80 | 100 tablet £6.72 DT = £3.99
  Thiamine hydrochloride 100 mg Thiamine 100mg tablets | 28 tablet £1.76–1.72 | 100 tablet £11.55 DT = £5.74
  ▶ Benerva (Teofarma)
  Thiamine hydrochloride 50 mg Benerva 50mg tablets | 100 tablet £4.00 DT = £3.99
  Thiamine hydrochloride 100 mg Benerva 100mg tablets | 100 tablet £6.29 DT = £5.74

**Vitamin B complex**

**INDICATIONS AND DOSE**

Treatment of deficiency
▶ BY MOUTH USING TABLETS
▶ Adult: 1–2 tablets 3 times a day, this dose is for vitamin B compound tablets

**Prophylaxis of deficiency**
▶ BY MOUTH USING TABLETS
▶ Adult: 1–2 tablets daily, this dose is for vitamin B compound tablets

- **LESS SUITABLE FOR PRESCRIBING** Vitamin B compound tablets, vitamin B compound strong tablets, and Vigranon ® syrup are less suitable for prescribing.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Vitamin B complex (Non-proprietary)**
  Riboflavin 1 mg, Thiamine hydrochloride 1 mg, Nicotinamide 15 mg Vitamin B compound tablets | 28 tablet £21.30 DT = £26.63
  Pyridoxine hydrochloride 2 mg, Riboflavin 2 mg, Thiamine hydrochloride 5 mg, Nicotinamide 20 mg Vitamin B compound strong tablets | 28 tablet £7.00 DT = £8.81

**Vitamin B substances with ascorbic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, thiamine p. 1080, ascorbic acid p. 1082.

- **INDICATIONS AND DOSE**
  Parenteral vitamins B and C for rapid correction of severe depletion or malabsorption (e.g. in alcoholism, after acute infections, postoperatively, or in psychiatric states) | Maintenance of vitamins B and C in chronic intermittent haemodialysis
  ▶ BY INTRAVENOUS INFUSION
  ▶ INITIALLY BY INTRAVENOUS INFUSION
  ▶ Adult: See MHRA/CHM advice in thiamine p. 1080 monograph (consult product literature).

**Treatment of Wernicke's encephalopathy**
▶ BY INTRAVENOUS INFUSION OR BY DEEP INTRAMUSCULAR INJECTION
▶ Adult: 1 pair once daily for at least 3–5 days, give deep intramuscular injection into the gluteal muscle

**Prophylaxis of Wernicke's encephalopathy in alcohol dependence**
▶ BY INTRAVENOUS INFUSION OR BY DEEP INTRAMUSCULAR INJECTION
▶ Adult: 1 pair twice daily for up to 7 days, give deep intramuscular injection into the gluteal muscle

**Haemodialysis**
▶ BY INTRAVENOUS INFUSION
▶ Adult: 1 pair every 2 weeks

**UNLICENSED USE**

- **Pabrinex** ® doses in BNF may differ from those in product literature.

**INTERACTIONS**
▶ Appendix 1: ascorbic acid

**DIRECTIONS FOR ADMINISTRATION**

Give (Pabrinex ® I/V High Potency) intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Ampoules contents should be mixed, diluted, and administered without delay; give over 30 minutes.

**PRESCRIBING AND DISPENSING INFORMATION**

Some formulations of Pabrinex ® may contain benzyl alcohol (avoid in neonates). Pabrinex ® I/V High Potency injection is for intramuscular use only. Pabrinex ® I/V High Potency injection is for intravenous use only.

**MEDICINAL FORMS**

- **There can be variation in the licensing of different medicines containing the same drug.**

**Solution for injection**

- **EXCipients:** May contain Benzyl alcohol
  ▶ **Pabrinex Intramuscular High Potency** (Kyowa Kirin Ltd)
  Pabrinex Intramuscular High Potency solution for injection 5ml and 2ml ampoules | 20 ampoule (£90) £22.53 DT = £22.53
  ▶ **Pabrinex Intravenous High Potency** (Kyowa Kirin Ltd)
  Pabrinex Intravenous High Potency solution for injection 5ml and 5ml ampoules | 12 ampoule (£90) £16.23 | 20 ampoule (£90) £22.53 DT = £22.53

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Vitamins with minerals and trace elements

**INDICATIONS AND DOSE**

**FORCEVAL® CAPSULES**

Vitamin and mineral deficiency and as adjunct in synthetic diets

- **BY MOUTH**
  - Adult: 1 capsule daily, one hour after a meal

**KETOVITE® LIQUID**

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism | Adjunct in restricted, specialised, or synthetic diets

- **BY MOUTH**
  - Adult: 5 mL daily, use with Ketovite® Tablets for complete vitamin supplementation.

**KETOVITE® TABLETS**

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism | Adjunct in restricted, specialised, or synthetic diets

- **BY MOUTH**
  - Adult: 1 tablet 3 times a day, use with Ketovite® Liquid for complete vitamin supplementation.

**PRESCRIBING AND DISPENSING INFORMATION**

To avoid potential toxicity, the content of all vitamin preparations, particularly vitamin A, should be considered when used together with other supplements.

**PATIENT AND CARER ADVICE**

KETOVITE® LIQUID

Ketovite® liquid may be mixed with milk, cereal, or fruit juice.

KETOVITE® TABLETS

Tablets may be crushed immediately before use.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral emulsion**

- **Ketovite** (Essential Pharmaceuticals Ltd)
  - Cyanocobalamin 2.5 microgram per 1 ml, Choline chloride 30 mg per 1 ml, Ergocalciferol 80 unit per 1 ml, Vitamin A 500 unit per 1 ml Ketovite liquid sugar-free | 150 ml $19.10

**Tablet**

- **Ketovite** (Essential Pharmaceuticals Ltd)
  - Biotin 170 microgram, Folic acid 250 microgram, Pyridoxine hydrochloride 330 microgram, Acetomenaphthone 500 microgram, Riboflavin 1 mg, Thiamine hydrochloride 1 mg, Calcium pantothenate 1.16 mg, Nicotinamide 3.3 mg, Alpha tocopheryl acetate 5 mg, Ascorbic acid 16.6 mg, Inositol 50 mg
  - Capsule tablets | 100 tablet price $9.21

**Capsule**

- **Forceval** (Forum Health Products Ltd)
  - Cyanocobalamin 3 microgram, Selenium 50 microgram, Biotin 100 microgram, Iodine 140 microgram, Chromium 200 microgram, Molybdenum 250 microgram, Folic acid 400 microgram, Thiamine 1.2 mg, Riboflavin 1.6 mg, Copper 2 mg, Pyridoxine 2 mg, Manganese 3 mg, Pantothenic acid 4 mg, Potassium 4 mg, Tocopheryl acetate 10 mg, Iron 12 mg, Zinc 15 mg, Nicotinamide 18 mg, Magnesium 30 mg, Ascorbic acid 60 mg, Phosphorus 77 mg, Calcium 100 mg, Ergocalciferol 400 unit, Vitamin A 2500 unit
  - Forceval capsules | 15 capsule price $5.46 | 30 capsule price $9.32 | 90 capsule price $28.77

**VITAMINS AND TRACE ELEMENTS › VITAMIN C**

**Ascorbic acid**

(Vitamin C)

**INDICATIONS AND DOSE**

Prevention of scurvy

- **BY MOUTH**
  - Adult: 25–75 mg daily

**TREATMENT OF SCURVY**

- **BY MOUTH**
  - Adult: Not less than 250 mg daily in divided doses

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

- Iron overload Ascorbic acid should not be given to patients with cardiac dysfunction.

  In patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine.

**SIDE-EFFECTS**

Diarrhoea - gastrointestinal disorder - hypercalcaemia - oxalate nephrolithiasis - polyuria

**PRESCRIBING AND DISPENSING INFORMATION**

It is rarely necessary to prescribe more than 100 mg daily except early in the treatment of scurvy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution

**Tablet**

EXCIPIENTS: May contain Aspartame

- **Ascorbic acid (Non-proprietary)**
  - Ascorbic acid 50 mg | 10 tablet | $0.62
  - Ascorbic acid 100 mg | 28 tablet | $1.05 DT = $0.05
  - Ascorbic acid 200 mg | 28 tablet | $1.40 DT = $0.04
  - Ascorbic acid 250 mg | 28 tablet | $1.96 DT = $0.07
  - Ascorbic acid 500 mg | 28 tablet | $2.68 DT = $0.07
  - Ascorbic acid 1000 mg chewable tablets | 30 tablet | $3.95
  - Ascorbic acid (as Sodium ascorbate) 500 mg | 10 tablet | $0.26

**Chewable tablet**

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EXCIPIENTS: May contain Aspartame

- **Ascur (Ennogen Healthcare Ltd)**
  - Ascorbic acid 100 mg chewable tablets | 30 tablet | $3.95

Combination available: Vitamin B substances with ascorbic acid, p. 1081. Vitamins A, C and D, p. 1079

**VITAMINS AND TRACE ELEMENTS › VITAMIN D AND ANALOGUES**

**Vitamin D and analogues (systemic)**

**CONTRA-INDICATIONS**

- Hypercalcaemia - metastatic calcification

**SIDE-EFFECTS**

- Common or very common: Abdominal pain - headache - hypercalcaemia - hypercalciuria - nausea - skin reactions

- Uncommon: Appetite decreased - constipation - thirst - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Overdose**

Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation,
**Alfalcacidol (1,25-Hydroxycholecalciferol)**

**INDICATIONS AND DOSE**

Patients with severe renal impairment requiring vitamin D therapy

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Adult: Initially 1 microgram daily, dose to be adjusted to avoid hypercalcemia; maintenance 0.25–1 microgram daily
  - Elderly: Initially 500 nanograms daily, dose adjusted to avoid hypercalcemia; maintenance 0.25–1 microgram daily

**Prevention of vitamin D deficiency in renal or cholestatic liver disease**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Child 1 month–11 years: 25–50 nanograms/kg once daily, dose to be adjusted as necessary; maximum 1 microgram per day
  - Child 12–17 years: 1 microgram once daily, dose to be adjusted as necessary

**Hypophosphataemic rickets | Persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism**

- **BY MOUTH, OR BY INTRAVENOUS INJECTION**
  - Child 1 month–11 years: body-weight up to 20 kg: 15–30 nanograms/kg once daily (max. per dose 500 nanograms)
  - Child 1 month–11 years: body-weight 20 kg and above: 250–500 nanograms once daily, dose to be adjusted as necessary
  - Child 12–17 years: 250–500 nanograms once daily, dose to be adjusted as necessary

**DOSE EQUIVALENCES AND CONVERSION**

- One drop of alfalcacidol 2 microgram/mL oral drops contains approximately 100 nanograms alfalcacidol.

**INTERACTIONS**

- Nephrolithiasis • take care to ensure correct dose in infants
- Appendix 1: vitamin D substances
- Abdominal discomfort • rash pustular
- Asthenia • diarrhoea • malaise • myalgia • urolithiasis
- Rare • Dizziness
- Confusion • renal impairment
- Manufacturer advises avoid—no information available.
- Monitor plasma-calcium concentration in renal impairment.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Solution for injection**

- **EXCIPIENTS**: May contain Alcohol, propylene glycol
  - **One-Alpha (LEO Pharma)**
    - Alfalcacidol 2 microgram per 1 ml One-Alpha 2 micrograms/1 ml solution for injection ampoules | 10 ampoule [PDR] £41.13
    - One-Alpha 1 micrograms/0.5 ml solution for injection ampoules | 10 ampoule [PDR] £21.57

**Oral drops**

- **EXCIPIENTS**: May contain Alcohol
  - **One-Alpha (LEO Pharma)**
    - Alfalcacidol 2 microgram per 1 ml One-Alpha 2 micrograms/ml oral drops sugar-free | 10 ml [PDR] £21.30 DT = £21.30

**Capsules**

- **EXCIPIENTS**: May contain Sesame oil
  - **Alfalcacidol (Non-proprietary)**
    - Alfalcacidol 250 nanogram Alfalcacidol 250 nanogram capsules | 30 capsule [PDR] £5.00 DT = £4.94
    - Alfalcacidol 500 nanogram Alfalcacidol 500 nanogram capsules | 30 capsule [PDR] £10.00 DT = £9.89
    - Alfalcacidol 1 microgram Alfalcacidol 1 microgram capsules | 30 capsule [PDR] £13.82
    - **One-Alpha (LEO Pharma)**
      - Alfalcacidol 250 nanogram Alfalcacidol One-Alpha 250 nanogram capsules | 30 capsule [PDR] £3.37 DT = £4.94
      - Alfalcacidol 500 nanogram Alfalcacidol One-Alpha 0.5 microgram capsules | 30 capsule [PDR] £6.27 DT = £5.89
      - Alfalcacidol 1 microgram One-Alpha 1 microgram capsules | 30 capsule [PDR] £8.75 DT = £13.82

**Calcitriol (1,25-Dihydroxycholecalciferol)**

**INDICATIONS AND DOSE**

**Renal osteodystrophy**

- **BY MOUTH**
  - Adult: Initially 250 nanograms daily, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Renal osteodystrophy (in patients with normal or only slightly reduced plasma-calcium concentration)**

- **BY MOUTH**
  - Adult: Initially 250 nanograms once daily on alternate days, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Established postmenopausal osteoporosis**

- **BY MOUTH**
  - Adult: 250 nanograms twice daily, plasma-calcium concentration and creatinine to be monitored (consult product literature)

**INTERACTIONS**

- Appendix 1: vitamin D substances
- Common or very common Urinary tract infection
- Frequency not known Abdominal pain upper • apathy • arrhythmia • dehydration • drowsiness • fever • growth retardation • muscle weakness • paralytic ileus • polydipsia • psychiatric disorder • sensory disorder • urinary disorders • weight decreased

**RENA L IM PA IRMENT**

- Manufacturer advises avoid—no information available.
- Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS**

- Monitor plasma calcium, phosphate, and creatinine during dosage titration.
- Monitor plasma-calcium concentration in patients receiving high doses.
### DIRECTIONS FOR ADMINISTRATION
Contents of capsule may be administered by oral syringe.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**
- **Calcitriol (non-proprietary)**
  - Calcitriol 250 nanogram Calcitriol 250nanogram capsules | 30 capsule [PDP] £5.41–£18.04
  - Calcitriol 500 nanogram Calcitriol 500nanogram capsules | 30 capsule [PDP] £9.68–£32.25
- **Rocaltriol (Roche Products Ltd)**
  - Rocaltriol 250 nanogram Rocaltriol 250nanogram capsules | 100 capsule [PDP] £18.04 DT = £18.04
  - Rocaltriol 500 nanogram Rocaltriol 500nanogram capsules | 100 capsule [PDP] £32.25 DT = £32.25

**Oral solution**
- **Colecalciferol (Non-proprietary)**
  - Colecalciferol 400 unit Colecalciferol 400unit tablets | 60 tablet £15.50
  - Colecalciferol 800 unit Colecalciferol 800unit tablets | 30 tablet [PDP] £3.60–£4.32 DT = £3.60
  - Colecalciferol 3000 unit D3 3,000unit tablets | 60 tablet £5.00
- **Aciferol D3 (Rhodes Pharma Ltd)**
  - Aciferol D3 400Unit tablets | 90 tablet [PDP] £9.99
  - Aciferol D3 2,200Unit tablets | 90 tablet £25.99
  - Aciferol D3 3,000Unit tablets | 60 tablet £14.99
  - Aciferol D3 5,000Unit tablets | 60 tablet £19.99
  - Aciferol D3 10,000Unit tablets | 30 tablet £13.99
  - Aciferol D3 20,000Unit tablets | 30 tablet £18.99
- **Cubicole D3 (Cubic Pharmaceuticals Ltd)**
  - Cubicole D3 Cubicole D3 400unit tablets | 30 tablet £5.95
- **Desunin (Meda Pharmaceuticals Ltd)**
  - Desunin 800 unit Desunin 800unit tablets | 30 tablet [PDP] £3.60 DT = £3.60 | 90 tablet [PDP] £10.17

### INTERACTIONS
Monitor plasma-calcium concentration in patients receiving high doses.

### CAUTIONS
Take care to ensure correct dose in infants

### SIDE-EFFECTS
Laryngeal oedema

### RENAL IMPAIRMENT
Monitoring Monitor plasma-calcium concentration in renal impairment.

### MONITORING REQUIREMENTS
Monitor plasma-calcium concentration in patients receiving high doses.

### DIRECTIONS FOR ADMINISTRATION
**INVITD D** ORAL SOLUTION
May be mixed with a small amount of cold or lukewarm food immediately before administration.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution, oral drops

#### Tablet
- **Colecalciferol (Non-proprietary)**
  - Colecalciferol 400 unit Colecalciferol 400unit tablets | 70 tablet [PDP] £15.90 DT = £15.90
  - E-D3 (Ennogen Healthcare Ltd)
    - Colecalciferol 400 unit E-D3 400unit tablets | 30 tablet £78.50
    - Colecalciferol 10000 unit E-D3 10,000unit tablets | 30 tablet £95.00
    - Colecalciferol 20000 unit E-D3 20,000unit tablets | 30 tablet £95.90
  - Iso D3 (Nutri Advanced Ltd)
    - Colecalciferol 2000 unit Iso D3 2,000unit tablets | 90 tablet £16.72
  - Stekerol-D3 (Koywa Kirin Ltd)
    - Colecalciferol 1000 unit Stekerol-D3 1,000unit tablets | 28 tablet [PDP] £2.95 DT = £2.95
    - Colecalciferol 25000 unit Stekerol-D3 25,000unit tablets | 12 tablet [PDP] £17.00 DT = £17.00
  - SunVit D3 (SunVit-D3 Ltd)
    - Colecalciferol 2000 unit SunVit-D3 2,000unit tablets | 28 tablet £3.99
    - Colecalciferol 3000 unit SunVit-D3 3,000unit tablets | 28 tablet £5.40
    - Colecalciferol 5000 unit SunVit-D3 5,000unit tablets | 28 tablet £4.99
    - Colecalciferol 10000 unit SunVit-D3 10,000unit tablets | 28 tablet £6.99
    - Colecalciferol 20000 unit SunVit-D3 20,000unit tablets | 28 tablet £4.40
    - Colecalciferol 50000 unit SunVit-D3 50,000unit tablets | 15 tablet £119.99

#### Oral drops
- **Colecalciferol (Non-proprietary)**
  - Colecalciferol 1000 unit per 1 ml D3 Drops 1000 oral drops sugar-free | 30 ml £6.12
  - E-D3 (Ennogen Healthcare Ltd)
  - Colecalciferol 2000 unit per 1 ml E-D3 2,000units/ml oral drops sugar-free | 20 ml [PDP]
  - Fullum-D3 (Internis Pharmaceuticals Ltd)
  - Colecalciferol 2740 unit per 1 ml Fullum-D3 2,740units/ml oral drops sugar-free | 25 ml [PDP] £10.70 DT = £10.70
  - Invita D3 (Consilient Health Ltd)
  - Colecalciferol 2400 unit per 1 ml Invita D3 2,400units/ml oral drops sugar-free | 10 ml [PDP] £3.60 DT = £3.60
  - Pro D3 (Synergy Biologies Ltd)
  - Colecalciferol 2000 unit per 1 ml Pro D3 2,000units/ml liquid drops sugar-free | 20 ml £9.80
  - SapvIt-D3 (Starling Anglian Pharmaceuticals Ltd)
  - Colecalciferol 14400 unit per 1 ml SapvIt-D3 14,400units/ml oral drops sugar-free | 12.5 ml [PDP] £8.95 DT = £8.95
  - SunVit D3 (SunVit-D3 Ltd)
  - Colecalciferol 2000 unit per 1 ml SunVit-D3 2,000units/ml oral drops sugar-free | 20 ml £6.20
  - Thorens (Galien Ltd)
  - Colecalciferol 10000 unit per 1 ml Thorens 10,000units/ml oral drops sugar-free | 10 ml [PDP] £5.85 DT = £5.85

#### Oral solution
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- **Colecalciferol (Non-proprietary)**
  - Colecalciferol 3000 unit per 1 ml Colecalciferol 3,000units/ml oral solution | 100 ml [PDP] £144.00 DT = £144.00
  - Colecalciferol 10000 unit per 1 ml Zymad 10,000units/ml oral solution | 10 ml [PDP] [PDP]
  - Aciferol D3 (Rhodes Pharma Ltd)
  - Colecalciferol 2000 unit per 1 ml Aciferol D3 2,000units/ml liquid | 10 ml £18.00
  - Baby D (KoRa Healthcare)
  - Colecalciferol 1000 unit per 1 ml Baby D 1,000units/ml oral solution | 30 ml £4.50
  - E-D3 (Ennogen Healthcare Ltd)
  - Colecalciferol 10000 unit per 1 ml E-D3 10,000units/ml oral solution | 15 ml [PDP]
  - Invita D3 (Consilient Health Ltd)
  - Colecalciferol 25000 unit per 1 ml Invita D3 25,000units/ml oral solution sugar-free | 3 ampoule [PDP] £4.45 DT = £4.45
  - Colecalciferol 50000 unit per 1 ml InVita D3 50,000units/ml oral solution sugar-free | 3 ampoule [PDP] £6.25 DT = £6.25
  - Pro D3 (Synergy Biologies Ltd)
  - Colecalciferol 2000 unit per 1 ml Pro D3 2,000units/ml liquid | 50 ml £16.80 | 100 ml £22.50
Colecalciferol with calcium carbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecalciferol p. 1084, calcium carbonate p. 1045.

- **INDICATIONS AND DOSE**
  - Prevention and treatment of vitamin D and calcium deficiency
  - **BY MOUTH**
    - Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

- **INTERACTIONS**  
  - Appendix 1: calcium salts - vitamin D substances

- **PRESCRIBING AND DISPENSING INFORMATION**
  - **Accrete D3** contains calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol), colecalciferol 10 micrograms (400 units); **Adcal-D3** tablets contain calcium carbonate 1.5 g (calcium 600 mg or Ca2+ 15 mmol), colecalciferol 10 micrograms (400 units); **Calcio D3** contains calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet; **Calcios** contains calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet; **Calcios D3** contains calcium carbonate 2.5 g (calcium 1000 mg or Ca2+ 25 mmol), colecalciferol 22 micrograms (880 units)/sachet; **Calcios D3 Forte** contains calcium carbonate 3.75 g (calcium 1500 mg or Ca2+ 37.5 mmol), colecalciferol 33 micrograms (1320 units)/sachet; **Calcios D3 Forte** contains calcium carbonate 5.6 g (calcium 2200 mg or Ca2+ 56 mmol), colecalciferol 55 micrograms (2200 units)/sachet; 

  | Colecalciferol 20000 unit | Fulttium D3 20,000 unit capsules | 15 capsule (POT) £17.04 DT + £17.04 | 30 capsule (POT) £29.00 DT + £29.00 |
  | Colecalciferol 30000 unit | InVita D3 30,000 unit capsules | 28 capsule (POT) £13.85 DT + £13.85 |
  | Colecalciferol 10000 unit | InVita D3 10,000 unit capsules | 28 capsule (POT) £2.50 |
  | Colecalciferol 8000 unit | InVita D3 8000 unit capsules | 28 capsule (POT) £2.50 |
  | Colecalciferol 5000 unit | InVita D3 5000 unit capsules | 20 capsule (POT) £3.95 DT + £3.95 |
  | Colecalciferol 3000 unit | InVita D3 3000 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 3000 unit | InVita D3 3000 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 2000 unit | InVita D3 2000 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 1000 unit | InVita D3 1000 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 500 unit | InVita D3 500 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 250 unit | InVita D3 250 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 100 unit | InVita D3 100 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 50 unit | InVita D3 50 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |
  | Calcichew-D 20 unit | InVita D3 20 unit capsules | 20 capsule (POT) £4.95 DT + £4.95 |

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Carbonate (calcium 500 mg or Ca\(^{2+}\) 12.5 mmol), colecalciferol 10 micrograms (400 units); *Kalcipos-D\(^{®}\) contains calcium carbonate (calcium 500 mg or Ca\(^{2+}\) 12.5 mmol), colecalciferol 20 micrograms (800 units); *Natecal D\(^{®}\) contains calcium carbonate 1.5 g (calcium 600 mg or Ca\(^{2+}\) 15 mmol), colecalciferol 10 micrograms (400 units); consult product literature for details of other available products.

Flavours of chewable and soluble forms may include orange, lemon, aniseed, peppermint, molasses, or tutti-frutti.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Effervescent granules

- **Calcium carbonate 1.5 gram, Colecalciferol 880 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 880 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 800 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 800 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 440 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 440 unit**

#### Effervescent tablet

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 200 unit**
- **Calcium carbonate 1.25 gram, Colecalciferol 440 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 440 unit**

#### Chewable tablet

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**

#### Chewable caplet

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**

#### Chewable formulation

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**

#### Oral solution

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**

### Medicinal forms

- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 200 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**

### Colecalciferol with calcium phosphate

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecalciferol p. 1084, calcium phosphate p. 1046.

#### INDICATIONS AND DOSE

- **Calcium and vitamin D deficiency**
  - **By mouth**
  - **Adult:** (consult product literature)

#### INTERACTIONS

- Appendix 1: calcium salts - vitamin D substances

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Powder

- **Calcium carbonate 1.5 gram, Colecalciferol 800 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 800 unit**

#### Dihydrotachysterol

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**

#### Ergocalciferol (Calciferol; Vitamin D\(_3\))

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 1.5 gram, Colecalciferol 200 unit**

#### Oral solution

- **Calcium carbonate 1.5 gram, Colecalciferol 400 unit**
- **Calcium carbonate 2.5 gram, Colecalciferol 400 unit**

#### Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease

- **By mouth**
- **Adult:** Up to 40 000 units daily
Hypocalcaemia of hypoparathyroidism to achieve normocalcaemia

- **BY MOUTH**
  - Adult: Up to 100 000 units daily

**Prevention of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 400 units daily

**Treatment of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 800 units daily, higher doses may be necessary for severe deficiency

- **CAUTIONS** Take care to ensure correct dose in infants
- **INTERATIONS** → Appendix 1: vitamin D substances

**RENAL IMPAIRMENT**

Monitoring: Monitor plasma-calcium concentration in patients receiving high doses.

**MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.

**PRESCRIBING AND DISPENSING INFORMATION** The BP directs that when calciferol is prescribed or demanded, colecalciferol or ergocalciferol should be dispensed or supplied.

When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, capsule, oral suspension, oral solution

**Tablet**

- Ergo-02 (Enogen Healthcare Ltd)
  - Ergocalciferol 12.5 microgram: Ergo-02 12.5 microgram tablets | 30 tablet
- Ergoral (Cubic Pharmaceuticals Ltd)
  - Ergocalciferol 125 microgram: Ergoral D 5,000 unit tablets | 30 tablet
- Ergocalciferol 250 microgram: Ergoral D 10,000 unit tablets | 30 tablet

**Oral solution**

- Uvesterol (Imported (France))
  - Ergocalciferol 1500 unit per 1 ml: Uvesterol D 1,500 units/ml oral solution sugar-free | 20 ml [P ]
- Eciferal (Rhodes Pharma Ltd)
  - Ergocalciferol 3000 unit per 1 ml: Eciferal D 3,000 units/ml liquid | 60 ml [P ]

**Capsule**

- Eciferal (Rhodes Pharma Ltd)
  - Ergocalciferol 1.25 mg: Eciferal D 50,000 unit capsules | 10 capsule
- Ergoral (Cubic Pharmaceuticals Ltd)
  - Ergocalciferol 1.25 mg: Ergoral D 50,000 unit capsules | 10 capsule

**Ergocalciferol with calcium lactate and calcium phosphate**

**(Calcium and vitamin D)**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergocalciferol p. 1086, calcium lactate p. 1046.

- **INDICATIONS AND DOSE**
  - Prevention of calcium and vitamin D deficiency
  - Treatment of calcium and vitamin D deficiency
  - **BY MOUTH**
  - Adult: (consult product literature)

**INTERACTIONS** → Appendix 1: calcium salts - vitamin D substances

**DIRECTIONS FOR ADMINISTRATION** Tablets may be crushed before administration, or may be chewed.

**PRESCRIBING AND DISPENSING INFORMATION** Each tablet contains calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca²⁺ 2.4 mmol), ergocalciferol 10 micrograms (400 units).

**PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer calcium and ergocalciferol tablets.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - Ergocalciferol with calcium lactate and calcium phosphate (Non-proprietary)
    - Ergocalciferol 10 microgram, Calcium phosphate 150 mg, Calcium lactate 300 mg: Calcium and Ergocalciferol tablets | 28 tablet [P ] £25.55 DT = £22.94

**Paricalcitol**

**INDICATIONS AND DOSE**

Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease

- **BY MOUTH**
  - Adult: (consult product literature)

Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure in patients on haemodialysis

- Adult: To be administered via haemodialysis access (consult product literature)

**INTERACTIONS** → Appendix 1: vitamin D substances

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common: Asthenia, nausea, vomiting, weakness, paresthesia, dry mouth, malaise - muscle complaints - pain
- Uncommon: Angioedema, laryngeal oedema
- Frequency not known: Angioedema, laryngeal oedema

**SPECIFIC SIDE-EFFECTS**

- Uncommon
  - With oral use: Breast tenderness, gastrointestinal discomfort, gastroesophageal reflux disease, palpitations - peripheral oedema, pneumonia
  - With parenteral use: Alopecia, anaemia, anxiety, arrhythmias, asthma, appetite disturbance, breast cancer, breast pain, cardiac arrest, cerebrovascular insufficiency, chest pain, coma, condition aggravated - confusion, conjunctivitis, cough, delirium, depersonalisation, dyspepsia, dysphagia, dysphoria - ear disorder, erectile dysfunction, fever, gait abnormal - gastrointestinal disorders, glaucoma - haemorrhage, hirsutism, hyperhidrosis, hyperparathyroidism, hypertension, hypotension, increased risk of infection, insomnia, joint disorders, leucopenia, lymphadenopathy, myalgia, nausea, oedema, pulmonary oedema - sensation abnormal - sepsis - syncope - weight decreased
- PREGNANCY: Manufacturer advises avoid — toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid — no information available.

**MONITORING REQUIREMENTS**

- Monitor plasma calcium and phosphate during dose titration and at least monthly when stabilised.
- Monitor parathyroid hormone concentration.
**VITAMINS AND TRACE ELEMENTS**

### Vitamin E

#### Alpha tocopherol

**Tocopherol**

- **INDICATIONS AND DOSE**
  - Vitamin E deficiency because of malabsorption in congenital or hereditary chronic cholestasis
  - **BY MOUTH USING ORAL SOLUTION**
  - Child: 17 mg/kg daily, dose to be adjusted as necessary

- **CAUTIONS**
  - Predisposition to thrombosis

- **SIDE-EFFECTS**
  - Common or very common: Diarrhoea
  - Uncommon: Alopecia, amenorrhoea

- **PREGNANCY**
  - Manufacturer advises caution, no evidence of harm in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution. Risk of renal toxicity due to polyethylene glycol content.

- **MONITORING REQUIREMENTS**
  - Tocofersolan is a water-soluble form of D-alpha tocopherol.

#### Alpha tocopheryl acetate

**Tocopherol**

- **INDICATIONS AND DOSE**
  - Vitamin E deficiency
  - **BY MOUTH**
  - Child: 2–10 mg/kg daily, increased if necessary up to 20 mg/kg daily
  - Malabsorption in cystic fibrosis
  - **BY MOUTH**
  - Child 1–11 months: 50 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **EXCipients:** May contain ethanol, propylene glycol
  - **Zemplar** (AbbVie Ltd)
    - Paricalcitol 5 microgram per 1 ml Zemplar 5 micrograms/ml solution for injection vials | 5 vial (Rx) £62.00 (Hospital only)
  - **Capsule**
    - **EXCipients:** May contain ethanol
    - **Zemplar** (AbbVie Ltd)
      - Paricalcitol 1 microgram Zemplar 1 microgram capsules | 28 capsule (Rx) £69.44 DT = £69.44
      - Paricalcitol 2 microgram Zemplar 2 microgram capsules | 28 capsule (Rx) £138.88 DT = £138.88

#### Vitamin E deficiency

- Child 1-11 years: 100 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
- Child 12-17 years: 100–200 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
- Adult: 100–200 mg once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes

- **Vitamin E deficiency in cholestasis and severe liver disease**
  - **BY MOUTH**
  - Child 1-month-11 years: Initially 100 mg daily, adjusted according to response, increased if necessary up to 200 mg/kg daily
  - Child 12-17 years: Initially 200 mg daily, adjusted according to response, increased if necessary up to 200 mg/kg daily

#### Malabsorption in abetalipoproteinaemia

- **BY MOUTH**
  - Adult: 50–100 mg/kg once daily

- **CAUTIONS**
  - Predisposition to thrombosis

- **INTERACTIONS**
  - Appendix 1: vitamin E substances

- **SIDE-EFFECTS**
  - Abdominal pain

- **PREGNANCY**
  - No evidence of safety of high doses.

- **BREAST FEEDING**
  - Excreted in milk; minimal risk, although caution with large doses.

- **MONITORING REQUIREMENTS**
  - Increased bleeding tendency in vitamin-K deficient patients or those taking anticoagulants (prothrombin time and INR should be monitored).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: chewable tablet

#### Oral suspension

- **EXCipients:** May contain Sucrose
  - **Alpha tocopheryl acetate (Non-proprietary)**
    - Alpha tocopheryl acetate 100 mg per 1 ml
      - Alpha tocopheryl acetate 500 mg/5 ml oral suspension | 100 ml (Rx) £67.97 DT = £67.97
    - **Liqua-E** (TriOn Pharma Ltd)
      - Alpha tocopheryl acetate 100 mg per 1 ml
        - Liqua-E 500 mg/5 ml oral suspension | 100 ml £52.96 DT = £67.97

#### Chewable tablet

- **E-Tabs** (Ennogen Healthcare Ltd)
  - Alpha tocopheryl acetate 100 mg | E-Tabs 100 mg chewable tablets | 30 tablet £87.30
- **Ephynal** (Imported (Italy))
  - Alpha tocopheryl acetate 100 mg | Ephynal 100 mg chewable tablets | 30 tablet £163.65

- **Capsule**
  - **Alpha tocopheryl acetate (Non-proprietary)**
    - Alpha tocopheryl acetate 75 unit | Vitamin E 75 unit capsules | 100 capsule £13.05
    - Alpha tocopheryl acetate 200 unit | Vitamin E 200 unit capsules | 30 capsule £10.05
    - Alpha tocopheryl acetate 400 unit | Vitamin E 400 unit capsules | 30 capsule £15.12
  - **E-Caps** (Ennogen Healthcare Ltd)
    - Alpha tocopheryl acetate 75 unit | E-Caps 75 unit capsules | 100 capsule £109.50
    - Alpha tocopheryl acetate 100 unit | E-Caps 100 unit capsules | 30 capsule £94.40
    - Alpha tocopheryl acetate 200 unit | E-Caps 200 unit capsules | 30 capsule £189.50
    - Alpha tocopheryl acetate 400 unit | E-Caps 400 unit capsules | 30 capsule £128.50
    - Alpha tocopheryl acetate 1000 unit | E-Caps 1,000 unit capsules | 30 capsule £130.20

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VITAMINS AND TRACE ELEMENTS  >  VITAMIN K

**Menadiol sodium phosphate**

- **INDICATIONS AND DOSE**
  - **Prevention of Vitamin K deficiency in malabsorption syndromes**
    - **BY MOUTH**
      - **Adult:** 10–40 mg daily, dose to be adjusted as necessary

- **CONTRA-INDICATIONS**
  - Infants - neonates

- **CAUTIONS**
  - G6PD deficiency (risk of haemolysis), vitamin E deficiency (risk of haemolysis)

- **PREGNANCY**
  - Avoid in late pregnancy and labour unless benefit outweighs risk of neonatal haemolytic anaemia, hyperbilirubinaemia, and kernicterus in neonate.

- **MEDICINAL FORMS**
  - No licensed medicines listed.

**Phytomenadione**

*(Vitamin K₃)*

- **INDICATIONS AND DOSE**
  - **Major bleeding in patients on warfarin (in combination with dried prothrombin complex or fresh frozen plasma)**
    - **BY MOUTH**
      - **Adult:** 5 mg for 1 dose, stop warfarin treatment
    - **INR > 8.0 with minor bleeding in patients on warfarin**
      - **BY SLOW INTRAVENOUS INJECTION**
        - **Adult:** 1–3 mg, stop warfarin treatment, dose may be repeated if INR still too high after 24 hours, restart warfarin treatment when INR <5
    - **INR > 8.0 with no bleeding in patients on warfarin**
      - **BY MOUTH**
        - **Adult:** 1–5 mg, intravenous preparation to be used orally, stop warfarin treatment, repeat dose if INR still too high after 24 hours, restart warfarin treatment when INR <5
    - **INR 5.0–8.0 with minor bleeding in patients on warfarin**
      - **BY SLOW INTRAVENOUS INJECTION**
        - **Adult:** 1–3 mg, stop warfarin treatment, restart warfarin treatment when INR <5
    - **Reversal of anticoagulation prior to elective surgery (after warfarin stopped)**
      - **BY MOUTH**
        - **Adult:** 1–5 mg, intravenous preparation to be used orally, dose to be given the day before surgery if INR ≥1.5
    - **Reversal of anticoagulation prior to emergency surgery (when surgery can be delayed 6–12 hours)**
      - **BY INTRAVENOUS INJECTION**
        - **Adult:** 5 mg as a single dose, if surgery cannot be delayed, dried prothrombin complex can be given in addition to phytomenadione and the INR checked before surgery

- **UNLICENSED USE**
  - Oral use of intravenous preparations is unlicensed.

- **CAUTIONS**
  - Intravenous injections should be given very slowly—risk of vascular collapse

- **PREGNANCY**
  - Use if potential benefit outweighs risk.

- **BREAST FEEDING**
  - Present in milk.

- **HEPATIC IMPAIRMENT**

- **DIRECTIONS FOR ADMINISTRATION**
  - Konakion® MM Paediatric Konakion® MM Paediatric may be administered by mouth or by intramuscular injection or by intravenous injection. For intravenous injection, may be diluted with Glucose 5% if necessary.
  - Konakion® MM Konakion® MM may be administered by slow intravenous injection or by intravenous infusion in glucose 5%; *not* for intramuscular injection. For intravenous infusion (Konakion® MM), give intermittently in Glucose 5%; dilute with 55 ml; may be injected into lower part of infusion apparatus.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule, oral suspension, oral solution

- **Solution for injection**

  - **EXCIPIENTS:** May contain Glycocholic acid, lecithin
  - Konakion MM (Cheplapharm Arzneimittel GmbH)
    - Phytomenadione 10 mg per 1 ml Konakion MM Paediatric 2mg/0.2ml solution for injection ampoules | 5 ampoules | £4.71
    - Konakion MM 10mg/1ml solution for injection ampoules | 10 ampoule | £3.78

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**Neural tube defects (prevention in pregnancy)**

**Neural tube defects (prevention in pregnancy)**

**Description of condition**

Neural tube defects represent a group of congenital defects, caused by incomplete closure of the neural tube within 28 days of conception. The most common forms are anencephaly, spina bifida and encephalocele. The main risk factors are maternal folate deficiency, maternal vitamin B₁₂ deficiency, previous history of having an infant with a neural tube defect, smoking, diabetes, obesity, and use of antiepileptic drugs. For information on smoking cessation see Smoking cessation p. 497.

**Prevention in pregnancy**

- **LEGO** Pregnant women or women who wish to become pregnant should be advised to take supplementation with folic acid p. 1025 before conception and until week 12 of pregnancy.
- A higher daily dose (see folic acid) is recommended for women at a high risk of conceiving a child with a neural tube defect, including women who have previously had an infant with a neural tube defect, who are receiving antiepileptic medication (see Epilepsy p. 305), or who have diabetes or sickle-cell disease.
Useful Resources
www.nice.org.uk/guidance/cg62
www.nice.org.uk/guidance/cg156
# Chapter 10
## Musculoskeletal system

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## 1 Arthritis

### Osteoarthritis and soft-tissue disorders

**Overview**

For pain relief in osteoarthritis and soft-tissue disorders, paracetamol p. 444 should be used first and may need to be taken regularly. A topical NSAID or topical capsaicin 0.025% p. 483 should also be considered, particularly in knee or hand osteoarthritis. An oral NSAID can be substituted for, or used in addition to, paracetamol. If further pain relief is required in osteoarthritis, then the addition of an opioid analgesic may be considered, but with a substantial risk of adverse effects; however, an opioid analgesic should be considered before a NSAID in patients taking low-dose aspirin.

Intra-articular corticosteroid injections may produce temporary benefit in osteoarthritis, especially if associated with soft-tissue inflammation. Non-drug measures, such as weight reduction and exercise, should also be encouraged.

Glucosamine p. 1095 and rabeprazole sodium are not recommended for the treatment of osteoarthritis. Hyaluronic acid and its derivatives are available for osteoarthritis of the knee, but are not recommended. Sodium hyaluronate p. 1169 (Durolane®, Euflexxa®, Femhylar®, Orthovisc®, Ostenil®, Ostenil Plus®, Renexa®, Suplasyrn®, Synocrom®, Synvisc®) or hylan G-F 20 (Synvisc®) is injected intra-articularly to supplement natural hyaluronic acid in the synovial fluid. These injections may reduce pain over 1–6 months, but are associated with a short-term increase in knee inflammation. Sodium hyaluronate (SportVis®) is also licensed for the relief of pain and optimisation of recovery following ankle sprain, and for the relief of chronic pain and disability associated with tennis elbow.

### Rheumatoid arthritis

**Description of condition**

Rheumatoid arthritis is a chronic systemic inflammatory disease that causes persistent symmetrical joint synovitis (inflammation of the synovial membrane) typically of the small joints of the hands and feet, although any synovial joint can be affected. Synovitis presents as pain and prolonged stiffness that tends to be worse at rest or following periods of inactivity, swelling, tenderness, and heat in the affected joints. Other symptoms of rheumatoid arthritis include rheumatoid nodules and non-specific symptoms such as malaise, fatigue, fever, and weight loss.

As the disease progresses, it can cause joint deformity and affect different organs of the body, such as the heart, lungs, and eyes; therefore early diagnosis and treatment of rheumatoid arthritis is essential to reduce the impact of the disease.

Palindromic rheumatism is a rare form of inflammatory arthritis which causes attacks of joint pain and swelling similar to rheumatoid arthritis, but the joints return to normal in between attacks. Patients with palindromic rheumatism may later develop rheumatoid arthritis.

**Aims of treatment**

The aims of treatment are to relieve the symptoms of rheumatoid arthritis, achieve disease remission or low disease activity if remission cannot be achieved, and to improve the patient’s ability to perform daily activities.

**Non-drug treatment**

Patients with rheumatoid arthritis should have access to a multidisciplinary team, and may benefit from physiotherapy to encourage exercise, enhance flexibility of joints and strengthen muscles. Psychological interventions such as relaxation, stress management, and cognitive coping skills to support patients with their perception and management of their disease can also be offered.

**Drug treatment**

All patients with suspected persistent synovitis of unknown cause should be referred to a specialist for advice as soon as possible to confirm diagnosis and evaluate disease activity.

In patients with newly diagnosed active rheumatoid arthritis, monotherapy with a conventional disease-modifying antirheumatic drug (DMARD), either oral methotrexate p. 913, leflunomide p. 1096, or sulfasalazine p. 44, should be given as first-line treatment; hydroxychloroquine sulfate p. 1095, a weak DMARD, is an alternative in patients with mild rheumatoid arthritis or those with palindromic rheumatism. Treatment should be started as soon as possible, ideally within 3 months of onset of persistent symptoms, and the dose should be titrated to the maximum tolerated effective dose.

Conventional DMARDs have a slow onset of action and can take 2–3 months to take effect. Consider short-term bridging treatment with a corticosteroid (by oral, intramuscular, or intra-articular administration) when starting treatment with a new DMARD to provide rapid symptomatic control, while waiting for the DMARD to take
effect. Short-term corticosteroids should also be given to rapidly decrease inflammation during flare-ups.

If symptoms of rheumatoid arthritis are inadequately controlled despite dose escalation on DMARD monotherapy, combination therapy with another conventional DMARD (either oral methotrexate p. 913, leflunomide p. 1096, sulfasalazine p. 44, or hydroxychloroquine sulfate p. 1095) should be given.

Treatment with a tumour necrosis factor (TNF) alpha inhibitor (either adalimumab p. 1108, certolizumab pegol p. 1111, etanercept p. 1113, golimumab p. 1115, or infliximab p. 1116), other biological DMARD (either abatacept p. 1107, sarilumab p. 1099, or tocilizumab p. 1101), or targeted synthetic DMARD (either baricitinib p. 1104 or tofacitinib p. 1105) is recommended if there has been an inadequate response to combination therapy with conventional DMARDS. See National funding/access decisions for individual drugs for full prescribing information.

Rituximab p. 882 in combination with methotrexate p. 913 is an alternative option for patients with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of other DMARDS, including at least one TNF alpha inhibitor. See National funding/access decisions for rituximab p. 882.

In patients with established rheumatoid arthritis, the long-term use of corticosteroids should only be continued if all other treatments options (including biological and targeted synthetic DMARDS) have been offered.

Patients with active rheumatoid arthritis should be monitored monthly until the treatment target (either remission or low disease activity) has been achieved, and all patients with rheumatoid arthritis should be reviewed annually. In patients who have maintained the treatment target for at least 1 year without corticosteroids, cautiously reducing drug doses to the lowest that are clinically effective, or tapering and stopping at least one drug if the patient is being treated with two or more DMARDS should be considered.

Older conventional DMARDS such as sodium aurothiomalate p. 1098 (gold), azathioprine p. 836, cyclosporin p. 838 and penicillamine p. 1097 are no longer commonly used in practice due to the availability of newer, more effective drugs.

Pain relief

Short-term use of an oral non-steroidal anti-inflammatory drug (NSAID) or a selective cyclo-oxygenase-2 inhibitor should be considered for additional control of pain in patients whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

Surgery

Surgery may be an option for some patients if drug treatment has failed to adequately manage persistent pain due to joint damage or other identifiable soft tissue causes, if there is worsening of joint function, progressive deformity, or persistent localised synovitis.

Useful Resources

Psoriatic arthritis and other peripheral spondyloarthritides

Monotherapy with local corticosteroid injections should be considered for non-progressive monoarthritis (see Corticosteroids, inflammatory disorders p. 1153).

Standard DMARDs, such as methotrexate p. 913, leflunomide p. 1096 or sulfasalazine p. 44, can be used for patients with peripheral polyarthritis, oligoarthritis, or persistent or progressive monoarthritis associated with peripheral spondyloarthritis.

Standard DMARDs, such as methotrexate p. 913 or leflunomide p. 1096 can also be used for patients with psoriatic arthritis.

The choice of DMARD will depend on numerous factors such as the patient’s circumstances (such as pregnancy planning and alcohol consumption), comorbidities (such as uveitis, psoriasis and inflammatory bowel disease), and potential side-effects.

If a standard DMARD taken at the maximum tolerated dose for at least 3 months does not provide adequate relief from symptoms, a switch to, or the addition of, another standard DMARD can be considered.

An NSAID can be used as an adjunct to standard DMARDs or biological DMARDs to manage symptoms. If NSAIDs do not provide adequate relief from symptoms, consider corticosteroid injections or short-term oral corticosteroid therapy as an adjunct to standard DMARDs or biological DMARDs to manage symptoms.

If extra-articular disease is adequately controlled by an existing standard DMARD but peripheral spondyloarthritides is not, consider adding another standard DMARD.

Further options for psoriatic arthritis

The targeted DMARD apremilast p. 1119, used alone or in combination with standard DMARDs, is recommended for the treatment of active and progressive psoriatic arthritis if the patient has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, and the psoriatic arthritis has not responded to at least 2 standard DMARDs given alone or in combination.

The biological DMARDs etanercept p. 1113, infliximab p. 1116, golimumab p. 1115 and adalimumab p. 1108 (TNF-alpha inhibitors) are recommended for the treatment of active and progressive psoriatic arthritis if the patient has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, and the psoriatic arthritis has not responded to at least 2 standard DMARDs given alone or in combination.

Ustekinumab p. 1103, alone or in combination with methotrexate, is recommended for treating active psoriatic arthritis when treatment with TNF-alpha inhibitors is contra-indicated but would otherwise be considered or the patient has had treatment with one or more TNF-alpha inhibitors. The response to treatment should be assessed at 24 weeks and should only be continued if there is clear evidence of response.

Reactive arthritis

After treating the initial infection, do not offer long-term (4 weeks or longer) treatment with an antibacterial solely to manage reactive arthritis caused by a gastrointestinal or genito-urinary infection.

Useful Resources


Rheumatic disease, suppressing drugs

Overview

Certain drugs such as those affecting the immune response can suppress the disease process in rheumatoid arthritis and psoriatic arthritis, see Rheumatoid arthritis p. 1091 or Spondyloarthritis p. 1092. Systemic and discoid lupus erythematosus are sometimes treated with chloroquine p. 616 or hydroxychloroquine sulfate p. 1095.

The choice of a disease-modifying antirheumatic drug (DMARD) should take into account co-morbidity and patient preference. Methotrexate p. 913, sulfasalazine p. 44, intramuscular gold, and penicillamine p. 1097 are similar in efficacy. However, methotrexate or sulfasalazine may be better tolerated.

Gold

Gold, given as sodium aurothiomalate p. 1098, is licensed for active progressive rheumatoid arthritis; it must be given by deep intramuscular injection and the area gently massaged. A test dose must be given followed by doses at weekly intervals until there is definite evidence of remission. In patients who do respond, the interval between injections is then gradually increased to 4 weeks and treatment is continued for up to 5 years after complete remission. If relapse occurs the dosage frequency may be immediately increased and only once control has been obtained again should the dosage frequency be decreased; if no response is seen within 2 months, alternative treatment should be sought. It is important to avoid complete relapse since second courses of gold are not usually effective.

Penicillamine

Penicillamine has a similar action to gold. More patients are able to continue treatment than with gold but side-effects are common.

Patients should be warned not to expect improvement for at least 6 to 12 weeks after treatment is initiated. Penicillamine should be discontinued if there is no improvement within 1 year.

Sulfasalazine

Sulfasalazine has a beneficial effect in suppressing the inflammatory activity of rheumatoid arthritis. Sulfasalazine may also be used by specialists, in the management of psoriatic arthritis affecting peripheral joints [unlicensed indication]. Haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment.

Antimalarials

The antimalarial hydroxychloroquine sulfate is used to treat rheumatoid arthritis of mild inflammatory activity; chloroquine is also licensed for treating inflammatory disorders but is used much less frequently and is generally reserved for use if other drugs have failed.

Chloroquine and hydroxychloroquine sulfate are effective for mild systemic lupus erythematosus, particularly involving the skin and joints. These drugs should not be used for psoriatic arthritis. Chloroquine and hydroxychloroquine sulfate are better tolerated than gold or penicillamine. Retinopathy rarely occurs provided that the recommended doses are not exceeded; in the elderly it is difficult to distinguish drug-induced retinopathy from changes of ageing.

Mepacrine hydrochloride p. 505 is sometimes used in discoid lupus erythematosus [unlicensed].
Drugs affecting the immune response

Methotrexate is a DMARD used in active rheumatoid arthritis. Methotrexate is usually given by mouth once a week, adjusted according to response. In patients who experience mucosal or gastro-intestinal side-effects with methotrexate, folic acid p. 1025 given every week [unlicensed indication], on a different day from the methotrexate, may help to reduce the frequency of such side-effects.

Leflunomide p. 1096 acts on the immune system as a DMARD. Its therapeutic effect starts after 4–6 weeks and improvement may continue for a further 4–6 months.

Drugs that affect the immune response are also used in the management of severe cases of systemic lupus erythematosus and other connective tissue disorders. They are often given in conjunction with corticosteroids for patients with severe or progressive renal disease. They may be used in cases of polymyositis that are resistant to corticosteroids. They are used for their corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive. Azathioprine p. 836 is usually used.

In the specialist management of psoriatic arthritis affecting peripheral joints, leflunomide, methotrexate, or azathioprine [unlicensed indication] may be used.

Juvenile idiopathic arthritis

Many children with juvenile idiopathic arthritis (juvenile chronic arthritis) do not require DMARDs. Methotrexate is effective; sulfasalazine is an alternative [unlicensed indication] but it should be avoided in systemic-onset juvenile idiopathic arthritis. Gold and penicillamine are no longer used. Cytokine modulators have a role in juvenile idiopathic arthritis.

Cytokine modulators

Cytokine modulators should be used under specialist supervision.


Adalimumab is licensed for moderate to severe active rheumatoid arthritis when response to other DMARDs (including methotrexate) has been inadequate; it is also licensed for severe, active, and progressive disease in adults not previously treated with methotrexate. In the treatment of rheumatoid arthritis, adalimumab should be used in combination with methotrexate, but it can be given alone if methotrexate is inappropriate. Adalimumab is also licensed for the treatment of active and progressive psoriatic arthritis and severe active ankylosing spondylitis that have not responded adequately to other DMARDs. It is also licensed for the treatment of severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs.

Adalimumab also has a role in inflammatory bowel disease and plaque psoriasis.

Certolizumab pegol is licensed for use in patients with moderate to severe active rheumatoid arthritis when response to DMARDs (including methotrexate) has been inadequate. Certolizumab pegol can be used in combination with methotrexate, or as a monotherapy if methotrexate is not tolerated or is contra-indicated. Certolizumab pegol is also licensed for the treatment of severe active ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of NSAIDs. It is also licensed for the treatment of severe active axial spondyloarthritis, without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs.

Etanercept is licensed for the treatment of moderate to severe active rheumatoid arthritis either alone or in combination with methotrexate when the response to other DMARDs is inadequate and in severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate. It is also licensed for the treatment of active and progressive psoriatic arthritis inadequately responsive to other DMARDs, and for severe ankylosing spondylitis inadequately responsive to conventional therapy. Etanercept also has a role in plaque psoriasis.

Golimumab is licensed in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis when response to DMARD therapy (including methotrexate) has been inadequate; it is also licensed in combination with methotrexate for patients with severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate. Golimumab is also licensed for the treatment of active and progressive psoriatic arthritis, as monotherapy or in combination with methotrexate p. 913, when response to DMARD therapy has been inadequate; it is also licensed for the treatment of severe active ankylosing spondylitis when there is an inadequate response to conventional treatment.

Infliximab p. 1116 is licensed for the treatment of active rheumatoid arthritis in combination with methotrexate when the response to other DMARDs, including methotrexate, is inadequate; it is also licensed in combination with methotrexate for patients not previously treated with methotrexate or other DMARDs who have severe, active, and progressive rheumatoid arthritis. Infliximab is also licensed for the treatment of ankylosing spondylitis, in patients with severe axial symptoms who have not responded adequately to conventional therapy, and in combination with methotrexate (or alone if methotrexate is not tolerated or is contra-indicated) for the treatment of active and progressive psoriatic arthritis which has not responded adequately to DMARDs.

Rituximab p. 882 is licensed in combination with methotrexate for the treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other DMARDs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them. Rituximab has a role in malignant disease.

Abatacept p. 1107 prevents the full activation of T-lymphocytes. It is licensed for moderate to severe active rheumatoid arthritis in combination with methotrexate, in patients unresponsive to other DMARDs (including methotrexate or a tumour necrosis factor (TNF) inhibitor). Abatacept is not recommended for use in combination with TNF inhibitors.

Anakinra p. 1098 inhibits the activity of interleukin-1.

Anakinra (in combination with methotrexate) is licensed for the treatment of rheumatoid arthritis which has not responded to methotrexate alone. Anakinra is no longer recommended for the treatment of rheumatoid arthritis except when used in a controlled long-term clinical study. Patients who are already receiving anakinra for rheumatoid arthritis should continue treatment until they and their specialist consider it appropriate to stop.

Baricitinib p. 1104 and tofacitinib p. 1105 are licensed alone or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in patients who have had an inadequate response to, or who are intolerant to, one or more DMARDs.

Belimumab p. 845 inhibits the activity of B-lymphocyte stimulator. Belimumab is licensed as an adjunctive therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy.

Sarilumab p. 1099 is a recombinant human monoclonal antibody that specifically binds to interleukin-6 receptors and blocks the activity of pro-inflammatory cytokines; it is...
licensed alone or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in patients who have had an inadequate response to, or are intolerant to one or more DMARDs.

Secukinumab p. 1100 inhibits the activity of interleukin-17A. Secukinumab is licensed for the treatment of active psoriatic arthritis, in combination with methotrexate or alone, which has not responded adequately to DMARDs; it is also licensed for the treatment of ankylosing spondylitis, in patients who have not responded adequately to conventional therapy. Secukinumab also has a role in plaque psoriasis. Tocilizumab p. 1101 antagonises the actions of interleukin-6. Tocilizumab is licensed for use in patients with moderate to severe active rheumatoid arthritis when response to at least one DMARD or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs. Tocilizumab can be used in combination with methotrexate, or as monotherapy if methotrexate is not tolerated or is contra-indicated.

Ustekinumab p. 1103 inhibits the activity of interleukins 12 and 23. It is licensed for the treatment of active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more DMARDs.

**Other drugs used for Arthritis**

Aceclofenac, p. 1132 • Celecoxib, p. 1132 • Cyclophosphamide, p. 894 • Dexamethasone, p. 1132 • Diclofenac sodium, p. 1135 • Etodolac, p. 1138 • Etoricoxib, p. 1139 • Flurbiprofen, p. 1140 • Ibuprofen, p. 1141 • Indomethacin, p. 1143 • Ixekizumab, p. 1259 • Ketoprofen, p. 1144 • Mefenamic acid, p. 1145 • Meloxicam, p. 1146 • Nabumetone, p. 1147 • Naproxen, p. 1148 • Piroxicam, p. 1149 • Salicylic acid, p. 1150 • Tenoxicam, p. 1151 • Tiaprofenic acid, p. 1152

**Glucosamine**

*Drug Action* Glucosamine is a natural substance found in mucopolysaccharides, mucoproteins, and chitin.

**Indications and Dose**

**ALETIS®**

Symptomatic relief of mild to moderate osteoarthritides of the knee

- **By mouth**
- Adult: 1250 mg once daily, review treatment if no benefit after 2–3 months

**DOLENIO®**

Symptomatic relief of mild to moderate osteoarthritides of the knee

- **By mouth**
- Adult: 1500 mg once daily, review treatment if no benefit after 2–3 months

**GLUSARTEL®**

Symptomatic relief of mild to moderate osteoarthritides of the knee

- **By mouth**
- Adult: 1500 mg once daily, dose to be dissolved in at least 250 mL of water, review treatment if no benefit after 2–3 months

**Caution** Asthma - impaired glucose tolerance - predisposition to cardiovascular disease

**Interactions** → Appendix 1: glucosamine

**Side-effects**

- Common or very common Constipation - diarrhoea - fatigue - gastrointestinal discomfort - headache - nausea

**Hydroxychloroquine sulfate**

*Drug Action* Active rheumatoid arthritis (administered on expert advice) • Systemic and discoid lupus erythematosus (administered on expert advice) • Dermatological conditions caused or aggravated by sunlight (administered on expert advice)

- **By mouth**
  - Adult: 200–400 mg daily, daily maximum dose to be based on ideal body-weight; maximum 6.5 mg/kg per day

**Caution** Acute porphyrias p. 1058 • Diabetes (may lower blood glucose) • Elderly • G6PD deficiency • May aggravate myasthenia gravis • May exacerbate psoriasis • Neurological disorders (especially in those with a history of epilepsy—may lower seizure threshold) • Severe gastro-intestinal disorders

**Caution: Further Information** Screening for retinopathy A review group convened by the Royal College of Ophthalmologists has updated guidelines on screening for chloroquine and hydroxychloroquine retinopathy (Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Screening 2018). Recent data have highlighted that hydroxychloroquine retinopathy is more common than previously reported. Screening recommendations for hydroxychloroquine:
Arthritis

- All patients planning to be on long-term treatment should receive a baseline examination (including fundus photography and spectral domain optical coherence tomography) within 6–12 months of treatment initiation.
- Annual screening is recommended in all patients who have taken hydroxychloroquine for greater than 5 years.
- Annual screening may be commenced before 5 years of treatment if additional risk factors for retinal toxicity exist, such as concomitant tamoxifen therapy, impaired renal function (eGFR less than 60 mL/minute/1.73 m²) or high-dose therapy (greater than 5 mg/kg/day of hydroxychloroquine sulfate).

INTERACTIONS → Appendix 1: hydroxychloroquine

SIDE-EFFECTS
- Common or very common Abdominal pain - appetite decreased - diarrhoea - emotional lability - headache - nausea - skin reactions - vision disorders - vomiting
- Uncommon Alopecia - corneal oedema - dizziness - eye disorders - hair colour changes - nervousness - neuromuscular dysfunction - retinopathy - seizure - tinnitus - vertigo
- Frequency not known Acute hepatic failure - agranulocytosis - anaemia - angioedema - bone marrow disorders - bronchospasm - cardiac conduction disorders - cardiomyopathy - hearing loss - hypoglycaemia - leucopenia - movement disorders - muscle weakness - myopathy - photosensitivity reaction - psychosis - reflexes absent - severe cutaneous adverse reactions (SCARs) - thrombocytopenia - tremor - ventricular hypertrophy

OVERDOSE Hydroxychloroquine is very toxic in overdosage; overdosage is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

PREGNANCY It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease is well controlled; however, the manufacturer of hydroxychloroquine advises avoiding use.

BREAST FEEDING Avoid—risk of toxicity in infant.

HEPATIC IMPAIRMENT Caution in moderate to severe hepatic impairment.

RENAL IMPAIRMENT Manufacturer advises caution.

Monitoring Monitor plasma-hydroxychloroquine concentration in severe renal impairment.

MONITORING REQUIREMENTS Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory (see advice of the Royal College of Ophthalmologists).

PRESCRIBING AND DISPENSING INFORMATION To avoid excessive dosage in obese patients, the dose of hydroxychloroquine should be calculated on the basis of ideal body-weight.

MEDICINAL FORMS There can be a variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 21
- Hydroxychloroquine sulfate (non-proprietary)
  - Hydroxychloroquine sulfate 200 mg Hydroxychloroquine 200mg tablets | 60 tablet [PHB] £32.49 DT = £3.70
  - Quinoric (Bristol Laboratories Ltd)
  - Hydroxychloroquine sulfate 200 mg Quinoric 200mg tablets | 60 tablet [PHB] £4.75 DT = £3.70

Leflunomide

MODERATE AND DOSE

Moderate to severe active rheumatoid arthritis (specialist use only)

BY MOUTH
- Adult: Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily

Active psoriatic arthritis (specialist use only)

BY MOUTH
- Adult: Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily

CONTRA-INDICATIONS Serious infection - severe hypoproteinaemia - severe immunodeficiency

CAUTIONS Anaemia (avoid if significant and due to causes other than rheumatoid arthritis). History of tuberculosis - impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis). Leucopenia (avoid if significant and due to causes other than rheumatoid arthritis). Thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis)

INTERACTIONS → Appendix 1: leflunomide

SIDE-EFFECTS
- Common or very common Abdominal pain - accelerated hair loss - appetite decreased - asthenia - diarrhoea - dizziness - gastrointestinal disorders - headache - leucopenia - nausea - oral disorders - paraesthesia - peripheral neuropathy - skin reactions - tendon disorders - vomiting - weight decreased
- Uncommon Anaemia - anxiety - electrolyte imbalance - hyperlipidaemia - taste altered - thrombocytopenia
- Rare or very rare Agranulocytosis - eosinophilia - hepatic disorders - infection - pancreatitis - pancytopenia - respiratory disorders - sepsis - severe cutaneous adverse reactions (SCARs) - vasculitis
- Frequency not known Cutaneous lupus erythematosus - hypuricaemia - pulmonary hypertension - renal failure

SIDE-EFFECTS, FURTHER INFORMATION Discontinue treatment and institute washout procedure in case of serious side-effect (consult product literature).

Hepatotoxicity Potentially life-threatening hepatotoxicity reported usually in the first 6 months. Discontinue treatment and institute washout procedure—consult product literature or reduce dose according to liver-function abnormality; if liver-function abnormality persists after dose reduction, discontinue treatment and institute washout procedure.

CONCEPTION AND CONTRACEPTION Effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required; waiting time before conception may be reduced with washout procedure—consult product literature). The concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception—consult product literature.

PREGNANCY Avoid—active metabolite teratogenic in animal studies.

BREAST FEEDING Present in milk in animal studies—manufacturer advises avoid.

HEPATIC IMPAIRMENT Manufacturer advises avoid—active metabolite may accumulate.

RENAL IMPAIRMENT Manufacturer advises avoid in moderate or severe impairment—no information available.

PRE-TREATMENT SCREENING Exclude pregnancy before treatment.

www.getintopharma.com
\[ \text{TREATMENT CESSION} \]
Washout Procedure The active metabolite persists for a long period; to aid drug elimination in case of serious adverse effect, or before starting another disease-modifying antirheumatic drug, or before conception, stop treatment and give either colestyramine p. 197 or charcoal, activated p. 1366. Procedure may be repeated as necessary.

\[ \text{MONITORING REQUIREMENTS} \]
- Monitor full blood count (including differential white cell count and platelet count) before treatment and every 2 weeks for 6 months then every 8 weeks.
- Monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks.
- Monitor blood pressure.

\[ \text{INTERACTIONS} \]
- Lupus erythematosus
- Neurological involvement in Wilson’s disease

\[ \text{SIDE-EFFECTS} \]
- Common or very common: Proteinuria - thrombocytopenia
- Rare or very rare: Alopeica - breast enlargement (males and females) - connective tissue disorders - haematuria (discontinue immediately if cause unknown)
- Hypersensitivity - oral disorders - skin reactions

\[ \text{FURTHER INFORMATION} \]
Proteinuria occurs in up to 30% of patients — can be a sign of immune-mediated nephropathy. Discontinue immediately if nephrotoxicity occurs.

Nausea and rash more common early in treatment if full dose used from initiation. Delayed rash can occur after months or years of treatment — manufacturer advises reduce dose.

\[ \text{CONTRA-INDICATIONS} \]
Lupus erythematosus

\[ \text{CAUTIONS} \]
Neurological involvement in Wilson’s disease

\[ \text{MEDICINAL FORMS} \]
There can be variation in the licensing of different medicines containing the same drug.

\[ \text{DRUG ACTION} \]
Penicillamine aids the elimination of copper ions in Wilson’s disease (hepatolenticular degeneration).

\[ \text{INDICATIONS AND DOSE} \]
Severe active rheumatoid arthritis (administered on expert advice)
- BY MOUTH: Initially 125–250 mg daily for 1 month, then increased in steps of 125–250 mg, at intervals of not less than 4 weeks; maintenance 500–750 mg daily in divided doses, then reduced in steps of 125–250 mg every 12 weeks, dose reduction attempted only if remission sustained for 6 months; maximum 1.5 g per day.
- Elderly: Initially up to 125 mg daily for 1 month, then increased in steps of up to 125 mg, at intervals of at least 4 weeks; maximum 1 g per day.

Wilson’s disease
- BY MOUTH: Initially 1.5–2 g daily in divided doses, adjusted according to response, to be taken before food; maintenance 0.75–1 g daily, a dose of 2 g daily should not be continued for more than one year; maximum 2 g per day.
- Elderly: 20 mg/kg daily in divided doses, adjusted according to response.

Autoimmune hepatitis (used rarely; after disease controlled with corticosteroids)
- BY MOUTH
- Adult: Initially 500 mg daily in divided doses, to be increased slowly over 3 months; maintenance 1.25 g daily.

Cystinuria, prophylactic
- BY MOUTH
- Adult: 0.5–1 g daily, maintain urinary cystine below 300 mg/litre and adequate fluid intake (at least 3 litres daily), to be taken at bedtime.
- Elderly: Minimum dose to maintain urinary cystine below 200 mg/litre is recommended.

\[ \text{SIDE-EFFECTS} \]
- Common or very common: Proteinuria - thrombocytopenia
- Rare or very rare: Alopeica - breast enlargement (males and females) - connective tissue disorders - haematuria (discontinue immediately if cause unknown)
- Hypersensitivity - oral disorders - skin reactions

\[ \text{SIDE-EFFECTS, FURTHER INFORMATION} \]
Proteinuria occurs in up to 30% of patients — can be a sign of immune-mediated nephropathy. Discontinue immediately if nephrotoxicity occurs.

Nausea and rash more common early in treatment if full dose used from initiation. Delayed rash can occur after months or years of treatment — manufacturer advises reduce dose.

\[ \text{ALLERGY AND CROSS-SENSITIVITY} \]
Patients who are hypersensitive to penicillin may react rarely to penicillamine.

\[ \text{PREGNANCY} \]
Fetal abnormalities reported rarely; avoid if possible.

\[ \text{BREAST FEEDING} \]
Manufacturer advises avoid unless potential benefit outweighs risk — no information available.

\[ \text{RENAL IMPAIRMENT} \]
Dose adjustments: Reduce dose and monitor renal function or avoid (consult product literature).

\[ \text{MONITORING REQUIREMENTS} \]
Consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 2500/mm³ or if 3 successive falls within reference range (can restart at reduced dose when counts return to known reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia).

Blood counts, including platelets, and urine examinations should be carried out before starting treatment and then every 1 or 2 weeks for the first 2 months then every 4 weeks to detect blood disorders and proteinuria (they should also be carried out in the week after any dose increase).

A reduction in platelet count calls for discontinuation with subsequent re-introduction at a lower dosage and then, if possible, gradual increase.

Longer intervals may be adequate in cystinuria and Wilson’s disease.

\[ \text{PATIENT AND CARER ADVICE} \]
Counselling on the symptoms of blood disorders is advised. Warn patient and carers to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop.
**Sodium aurothiomalate**

**INDICATIONS AND DOSE**

**Active progressive rheumatoid arthritis (administered on expert advice)**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: Test dose 10 mg, followed by 50 mg once weekly until there is definite evidence of remission, then reduced to 50 mg every 4 weeks continued for up to 5 years after complete remission, dose to be reduced gradually. Benefit is not expected until 300–500 mg has been given; it should be discontinued if there is no remission after 1 g has been given.

**Relapse in patients who have previously received sodium aurothiomalate therapy for active progressive rheumatoid arthritis (administered on expert advice)**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 50 mg once weekly until control has been obtained again, then reduced to 50 mg every 4 weeks continued for up to 5 years after complete remission, if no response is seen within 2 months, alternative treatment should be sought.

**CONTRA-INDICATIONS**
- Exfoliative dermatitis
- Blood disorders
- History of bone marrow aplasia
- Necrotising enterocolitis
- Pulmonary fibrosis
- Systemic lupus erythematosus

**CAUTIONS**
- Colitis
- Eczema
- Elderly
- History of urticaria

**CAUTIONS, FURTHER INFORMATION**
- Sodium aurothiomalate should be discontinued in the presence of blood disorders, gastro-intestinal bleeding (associated with ulcerative enterocolitis), or unexplained proteinuria (associated with immune complex nephritis) which is repeatedly above 300 mg/litre.

**INTERACTIONS**
- Appendix 1: sodium aurothiomalate

**SIDE-EFFECTS**
- Abdominal pain
- Agranulocytosis
- Albuminuria
- Alopecia
- Asthenia
- Blood disorder
- Bone marrow disorders
- Circulatory collapse
- Dry cough
- Dyspnoea
- Encephalopathy
- Enterocolitis
- Eosinophilia
- Flashing
- Hepatic disorders
- Hypersensitivity
- Hypotension
- Leucopenia
- Nephrotic syndrome
- Nerve disorders
- Neutropenia
- Palpitations
- Respiratory disorders
- Shock
- Skin reactions
- Tachycardia
- Thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**
- Rash with pruritus often occur after 2 to 6 months of treatment and may necessitate discontinuation.

**PREGNANCY**
- Manufacturer advises avoid but limited data suggests usually not necessary to withdraw if condition well controlled.
- **Dose adjustments**
  - Consider reducing dose and frequency.

**BREAST FEEDING**
- Manufacturer advises avoid—present in milk; theoretical possibility of rashes and idiosyncratic reactions.

**HEPATIC IMPAIRMENT**
- Manufacturer advises avoid in severe impairment.

**RENAI IMPAIRMENT**
- Caution in mild to moderate impairment. Avoid in severe impairment.

**MONITORING REQUIREMENTS**
- Urine tests and full blood counts (including total and differential white cell and platelet counts) must be performed before starting treatment and before each intramuscular injection.
- Monitor for pulmonary fibrosis with annual chest X-ray.

**PATIENT AND CARER ADVICE**
- Patients should be advised to seek prompt medical attention if diarrhoea, sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, metallic taste, rash, breathlessness, or cough develop.

**SIDE-EFFECTS, FURTHER INFORMATION**
- Exfoliative dermatitis
- Rashes with pruritus
- Urticaria
- Fainting
- Shock
- Tachycardia
- Albuminuria
- Abdominal pain
- Dyspnoea
- Agranulocytosis
- Neutropenia
- Albuminuria
- Rash
- Pruritus
- Urticaria
- Fainting
- Shock
- Tachycardia
- Neutropenia
- Alopecia
- Asthenia
- Blood disorder
- Bone marrow disorders
- Circulatory collapse
- Dry cough
- Dyspnoea
- Encephalopathy
- Enterocolitis
- Eosinophilia
- Flashing
- Hepatic disorders
- Hypersensitivity
- Hypotension
- Leucopenia
- Nephrotic syndrome
- Nerve disorders
- Neutropenia
- Palpitations
- Respiratory disorders
- Shock
- Skin reactions
- Tachycardia
- Thrombocytopenia

**IMMUNOSUPPRESSANTS > INTERLEUKIN INHIBITORS**

**Anakinra**

**INDICATIONS AND DOSE**
- **Rheumatoid arthritis (in combination with methotrexate) which has not responded to methotrexate alone (specialist use only)**
  - **BY SUBCUTANEOUS INJECTION**
    - Adult: 100 mg once daily.
    - **Cryoisyrin-associated periodic syndromes (specialist use only)**
      - **BY SUBCUTANEOUS INJECTION**
        - Adult: 1–2 mg/kg daily.
        - **Still's disease (specialist use only)**
          - **BY SUBCUTANEOUS INJECTION**
            - Adult (body-weight up to 49 kg): 1–2 mg/kg daily.
            - Adult (body-weight 50 kg and above): 100 mg daily.

**CONTRA-INDICATIONS**
- Active infection - neutropenia (absolute neutrophil count less than 1.5 × 10^9/litre)—do not initiate — pre-existing malignancy.

**CAUTIONS**
- Elderly
- History of asthma (increased risk of serious infection)
- History of recurrent infection
- Predisposition to infection

**INTERACTIONS**
- Appendix 1: anakinra

**SIDE-EFFECTS**
- Common or very common
  - Headache
  - Infection
  - Neutropenia
  - Thrombocytopenia
- Uncommon
  - Skin reactions
- Frequency not known
  - Hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**
- Neutropenia reported commonly—discontinue if neutropenia develops.

**PREGNANCY**
- Manufacturer advises avoid.

**BREAST FEEDING**
- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- Manufacturer advises caution in severe impairment.

**RENAI IMPAIRMENT**
- Manufacturer advises caution in moderate impairment.
- **Dose adjustments**
  - Manufacturer advises consider alternate day dosing in severe impairment.
Sarilumab

**DRUG ACTION** Sarilumab is a recombinant human monoclonal antibody that specifically binds to interleukin-6 receptors and blocks the activity of pro-inflammatory cytokines.

**INDICATIONS AND DOSE** Moderate-to-severe active rheumatoid arthritis in patients who have had an inadequate response to, or are intolerant to one or more disease-modifying anti-rheumatic drugs (as monotherapy or in combination with methotrexate) (specialist use only)

- **BY SUBCUTANEOUS INJECTION**
  - **Adults:** 200 mg every 2 weeks, for dose adjustments due to neutropenia, thrombocytopenia, or liver enzyme elevations—consult product literature

**CONTRA-INDICATIONS** Do not initiate if absolute neutrophil count less than 2 \( \times 10^9 \)/litre · do not initiate if platelet count less than 150 \( \times 10^9 \)/microlitre · do not initiate if serum transaminases (ALT or AST) greater than 1.5 times the upper limit of normal · severe active infection

**CAUTIONS** Chronic or recurrent infection · elderly (increased risk of infection) · history of diverticulitis · history of intestinal ulceration · history of serious or opportunistic infection · predisposition to infection

**CAUTIONS, FURTHER INFORMATION**

- **Infection** Manufacturer advises caution in patients who have been exposed to tuberculosis, or who have lived in or travelled to areas of endemic tuberculosis or mycoses. Patients with latent tuberculosis should complete anti-tuberculosis therapy before initiation of sarilumab; consider anti-tuberculosis therapy before initiation of sarilumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for those with a negative test for latent tuberculosis but have risk factors for tuberculosis—consultation with a tuberculosis specialist may be appropriate.

  Manufacturer advises patients should be brought up-to-date with current immunisation schedule before initiating treatment.

**INTERACTIONS** → Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

- Common or very common Dyslipidaemia · increased risk of infection · neutropenia · thrombocytopenia
- Frequency not known Hypersensitivity · skin reactions

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception in women of childbearing potential during treatment and for up to 3 months after treatment.

**PREGNANCY** Manufacturer advises avoid unless essential—limited information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid—no information available.

**PRE-TREATMENT SCREENING** Manufacturer advises that patients should be evaluated for tuberculosis before treatment.

**MONITORING REQUIREMENTS**

- Manufacturer advises monitor for signs and symptoms of infection; monitor neutrophil count 4 to 8 weeks after treatment initiation and according to clinical judgement thereafter—discontinue if absolute neutrophil count less than 0.5 \( \times 10^9 \)/litre.
- Manufacturer advises monitor platelet count 4 to 8 weeks after treatment initiation and according to clinical judgement thereafter—discontinue if platelet count less than 50 \( \times 10^9 \)/microlitre.
- Manufacturer advises monitor hepatic transaminases (ALT and AST) 4 to 8 weeks after treatment initiation and every 3 months thereafter, and consider other liver function tests if clinically indicated—discontinue if ALT is greater than 5 times the upper limit of normal.
- Manufacturer advises monitor lipid profile approximately 4 to 8 weeks after treatment initiation and approximately every 6 months thereafter—hyperlipidaemia should be managed according to clinical guidelines.

**DIRECTIONS FOR ADMINISTRATION** Manufacturer advises to avoid injecting into areas of the skin that are tender, damaged, or have bruises or scars; patients may self-administer Kevzara®, after appropriate training in subcutaneous injection technique.

**PRESCRIBING AND DISPENSING INFORMATION** Sarilumab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name; see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1; manufacturer advises to record the brand name and batch number after each administration.
1100 Arthritis

Musculoskeletal system

Sarilumab for moderate-to-severe rheumatoid arthritis

PATIENT AND CARER ADVICE

HANDLING AND STORAGE
Manufacturer advises store in a refrigerator (2–8°C) and protect from light—consult product literature for further information regarding storage outside refrigerator.

PATIENT AND CARER ADVICE
Manufacturer advises patients should be advised to seek immediate medical attention if symptoms of a hypersensitivity reaction occur. Self-administration. Manufacturer advises patients and their carers should be given training in subcutaneous injection technique if appropriate.

Alert card
An alert card should be provided.

Missed doses
Manufacturer advises if a dose is more than 3 days late, the missed dose should not be taken and the next dose should be taken at the normal time.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
- Sarilumab for moderate-to-severe rheumatoid arthritis (November 2017) NICE TA485
  - Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if:
    - disease is severe (a disease activity score [DAS28] of more than 5.1), and
    - the manufacturer provides sarilumab with the discount agreed in the patient access scheme.

- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1), and
  - they cannot have rituximab, and
  - the manufacturer provides sarilumab with the discount agreed in the patient access scheme.

- Sarilumab can be used as monotherapy for people who cannot take methotrexate because it is contra-indicated or because of intolerance, when the above criteria are met.

- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1), and
  - they cannot have rituximab, and
  - the manufacturer provides sarilumab with the discount agreed in the patient access scheme.

- Sarilumab can be used as monotherapy for people who cannot take methotrexate because it is contra-indicated or because of intolerance, when the above criteria are met.

- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1), and
  - the manufacturer provides sarilumab with the discount agreed in the patient access scheme.

- Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

- Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

Scottish Medicines Consortium (SMC) decisions

SCM No. 1314/18
The Scottish Medicines Consortium has advised (April 2018) that sarilumab (Kevzara®) is accepted for restricted use within NHS Scotland for treatment of severely active rheumatoid arthritis (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs). In patients with severe disease inadequately controlled by a TNF antagonist, it may be used in patients ineligible to receive rituximab. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

Kevzara (Sandofi)▼
- Sarilumab 131.6 mg per 1 ml Kevzara 150mg/1.14ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £912.25
- Sarilumab 175 mg per 1 ml Kevzara 200mg/1.14ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £912.25
- Kevzara 200mg/1.14ml solution for injection pre-filled pen | 2 pre-filled disposable injection £912.25

Secukinumab

15-Aug-2017

DRUG ACTION
Secukinumab is a recombinant human monoclonal antibody that selectively binds to cytokine interleukin-17A (IL-17A) and inhibits the release of proinflammatory cytokines and chemokines.

INDICATIONS AND DOSE

Ankylosing spondylitis (initiated by a specialist)
- BY SUBCUTANEOUS INJECTION
  - Adult: 150 mg every week for 5 doses, then maintenance 150 mg every month, review treatment if no response within 16 weeks of initial dose

Psoriatic arthritis (initiated by a specialist)
- BY SUBCUTANEOUS INJECTION
  - Adult: 150 mg every week for 5 doses, then maintenance 150 mg every month, dose may be increased to 300 mg according to clinical response. Review treatment if no response within 16 weeks of initial dose

Psoriatic arthritis with concomitant moderate to severe plaque psoriasis or if inadequate response to anti-TNFα treatment (initiated by a specialist) Plaque psoriasis (initiated by a specialist)
- BY SUBCUTANEOUS INJECTION
  - Adult: 300 mg every week for 5 doses, then maintenance 300 mg every month, review treatment if no response within 16 weeks of initial dose

CONTRA-INDICATIONS
Severe active infection

CAUTIONS
Chronic infection - Crohn’s disease (monitor for exacerbations) - history of recurrent infection - predisposition to infection (discontinue if new serious infection develops)

CAUTIONS, FURTHER INFORMATION
Tuberculosis
Manufacturer advises that patients with latent tuberculosis should complete anti-tuberculosis therapy before starting secukinumab.

INTERACTIONS
- Appendix 1: monoclonal antibodies

SIDE-EFFECTS
Common or very common Diarrhoea - increased risk of infection - rhinorrhoea
Uncommon Conjunctivitis - neutropenia (usually mild and reversible) - urticaria

CONCEPTION AND CONTRACEPTION
Manufacturer advises that women of childbearing potential should use effective contraception during treatment and for at least 20 weeks after stopping treatment.

PREGNANCY
Manufacturer advises avoid—no information available.

BREAST FEEDING
Manufacturer advises avoid during treatment and for up to 20 weeks after discontinuing treatment—no information available.

DIRECTIONS FOR ADMINISTRATION
Manufacturer advises to take the syringe or pen out of the refrigerator
20 minutes before skin administration and to avoid injecting into areas of the skin that show psoriasis. Patients may self-administer Cosentyx® pre-filled pen.

**PATIENT AND CARER ADVICE**
- Self-administration: Patients and their carers should be given training in subcutaneous injection technique.
- Infection: Patients and their carers should be advised to seek immediate medical attention if symptoms of infection develop during treatment with secukinumab.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Secukinumab for treating moderate to severe plaque psoriasis (July 2015) NICE TA350
  - Secukinumab is recommended as an option for the treatment of moderate to severe plaque psoriasis in adults if:
    - the disease has failed to respond to standard systemic treatments (including ciclosporin, methotrexate, and PUVA), or when standard treatments are contra-indicated or not tolerated; and
    - the manufacturer provides secukinumab with the discount agreed in the patient access scheme.
  - Secukinumab should be withdrawn in patients whose psoriasis has not responded adequately within 12 weeks of initial dose; further treatment cycles are not recommended.
  - Patients whose treatment with secukinumab was started before this guidance was published, but does not meet these criteria, should have the option to continue treatment until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/TA350

- Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (September 2016) NICE TA407
  - Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults who have responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors) only if the manufacturer provides secukinumab with the discount agreed in the patient access scheme.
  - Assess response to secukinumab after 16 weeks of treatment and continue only if there is clear evidence of response, defined as a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.
  - www.nice.org.uk/TA407

- Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (May 2017) NICE TA445
  - Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:
    - it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (TA199 recommendations 1.1 and 1.2) or,
    - the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or,
    - TNF-alpha inhibitors are contra-indicated but would otherwise be considered.
  - Secukinumab is only recommended if the manufacturer provides it as agreed in the patient access scheme.
  - Assess the response to secukinumab after 16 weeks of treatment. Treatment should only be continued if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist.
  - Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/guidance/TA445

**Scottish Medicines Consortium (SMC) decisions**
- The Scottish Medicines Consortium has advised (June 2015) that secukinumab (Cosentyx®) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), or when standard treatments cannot be used because of intolerance or contra-indications.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Cosentyx** (Novartis Pharmaceuticals UK Ltd) ▼
  - Secukinumab 150 mg per 1 ml Cosentyx 150mg/1ml solution for injection pre-filled pens | 2 pre-filled disposable injection £123.84
  - Cosentyx 150mg/1ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £86

**Tocilizumab**
24-May-2018

**INDICATIONS AND DOSE**
- Rheumatoid arthritis [severe, active and progressive, not previously treated with methotrexate] / Rheumatoid arthritis [moderate-to-severe, in combination with methotrexate or alone if methotrexate inappropriate, when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs]
  - **By intravenous infusion**
    - Adult: 8 mg/kg every 4 weeks (max. per dose 800 mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature
  - **By subcutaneous injection**
    - Adult: 162 mg once weekly, administer to abdomen, thigh or upper arm, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature
    - Giant cell arteritis [in combination with a tapering course of glucocorticoid or alone following discontinuation of glucocorticoid]
      - **By subcutaneous injection**
        - Adult: 162 mg once weekly, administer to abdomen, thigh or upper arm, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature, not to be used alone for acute relapses; review need for treatment beyond 52 weeks

**CONTRA-INDICATIONS**
- Do not initiate if absolute neutrophil count less than 2 × 10⁹/litre - severe active infection

**CAUTIONS**
- History of diverticulitis - history of intestinal ulceration - history of recurrent or chronic infection (interrupt treatment if serious infection occurs) - low absolute neutrophil count - low platelet count.
predisposition to infection (interrupt treatment if serious infection occurs)

**CAUTIONS, FURTHER INFORMATION**

- **Tuberculosis** Patients with latent tuberculosis should be treated with standard therapy before starting tocilizumab.

- **INTERACTIONS** → Appendix 1: monoclonal antibodies

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain - conjunctivitis - cough - dizziness - dyslipidaemia - dyspnoea - gastrointestinal disorders - headache - hypersensitivity - hypotension - increased risk of infection - leucopenia - neutropenia - oral disorders - peripheral oedema - skin reactions - weight increased
  - Uncommon Hypothyroidism - nephrolithiasis
  - Frequency not known Infusion related reaction - interstitial lung disease - pancytopenia - Stevens-Johnson syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**

Discontinue if absolute neutrophil count less than 0.5 x 10⁹/litre or platelet count less than 50 x 10⁹/microlitre).

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during and for 3 months after treatment.

- **PREGNANCY** Manufacturer advises avoid unless essential — toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid — no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution — consult product literature.

- **RENAL IMPAIRMENT**
  - With intravenous use Manufacturer advises monitor renal function closely in moderate-to-severe impairment — no information available.
  - With subcutaneous use Manufacturer advises monitor renal function closely in severe impairment — no information available.

- **PRE-TREATMENT SCREENING**
  - Tuberculosis Patients should be evaluated for tuberculosis before treatment.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor lipid profile 4–8 weeks after starting treatment and then as indicated.
  - Manufacturer advises monitor for demyelinating disorders.
  - Manufacturer advises monitor hepatic transaminases every 4–8 weeks for first 6 months of treatment, then every 12 weeks thereafter.
  - Manufacturer advises monitor neutrophil and platelet count 4–8 weeks after starting treatment and then as indicated.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use For intravenous infusion, manufacturer advises give intermittently in Sodium chloride 0.9%; dilute requisite dose to a volume of 100 mL with infusion fluid and give over 1 hour.
  - With subcutaneous use For subcutaneous injection, manufacturer advises rotate injection site and avoid skin that is tender, damaged or scarred. Patients may self-administer RoActemra®, after appropriate training in subcutaneous injection technique.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Manufacturer advises to record the brand name and batch number after each administration.

- **HANDLING AND STORAGE**
  - Manufacturer advises protect from light and store in a refrigerator (2–8 °C) — consult product literature for further information regarding storage conditions outside refrigerator and after preparation of the infusion.

- **PATIENT AND CARER ADVICE**
  - Manufacturer advises patients and their carers should be advised to seek immediate medical attention if symptoms of infection occur, or if symptoms of diverticular perforation such as abdominal pain, haemorrhage, or fever accompanying change in bowel habits occur.
  - An alert card should be provided.

**Driving and skilled tasks** Manufacturer advises patients should be counselled on the effects on driving and performance of skilled tasks — increased risk of dizziness.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE decisions**
  - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016)
  - NICE TA375 Tocilizumab (RoActemra®), in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:
    - disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
    - disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), and
    - the manufacturers provide tocilizumab as agreed in the patient access schemes.
  - Tocilizumab can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.
  - Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.
  - Patients currently receiving tocilizumab whose disease does not meet the above criteria should have the option to continue their treatment until they and their NHS clinician consider it appropriate to stop.
  - www.nice.org.uk/guidance/ta375

  **Tocilizumab for the treatment of rheumatoid arthritis (February 2012)**
  - NICE TA247 Tocilizumab (RoActemra®), in combination with methotrexate, is recommended as an option for the treatment of rheumatoid arthritis in adults if:
    - the disease has responded inadequately to DMARDs and a TNF inhibitor and the patient cannot receive rituximab because of contra-indications or intolerance, and
    - tocilizumab is used as described for TNF inhibitor treatments (specifically the recommendations on disease activity) in the NICE guidance Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010), or
    - the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab
    - and the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.
  - Patients currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet these criteria should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
  - www.nice.org.uk/guidance/ta247

  **Tocilizumab for treating giant cell arteritis (April 2018)**
  - NICE TA518 Tocilizumab (RoActemra®), when used with a tapering course of glucocorticoids (and when used alone after glucocorticoids), is recommended as an option for treating giant cell arteritis in adults, only if:
    - they have relapsing or refractory disease,
    - they have not already had tocilizumab,
    - tocilizumab is stopped after 1 year of uninterrupted treatment at most, and...
● the manufacturer provides it with the discount agreed in the patient access scheme. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta518

Scottish Medicines Consortium (SMC) decisions

SMC No. SMC2014

The Scottish Medicines Consortium has advised (September 2018) that tocilizumab (RoActemra) is accepted for restricted use within NHS Scotland for the treatment of giant cell arteritis in adults, subject to a 12-month clinical stopping rule. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

BY SUBCUTANEOUS INJECTION

Tocilizumab 180 mg per 1 ml RoActemra 162mg/0.9ml solution for injection pre-filled pen | 4 pre-filled disposable injection (POD) £913.12 DT = £913.12 RoActemra 162mg/0.9ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (POD) £913.12 DT = £913.12 (Hospital only)

Solution for infusion

ELECTROLYTES: May contain Sodium

RoActemra (Roche Products Ltd)
Tocilizumab 20 mg per 1 ml RoActemra 400mg/20ml concentrate for solution for infusion vials | 1 vial (POD) £512.00 (Hospital only)
RoActemra 200mg/10ml concentrate for solution for infusion vials | 1 vial (POD) £256.00 (Hospital only)
RoActemra 80mg/4ml concentrate for solution for infusion vials | 1 vial (POD) £102.40 (Hospital only)

Ustekinumab

03-Oct-2017

● INDICATIONS AND DOSE

Moderate-to-severe plaque psoriasis that has not responded to other systemic treatments or photochemotherapy, or when these treatments cannot be used because of intolerance or contra-indications (specialist use only)

BY SUBCUTANEOUS INJECTION

Adult (body-weight up to 100 kg): Initially 45 mg, then 45 mg after 4 weeks, then 45 mg every 12 weeks, consider discontinuation if no response within 28 weeks

Adult (body-weight 100 kg and above): Initially 90 mg, then 90 mg after 4 weeks, then 90 mg every 12 weeks, consider discontinuation if no response within 28 weeks

Active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (specialist use only)

BY SUBCUTANEOUS INJECTION

Adult: Initially 45 mg, then 45 mg after 4 weeks, then 45 mg every 12 weeks, consider discontinuation if no response within 28 weeks, higher doses of 90 mg may be used in patients with body-weight over 100 kg

Moderate to severe active Crohn’s disease in patients who have had an inadequate response with, lost response to, are intolerant to, or have contra-indications to either conventional therapy or a tumour necrosis factor alpha inhibitor (specialist use only)

BY INTRAVENOUS INFUSION

Adult (body-weight up to 56 kg): 260 mg, then (by subcutaneous injection) 90 mg after 8 weeks, then (by subcutaneous injection) 90 mg every 12 weeks, if response is inadequate 8 weeks after first subcutaneous dose, or if treatment is interrupted or response is lost, dosing frequency may be increased—consult product literature; review treatment if no response within 16 weeks of initial dose or increase in dosing frequency

Adult (body-weight 56-85 kg): 390 mg, then (by subcutaneous injection) 90 mg after 8 weeks, then (by subcutaneous injection) 90 mg every 12 weeks, if response is inadequate 8 weeks after first subcutaneous dose, or if treatment is interrupted or response is lost, dosing frequency may be increased—consult product literature; review treatment if no response within 16 weeks of initial dose or increase in dosing frequency

Adult (body-weight 86 kg and above): 520 mg, then (by subcutaneous injection) 90 mg after 8 weeks, then (by subcutaneous injection) 90 mg every 12 weeks, if response is inadequate 8 weeks after first subcutaneous dose, or if treatment is interrupted or response is lost, dosing frequency may be increased—consult product literature; review treatment if no response within 16 weeks of initial dose or increase in dosing frequency

CONTRA-INDICATIONS Active infection

CAUTIONS Development of malignancy · elderly · history of malignancy · predisposition to infection · start appropriate treatment if widespread erythema and skin exfoliation develop, and stop ustekinumab treatment if exfoliative dermatitis suspected

CAUTIONS, FURTHER INFORMATION

Tuberculosis Active tuberculosis should be treated with standard treatment for at least 2 months before starting ustekinumab. Patients who have previously received adequate treatment for tuberculosis can start ustekinumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting ustekinumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with ustekinumab.

INTERACTIONS → Appendix 1: monoclonal antibodies

SIDE-EFFECTS

Common or very common Arthralgia · asthenia · back pain · diarrhoea · dizziness · headache · increased risk of infection · myalgia · nausea · ophthalmological pain · skin reactions · vomiting

Uncommon Depression · facial paralysis · hypersensitivity (may be delayed) · nasal congestion

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during treatment and for 15 weeks after stopping treatment.

PREGNANCY Avoid.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

PRE-TREATMENT SCREENING

Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS

Monitor for non-melanoma skin cancer, especially in areas commonly sun-exposed, and dermatological malignancies.

DIRECTIONS FOR ADMINISTRATION Manufacturer advises for intravenous infusion (Stelara®), give intermittently in Sodium Chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and give over at least 1 hour
through an in-line low-protein binding filter (pore size 0.2 micron); use within 4 hours of dilution.

**PATIENT AND CARER ADVICE**

Exfoliative dermatitis  Patients should be advised to seek prompt medical attention if symptoms suggestive of exfoliative dermatitis or erythrodermic psoriasis (such as increased redness and shedding of skin over a larger area of the body) develop.

Tuberculosis  Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE decisions

- **Ustekinumab for treating active psoriatic arthritis (updated March 2017)** NICE TA180
  Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:
  - treatment with tumour necrosis factor (TNF) alpha inhibitors is contra-indicated but would otherwise be considered, or
  - the patient has had treatment with 1 or more TNF-alpha inhibitors.

- **Ustekinumab for treating active Crohn's disease after previous treatment (July 2017)** NICE TA456
  Ustekinumab is recommended as an option for treating moderately to severely active Crohn’s disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contra-indications to such therapies.

- **Ustekinumab for moderately to severely active Crohn's disease after previous treatment (July 2017)** NICE TA456
  Ustekinumab is recommended as an option for treating moderately to severely active Crohn's disease in adults either alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults who have responded inadequately to previous therapy with a non-biological disease-modifying anti-rheumatic drug, and failed on, or are unsuitable for, treatment with a TNF inhibitor.

The Scottish Medicines Consortium (SMC) has advised (July 2017) that ustekinumab (Stelara®) is accepted for use within NHS Scotland for the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist or have medical contra-indications to such therapies. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDI-CAL FORMS**

NICE decisions

- **Stelara (Janssen-Cilag Ltd)**
  Stelara 90 mg/ml solution for injection pre-filled syringes 1 pre-filled disposable injection
  £2,147.00
  Stelara 45 mg/ml solution for injection vials 1 vial
  £2,147.00
  Stelara 45 mg/ml solution for injection pre-filled syringes 1 pre-filled disposable injection
  £2,147.00

**SOLUTION FOR INFUSION**

NICE decisions

- **Stelara (Janssen-Cilag Ltd)**
  Stelara 5 mg/ml solution for infusion vials 1 vial
  £2,147.00

**IMMUNOSUPPRESSANTS > PROTEIN KINASE INHIBITORS**

**Baricitinib**

- **DRUG ACTION** Baricitinib selectively and reversibly inhibits the Janus-associated tyrosine kinases JAK1 and JAK2.

- **INDICATIONS AND DOSE** Moderate-to-severe active rheumatoid arthritis in patients who have had an inadequate response to, or are intolerant to, one or more disease-modifying anti-rheumatic drugs (as monotherapy or in combination with methotrexate) (initiated by a specialist)
  - **BY MOUTH**
    - Adult 18-74 years: 4 mg once daily, for dose adjustments due to side-effects or dose reduction due to history of infection or sustained control of disease activity, consult product literature
    - Adult 75 years and over: 2 mg once daily, for dose adjustments due to side-effects, consult product literature.

- **CONTRA-INDICATIONS** Absolute lymphocyte count less than 0.5 × 10^9 cells/litre (do not initiate) - absolute neutrophil count less than 1 × 10^9 cells/litre (do not initiate) - active tuberculosis - haemoglobin less than 8 g/dl (do not initiate)

- **CAUTIONS** Active, chronic or recurrent infection (interrupt treatment if no response to standard therapy) - risk of viral reactivation (consult product literature)

- **TUBERCULOSIS** Manufacturer advises consider anti-tuberculosis therapy prior to initiation of baricitinib in patients with previously untreated latent tuberculosis.

- **INTERACTIONS** → Appendix 1: baricitinib

- **SIDE-EFFECTS**
  - Common or very common  Dyslipidaemia · herpes zoster (interrupt treatment) · increased risk of infection · nausea · oropharyngeal pain · thrombocytosis
  - Uncommon Acne · neutropenia · weight increased
Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (September 2017) that baricitinib (Olumiant®) is accepted for restricted use within NHS Scotland for the treatment of active rheumatoid arthritis only if the following criteria are met:
- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and
- disease has not responded to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs, or
- disease inadequately controlled by a tumour necrosis factor antagonist and patients are ineligible to receive rituximab.

This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent of lower.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Table

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Olumiant (Eli Lilly and Company Ltd)</th>
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<tr>
<td>Baricitinib 2 mg</td>
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Tofacitinib

DRUG ACTION
Tofacitinib selectively inhibits the Janus-associated tyrosine kinases JAK1 and JAK3.

INDICATIONS AND DOSE
Moderate to severe active rheumatoid arthritis in patients who have had an inadequate response to, or are intolerant to one or more disease-modifying anti-rheumatic drugs (as monotherapy or in combination with methotrexate) (specialist use only) / Active psoriatic arthritis in patients who have had an inadequate response to, or are intolerant to one or more disease-modifying anti-rheumatic drugs (in combination with methotrexate) (specialist use only)

BY MOUTH

Adult: 5 mg twice daily, for dose adjustments due to side-effects—consult product literature

Moderate to severe active ulcerative colitis in patients who have had an inadequate or lost response to, or are intolerant to either conventional therapy or a biologic agent (specialist use only)

BY MOUTH

Adult: Initially 10 mg twice daily for 8 weeks, then maintenance 5 mg twice daily, if an adequate therapeutic response is not achieved after 8 weeks, the initial dose can be extended for an additional 8 weeks, discontinue treatment if no response. 16 weeks after initial dose, for dose adjustments due to side-effects, decreased response during maintenance treatment or following treatment interruption—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Manufacturer advises reduce dose with concurrent use of potent CYP3A4 inhibitors or drugs which are both moderate CYP3A4 and potent CYP2C19 inhibitors.
- Dose should be reduced to 5 mg once daily continued →
in patients receiving 5 mg twice daily. Dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily.

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE: TOFACITINIB (XELJANZ®): INCREASED RISK OF PULMONARY EMBOLISM AND MORTALITY IN RHEUMATOID ARTHRITIS PATIENTS RECEIVING 10 MG TWICE DAILY IN A CLINICAL TRIAL (MARCH 2019)**

Due to these increased risks, prescribers are advised to adhere to the licensed dose for rheumatoid arthritis. Patients receiving tofacitinib, regardless of indication, should be monitored for signs and symptoms of pulmonary embolism and advised to seek immediate medical attention if they occur.

- **CONTRA-INDICATIONS**
  - Absolute lymphocyte count less than 750 cells/mm³ (do not initiate).
  - Absolute neutrophil count less than 1000 cells/mm³ (do not initiate).
  - Active infection including localized infection, active tuberculosis, haemoglobin less than 9 g/dL (do not initiate).

- **CAUTIONS**
  - Active, chronic or recurrent infection.
  - Elderly predisposition to infection.
  - Previous or current malignancy.
  - Raised serum transaminases (particularly in combination with potentially hepatotoxic drugs).
  - Risk of gastrointestinal perforation.
  - New onset abdominal signs.
  - Risk of viral reactivation.

**CAUTIONS, FURTHER INFORMATION**

Manufacturer advises monitor lymphocytes at baseline.

- **SIDE-EFFECTS**
  - Common or very common
    - Anaemia — cough, decreased appetite.
    - Diarrhoea — dyspepsia, fatigue, fever, gastritis.
    - Gastrointestinal discomfort.
    - Headache.
    - Hypertension.
    - Increased risk of infection.
    - Insomnia.
    - Joint disorders.
    - Musculoskeletal pain.
    - Nausea.
    - Peripheral oedema.
    - Skin reactions.
    - Vomiting.
    - Weight increased.

- **Uncommon**
  - Dehydration.
  - Hepatic steatosis.
  - Gastritis.
  - Muscle strain.
  - Neutropenia.
  - Non-melanoma skin cancer.
  - Parasthesia.
  - Sepsis.
  - Sinus congestion.
  - Tendinitis.

- **Rare or very rare**
  - Meningitis.
  - Cryptococcal.

- **Frequency not known**
  - Increased risk of pulmonary embolism (with high doses).

- **CONCEPTION AND CONTRACEPTION**
  - Effective contraception during and for at least 4 weeks after treatment in women of child-bearing potential.

- **PREGNANCY**
  - Manufacturer advises avoid — toxicity in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid — present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in moderate impairment.
  - Avoid in severe impairment.

**Dose adjustments**

- Manufacturer advises dose reduction in moderate impairment.
  - Consult product literature.

- **RENAI IMPAIRMENT**
  - Dose adjustments
  - Manufacturer advises reduce dose in severe impairment.
  - Consult product literature.

- **PRE-TREATMENT SCREENING**
  - Manufacturer advises patients should be evaluated for tuberculosis and viral hepatitis before treatment.

**MONITORING REQUIREMENTS**

- Manufacturer advises monitor for signs and symptoms of infection during and after treatment.
- Manufacturer advises periodic skin examination in patients at increased risk for skin cancer.
- Manufacturer advises monitor liver function routinely; monitor lipid profile 8 weeks after treatment initiation.
- Manufacturer advises monitor lymphocytes at baseline and every 3 months thereafter; neutrophils and haemoglobin should be monitored at baseline, after 4 to 8 weeks of treatment and every 3 months thereafter.

**DIRECTIONS FOR ADMINISTRATION**

Manufacturer advises tablets may be crushed and taken with water.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE decisions

- Tofacitinib for moderate-to-severe rheumatoid arthritis (October 2017) NICE TA480
  - Tofacitinib (Xeljanz®), with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs, only if:
    - Disease is severe (a disease activity score [DAS28] of more than 5.1), and
    - The manufacturer provides tofacitinib with the discount agreed in the patient access scheme.

- Tofacitinib (Xeljanz®), with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot have, other DMARDs, including at least 1 biological DMARD, only if:
    - Disease is severe (a DAS28 of more than 5.1), and
    - They cannot have rituximab, and
    - The manufacturer provides tofacitinib with the discount agreed in the patient access scheme.

Tofacitinib can be used as monotherapy for adults who cannot take methotrexate because it is contra-indicated or because of intolerance, when the above criteria are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta480

- Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs (October 2018) NICE TA543
  - Tofacitinib (Xeljanz®), with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults, only if:
    - It is used as described in NICE’s technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (TA199 recommendations 1.1 and 1.2), or
    - The person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks, or
    - TNF-alpha inhibitors are contra-indicated but would otherwise be considered (as described in NICE’s technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

Tofacitinib is only recommended if the manufacturer provides it according to the commercial arrangement. Assess the response to treatment after 12 weeks. Treatment should only be continued if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria.
IMMUNOSUPPRESSANTS > T-CELL ACTIVATION INHIBITORS

Abatacept

**INDICATIONS AND DOSE**

Moderate-to-severe active rheumatoid arthritis (specialist use only) | Active psoriatic arthritis (specialist use only)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 125 mg once weekly, review treatment if no response within 6 months

Moderate-to-severe active rheumatoid arthritis (specialist use only) | Active psoriatic arthritis (specialist use only)

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 125 mg once weekly, review treatment if no response within 6 months, subcutaneous dosing may be initiated with or without an intravenous loading dose—consult product literature

**CONTRA-INDICATIONS**

- Severe infection

**CAUTIONS**

- Do not initiate until active infections are controlled - elderly (increased risk of side-effects) - predisposition to infection (screen for latent tuberculosis and viral hepatitis) - progressive multifocal leucoencephalopathy (discontinue treatment if neurological symptoms present)

**INTERACTIONS**

- > Appendix 1: abatacept

**SIDE-EFFECTS**

- **Common or very common**
  - Asthenia - cough - diarrhoea - dizziness - gastrointestinal discomfort - headaches - hypertension - increased risk of infection - nausea - oral ulceration - skin reactions - vomiting

- **Uncommon**

- **Rare or very rare**
  - Pelvic inflammatory disease - respiratory malignancy

**CONCEPTION AND CONTRACEPTION**

- Effective contraception required during treatment and for 14 weeks after last dose

**PREGNANCY**

- Manufacturer advises avoid unless essential

**BREAST FEEDING**

- Present in milk in animal studies—manufacturer advises avoid breast-feeding during treatment and for 14 weeks after last dose

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion, given intermittently in Sodium chloride 0.9%; reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided; dilute requisite dose in Sodium Chloride 0.9% to 100 mL (using the same silicone-free syringe); give over 30 minutes through a low protein-binding filter (pore size 0.2–1.2 micron).

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(PsA Re), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsA Re response does not justify continuing treatment should be assessed by a dermatologist.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

[www.nice.org.uk/guidance/ta543](http://www.nice.org.uk/guidance/ta543)

**Scottish Medicines Consortium (SMC) decisions**

**SMC No. SMC216**

The Scottish Medicines Consortium has advised (January 2019) that tofacitinib (Xeljanz®) is accepted for use within NHS Scotland in combination with methotrexate for the treatment of adults with psoriatic arthritis whose disease has not responded adequately to at least two conventional DMARDs, given either alone or in combination. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**SMC No. SMC212**

The Scottish Medicines Consortium has advised (February 2019) that tofacitinib (Xeljanz®) is accepted for use within NHS Scotland for the treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Xeljanz (Pfizer Ltd) ▼
  - Tofacitinib (as Tofacitinib citrate) 5 mg Xeljanz 5mg tablets | 56 tablet [Pres] £60.63 (Hospital only)
  - Tofacitinib (as Tofacitinib citrate) 10 mg Xeljanz 10mg tablets | 56 tablet [Pres] £1,380.06 (Hospital only)
NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195

Abatacept, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor, and who cannot use rituximab because of contra-indications or intolerance. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months.

www.nice.org.uk/TA195

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Abatacept, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
- the manufacturers provide abatacept as agreed in the patient access schemes.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving abatacept whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA375

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Orencia (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Abatacept 125 mg per 1 ml
  Orencia 125mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £120.96 DT | £120.96 (Hospital only)

- Orencia ClickJet (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Abatacept 125 mg per 1 ml
  Orencia ClickJet 125mg/1ml solution for injection pre-filled pen | 4 pre-filled disposable injection £120.96 DT | £120.96 (Hospital only)

Powder for solution for infusion

- Orencia (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Abatacept 250 mg
  Orencia 250mg powder for concentrate for solution for infusion vials | 1 vial £302.40 (Hospital only)

IMMUNOSUPPRESSANTS

TUMOR NECROSIS FACTOR ALPHA (TNF-α) INHIBITORS

Adalimumab

INDICATIONS AND DOSE

- Plaque psoriasis (initiated by a specialist)
  BY SUBCUTANEOUS INJECTION
  Adult: Initially 80 mg, then 40 mg every 2 weeks, to be started 1 week after initial dose, review treatment if no response within 16 weeks—consult product literature

- Psoriatic arthritis (initiated by a specialist)
  BY SUBCUTANEOUS INJECTION
  Adult: 40 mg every 2 weeks, then increased if necessary to 40 mg once weekly, alternatively 80 mg every 2 weeks; dose to be increased only in patients receiving adalimumab alone, review treatment if no response within 12 weeks

- Ankylosing spondylitis (initiated by a specialist)
  BY SUBCUTANEOUS INJECTION
  Adult: 40 mg every 2 weeks, review treatment if no response within 12 weeks

- Axial spondyloarthitis (initiated by a specialist)
  BY SUBCUTANEOUS INJECTION
  Adult: 40 mg every 2 weeks, review treatment if no response within 12 weeks

- Demyelinating disorders (risk of exacerbation)
  Adult: Initially 80 mg, then 40 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, alternatively 80 mg every 2 weeks, review treatment if no response within 12 weeks

- Adult: 20 mg once weekly, alternatively 40 mg every 2 weeks, review treatment if no response within 8 weeks

- Adult: 20 mg once weekly, alternatively 40 mg every 2 weeks, review treatment if no response within 8 weeks

- Adult: 20 mg once weekly, alternatively 40 mg every 2 weeks, review treatment if no response within 8 weeks

- Adult: 20 mg once weekly, alternatively 40 mg every 2 weeks, review treatment if no response within 8 weeks

- Adult: 20 mg once weekly, alternatively 40 mg every 2 weeks, review treatment if no response within 8 weeks

CONTRA-INDICATIONS

- Moderate or severe heart failure - severe infection

CAUTIONS

- Demyelinating disorders (risk of exacerbation) - do not initiate until active infections are controlled (discontinue if new serious infection develops) - hepatitis B virus—monitor for active infection - history of malignancy - mild heart failure (discontinue if symptoms develop or worsen) - predisposition to infection

CAUTIONS, FURTHER INFORMATION

- Tuberculosis Active tuberculosis should be treated with standard treatment for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin
test, chemoprophylaxis can be given concurrently with adalimumab.

- **INTERACTIONS** → Appendix 1: monoclonal antibodies

- **SIDE-EFFECTS**
  - Rare or very rare Cardiac arrest - pancrecytoma - Stevens-Johnson syndrome.

- **SIDE-EFFECTS, FURTHER INFORMATION** Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception required during treatment and for at least 5 months after last dose.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises can be used—excreted in breast milk at very low concentrations (limited information available).

- **PRE-TREATMENT SCREENING**
  - Tuberculosis: Manufacturer advises patients should be evaluated for active and latent tuberculosis before treatment.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor for infection before, during, and for 4 months after treatment.
  - Manufacturer advises monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy.
  - For uveitis, manufacturer advises patients should be assessed for pre-existing or developing central demyelinating disorders before and at regular intervals during treatment.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Adalimumab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

- **PATIENT AND CARER ADVICE** When used to treat hidradenitis suppurativa, patients and their carers should be advised to use a daily topical antiseptic wash on lesions during treatment with adalimumab.
  - Tuberculosis patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, or, and fever) develop.

- **Blood disorders** Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

- **Alert card** An alert card should be provided.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE decisions**
    - Adalimumab for plaque psoriasis in adults (June 2008) NICE TA146
    - Adalimumab is recommended for the treatment of severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Adalimumab should be withdrawn if the response is not adequate after 16 weeks.
    - **Infliximab and adalimumab for Crohn’s disease (May 2010) NICE TA187**
      - Adalimumab is recommended for the treatment of severe active Crohn’s disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.
      - Adalimumab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, adalimumab can be restarted.
    - **Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329**
      - Adalimumab is an option for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.
      - The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.
      - Adalimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
    - **Eタネリcept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) NICE TA199**
      - Adalimumab is recommended for the treatment of active and progressive psoriatic arthritis in adults who have peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination).
      - Adalimumab should be discontinued if there is an inadequate response at 12 weeks.
      - Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195
      - Adalimumab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other DMARDs including at least 1 TNF inhibitor, and who cannot use rituximab because of contra-indications or intolerance. In patients

- **BNF 78**

- **Musculoskeletal system**

- **Arthritis 1109**

- **www.getintopharma.com**
who cannot use methotrexate because of intolerance or contra-indications, adalimumab can be given as monotherapy. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months.

www.nice.org.uk/guidance/ta75

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimum, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Adalimumab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:
- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and,
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs).

Adalimumab can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving adalimumab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta375

- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthritis in patients whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF) - alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/guidance/ta383

- Adalimumab for treating moderate-to-severe hidradenitis suppurativa (June 2016) NICE TA392

Adalimumab is recommended, within its marketing authorisation, as an option for treating active moderate-to-severe hidradenitis suppurativa in adults whose disease has not responded to conventional systemic therapy. The drug is recommended only if the manufacturer provides it at the price agreed in the patient access scheme. Response should be assessed after 12 weeks of treatment, and the drug continued only if there is clear evidence of response, defined as a reduction of 25% or more in the total abscesses and inflammatory nodule count and no increase in abscesses and draining fistulas.

www.nice.org.uk/guidance/ta392

- Adalimumab and dexamethasone for treating non-infectious uveitis (July 2017) NICE TA460

Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:
- active disease (that is, current inflammation in the eye), and
- inadequate response or intolerance to immunosuppressants, and
- systemic disease or both eyes are affected (or one eye is affected if the second eye has poor visual acuity), and
- worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema).

Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is one of the following:
- new active inflammatory choroidal or inflammatory retinal vascular lesions, or both, or
- a two-step increase in vitreous haze or anterior chamber cell grade, or
- worsening of best corrected visual acuity by three or more lines or 15 letters.

Patients currently receiving adalimumab whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta460

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium issued similar advice for plaque psoriasis to NICE TA146 in May 2009.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS

- Amgevita (Amgen Ltd)
  - Adalimumab 50 mg per 1 ml Amgevita 20mg/0.4ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £158.40
  - Amgevita 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £633.60
  - Amgevita 40mg/0.8ml solution for injection pre-filled pen | 2 pre-filled disposable injection £633.60

- Hulio (Mylan)
  - Adalimumab 50 mg per 1 ml Hulio 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £616.25
  - Hulio 40mg/0.8ml solution for injection pre-filled pen | 2 pre-filled disposable injection £616.25

- Humira (Abbvie Ltd)
  - Adalimumab 100 mg per 1 ml Humira 40mg/0.4ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £704.28
  - Humira 20mg/0.2ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £352.14
  - Humira 80mg/0.8ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £704.28
  - Humira 40mg/0.4ml solution for injection pre-filled pen | 2 pre-filled disposable injection £704.28
  - Humira 80mg/0.8ml solution for injection pre-filled pen | 1 pre-filled disposable injection £704.28

- Imraldi (Sandoz Ltd)
  - Adalimumab 50 mg per 1 ml Imraldi 40mg/0.8ml solution for injection pre-filled pen | 2 pre-filled disposable injection £646.18
  - Imraldi 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £633.85

- Imraldi (Biogen Idec Ltd)
  - Adalimumab 50 mg per 1 ml Imraldi 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £633.85

www.getintopharma.com
Certolizumab pegol

**INDICATIONS AND DOSE**

Moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drugs (including methotrexate) has been inadequate (as monotherapy or in combination with methotrexate).

Severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate or other disease-modifying antirheumatic drugs (in combination with methotrexate). Active psoriatic arthritis when response to disease-modifying antirheumatic drugs has been inadequate (as monotherapy or in combination with methotrexate).

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Loading dose 400 mg every 2 weeks for 3 doses, then maintenance 200 mg every 2 weeks, once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered, review treatment if no response within 12 weeks.

Treatment of severe active ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of NSAIDs. Treatment of severe active axial spondyloarthritis, without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs.

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Loading dose 400 mg every 2 weeks for 3 doses, then maintenance 200 mg every 2 weeks, alternatively maintenance 400 mg every 4 weeks, review treatment if no response within 12 weeks.

Moderate to severe plaque psoriasis.

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Loading dose 400 mg every 2 weeks for 3 doses, then maintenance 200 mg every 2 weeks, an alternative maintenance dosing of 400 mg every 4 weeks can be considered in patients with insufficient response, review treatment if no response within 16 weeks.

**CONTRA-INDICATIONS**

Moderate to severe heart failure - severe active infection.

**CAUTIONS**

- Demyelinating CNS disorders (risk of exacerbation) - do not initiate until active infections are controlled (discontinue if new serious infection develops and until infection controlled) - hepatitis B virus (monitor for active infection) - history or development of malignancy - mild heart failure (discontinue if symptoms develop or worsen) - predisposition to infection.

**CAUTIONS, FURTHER INFORMATION**

- Tuberculosis: Active tuberculosis should be treated with standard treatment for at least 2 months before starting certolizumab pegol. Patients who have previously received adequate treatment for tuberculosis can start certolizumab pegol but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting certolizumab pegol. In patients at high risk of tuberculosis who cannot be assessed by tuberculosis skin test, chemoprophylaxis can be given concurrently with certolizumab pegol.

**INTERACTIONS**

- Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

- **Common or very common**
  - Abscess, asthenia, decreased leukocytes, eosinophilic disorders, fever, headaches, hepatic disorders, hypertension, increased risk of infection, nausea, neoplasms, neutropenia, pain, sensory disorder, skin reactions.

- **Uncommon**
  - Alopecia, anaemia, anxiety, appetite disorder, arthralgias, ascites, asthma, breast disorder, cardiomyopathy, chills, coronary artery disease, cough, cyst, dizziness, dyslipidaemia, electrolyte imbalance, embolism and thrombosis, eye inflammation, flushing, gastrointestinal discomfort, gastrointestinal disorders, haemorrhage, healing impaired, heart failure, hypercoagulation, influenza like illness, lactic acidosis, lymphopenia, menstrual cycle irregularities, mood disorder, muscle disorder, nail disorder, nerve disorders, oedema, oral disorders, oropharyngeal dryness, palpitations, photosensitivity reaction, renal impairment, respiratory disorders, sepsis, skin ulcer, solid organ neoplasms, skin reaction, syncope, systemic lupus erythematosus (SLE), temperature perception abnormal, thrombocytopenia, thrombosis, tinnitus, tremor, urinary tract disorder, vasculitis, vertigo, vision disorders, weight change.

- **Rare or very rare**
  - Atherosclerosis, atriointerventricular block, cholelithiasis, cognitive impairment, delirium, fistula, haemorrhoids, hair texture abnormal, movement disorders, nephritis, nephropathy, odynophagia, pancycopenia, panniculitis, pericarditis, polycythemia, Raynaud’s phenomenon, sarcoidosis, seizure, serum sickness, sexual dysfunction, splenomegaly, stroke, suicide attempt, telangiectasia, thyroid disorder.

- **Frequency not known**
  - Multiple sclerosis.

**SIDE-EFFECTS, FURTHER INFORMATION**

Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

**CONCEPTION AND CONTRAINDICATIONS**

Manufacturer advises adequate contraception in women of childbearing potential during treatment and for 5 months after last dose.

**PREGNANCY**

Manufacturer advises use only if benefit outweighs risk — limited information available.

**PRE-TREATMENT SCREENING**

Tuberculosis. Patients should be evaluated for tuberculosis before treatment.

**MONITORING REQUIREMENTS**

Monitor for infection before, during, and for 5 months after treatment.

**PATIENT AND CARER ADVICE**

Blood disorders. Patients should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop. Tuberculosis. Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss and fever) develop.

Alert card. An alert card should be provided.

**NATIONAL FUNDING/AFFORDABILITY DECISIONS**

- **NICE decisions**
  - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
- the manufacturers provide certolizumab pegol as agreed in the patient access schemes.

Certolizumab pegol can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After
initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving certolizumab pegol within the NHS whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/ta375

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in adult patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs.

Adalimumab, certolizumab pegol and etanercept are also recommended as options for treating severe non-radiographic axial spondyloarthritis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

The response to treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/ta383

Cimzia

Cimzia® (Certolizumab pegol) is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/ta445

Cimzia® for treating moderate to severe plaque psoriasis (April 2019) NICE TA574

Certolizumab pegol (Cimzia®) is recommended as an option for treating plaque psoriasis in adults, only if:

- the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10, and

- the disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated, and

- the lowest maintenance dosage of certolizumab pegol is used after the loading dosage, and

- the manufacturer provides the drug according to the commercial arrangements.

Stop certolizumab pegol at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:

- a 75% reduction in the PASI score (PASI 75) from when treatment started, or

- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta574

Scottish Medicines Consortium (SMC) decisions

SMC No. SMC2132

The Scottish Medicines Consortium has advised (April 2019) that certolizumab pegol (Cimzia®) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contraindication to these treatments. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

www.getintopharma.com

1112 Arthritis

Cimzia® (UCB Pharma Ltd)

Certolizumab pegol 200 mg per 1 ml Cimzia 200mg/1ml solution for injection pre-filled pen | 2 pre-filled disposable injection PFS £715.00

Cimzia 200mg/1ml solution for injection pre-filled syringes | 2 syringe POX £715.00

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS

Cimzia® (UCB Pharma Ltd)

Certolizumab pegol 200 mg per 1 ml Cimzia 200mg/1ml solution for injection pre-filled pen | 2 pre-filled disposable injection PFS £715.00

Cimzia 200mg/1ml solution for injection pre-filled syringes | 2 syringe POX £715.00

www.getintopharma.com
**Indications and Dose**

**Enbrel® Solution for Injection**

Moderate-to-severe active rheumatoid arthritis (alone or in combination with methotrexate) when the response to other disease-modifying antirheumatic drugs is inadequate 

Severe, active and progressive rheumatoid arthritis not previously treated with methotrexate 

Active and progressive psoriatic arthritis when the response to other disease-modifying antirheumatic drugs is inadequate 

Severe active ankylosing spondylitis when the response to conventional therapy is inadequate 

Severe, non-radiographic axial spondylarthropathy when the response to non-steroidal anti-inflammatory drugs is inadequate

**Adult:**

- **By Subcutaneous Injection**
  - Adult: 25 mg twice weekly, alternatively 50 mg once weekly, review treatment if no response within 12 weeks of initial dose

**Moderate-to-severe plaque psoriasis when the response to other systemic therapies or psoralen and ultraviolet-A light (PUVA) is inadequate, or when these therapies cannot be used because of intolerance or contraindications**

**By Subcutaneous Injection**

- Adult: 50 mg once weekly, review treatment if no response within 12 weeks of initial dose

**Severe, active ankylosing spondylitis when the response to conventional therapy is inadequate**

**Severe, non-radiographic axial spondylarthropathy when the response to non-steroidal anti-inflammatory drugs is inadequate**

**Frequency not known**

**Common or very common**

- Cystitis
- Fever
- Hypersensitivity
- Increased risk of infection
- Pain
- Skin reactions
- Swelling

**Uncommon**

- Abscess
- Bursitis
- Cholecystitis
- Diarrhoea
- Endocarditis
- Eye inflammation
- Gastritis
- Hepatic disorders
- Myositis
- Neoplasms
- Respiratory disorders
- Sepsis
- Skin ulcers
- Thrombocytopenia
- Vasculitis

**Rare or very rare**

- Anaemia
- Bone marrow disorders
- Congestive heart failure
- Cutaneous lupus erythematosus
- Demyelination
- Leucopenia
- Lupus-like syndrome
- Nerve disorders
- Neutropenia
- Sarcoidosis
- Seizure
- Severe cutaneous adverse reactions (SCARs)
- Transverse myelitis

**Frequency not known**

- Dermatomyositis exacerbated
- Hepatitis B reactivation

**Contra-Indications**

Active infection

**Caution**

Development of malignancy - diabetes mellitus - heart failure (risk of exacerbation) - hepatitis B virus - monitor for active infection - hepatitis C infection (monitor for worsening infection) - history of blood disorders - history of malignancy - history or increased risk of demyelinating disorders - predisposition to infection (avoid if predisposition to sepsis) - significant exposure to herpes zoster virus - significant exposure to hepatitis - neutropenia - severe ulceration of skin ulcers - thrombocytopenia - vasculitis

**Caution, Further Information**

- Tuberculosis: Active tuberculosis should be treated with standard treatment for at least 2 months before starting etanercept. Patients who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept.

**Interactions**

- Appendix 1: etanercept

**Side-Effects**

- Common or very common
  - Cystitis
  - Fever
  - Hypersensitivity
  - Increased risk of infection
  - Pain
  - Skin reactions
  - Swelling

- Uncommon
  - Abscess
  - Bursitis
  - Cholecystitis
  - Diarrhoea
  - Endocarditis
  - Eye inflammation
  - Gastritis
  - Hepatic disorders
  - Myositis
  - Neoplasms
  - Respiratory disorders
  - Sepsis
  - Skin ulcers
  - Thrombocytopenia
  - Vasculitis

- Rare or very rare
  - Anaemia
  - Bone marrow disorders
  - Congestive heart failure
  - Cutaneous lupus erythematosus
  - Demyelination
  - Leucopenia
  - Lupus-like syndrome
  - Nerve disorders
  - Neutropenia
  - Sarcoidosis
  - Seizure
  - Severe cutaneous adverse reactions (SCARs)
  - Transverse myelitis

- Frequency not known
  - Dermatomyositis exacerbated
  - Hepatitis B reactivation
Etanercept should be discontinued if there is an inadequate response at 12 weeks.  
www.nice.org.uk/TA199  
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDS or after conventional DMARDS only have failed (January 2016)  
NICE TA375  
Etanercept, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:  
- disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and  
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs).  
Etanercept can be used as monotherapy in patients who cannot take methotrexate because it is contra-indicated or because of intolerance, when the criteria above are met.  
Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.  
Patients currently receiving etanercept whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.  
www.nice.org.uk/TA375  
- TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016)  
NICE TA383  
Etanercept is recommended as an option for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).  
Etanercept is also recommended as an option for treating severe non-radiographic axial spondyloarthritis in patients whose disease has responded inadequately to, or who are intolerant of, NSAIDs.  
The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response. Treatment with another tumour necrosis factor (TNF) - alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.  
www.nice.org.uk/TA383  
- MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.  

<table>
<thead>
<tr>
<th>Solution for injection</th>
<th>CAUTIONARY AND ADVISORY LABELS 10</th>
</tr>
</thead>
</table>
| Etanercept 50 mg per 1 ml  | Benepali (Biogen Idec Ltd) ▼  
Benepali 50mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (£556.00 DT = £715.00)  
Benepali 50mg/1ml solution for injection pre-filled pen | 4 pre-filled disposable injection (£556.00)  
Embrel (Pfizer Ltd)  
Etanercept 50 mg per 1 ml  | Embrel 50mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (£715.00 DT = £715.00)  
Embrel 25mg/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (£357.50 DT = £357.50)  
Embrel MyClic (Pfizer Ltd)  
Etanercept 50 mg per 1 ml  | Embrel 50mg/1ml solution for injection pre-filled MyClic pen | 4 pre-filled disposable injection (£715.00)  
Embrel 25mg/0.5ml solution for injection pre-filled MyClic pen | 4 pre-filled disposable injection (£357.50)  

www.getintopharma.com
Golimumab

01-Mar-2018

INDICATIONS AND DOSE

Ulcerative colitis (initiated by a specialist)

- Adult (body-weight up to 80 kg): Initially 200 mg, then 100 mg after 2 weeks; maintenance 50 mg every 4 weeks, if inadequate response, review treatment if no response after 4 doses

Rheumatoid arthritis (initiated by a specialist) | Psoriatic arthritis (initiated by a specialist) | Ankylosing spondylitis (initiated by a specialist) | Non-radiographic axial spondyloarthritis (initiated by a specialist)

- BY SUBCUTANEOUS INJECTION
  - Adult (body-weight up to 100 kg): 50 mg once a month, on the same date each month, review treatment if no response after 3–4 doses

PRE-TREATMENT SCREENING

Tuberculosis Patients should be evaluated for tuberculosis before treatment.

SIDE-EFFECTS, FURTHER INFORMATION

Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

CONCEPTION AND CONTRACEPTION

Manufacturer advises adequate contraception during treatment and for at least 6 months after last dose.

PREGNANCY

Use only if essential.

BREAST FEEDING

Manufacturer advises avoid during and for at least 6 months after treatment—present in milk in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution (no information available).

PRE-TREATMENT SCREENING

Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS

Monitor for infection before, during, and for 5 months after treatment.

DIRECTIONS FOR ADMINISTRATION

For doses requiring multiple injections, each injection should be administered at a different site. Missed dose If dose administered more than 2 weeks late, subsequent doses should be administered on the new monthly due date.

PATIENT AND CARER ADVICE

Tuberculosis All patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

Blood disorders Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Alert card An alert card should be provided.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Golimumab for the treatment of psoriatic arthritis (April 2011) NICE TA220

Golimumab is an option for the treatment of active and progressive psoriatic arthritis in adults only if:

- golimumab is used as described in the NICE guidance (August 2010) for other tumour necrosis factor (TNF) inhibitors, and
- the manufacturer provides the 100 mg dose of golimumab at the same price as the 50 mg dose.

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375

Golimumab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if all the following criteria are met:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1,
Arthritis

- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs),
- the manufacturers provides golimumab as agreed in the patient access schemes.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving treatment with golimumab whose disease do not meet the above criteria should have the option to continue their treatment until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta375

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs (June 2013) NICE TA225

Golimumab, in combination with methotrexate, is an option for the treatment of rheumatoid arthritis in patients who have had an inadequate response to DMARDs, including a TNF inhibitor, if golimumab is used as described in the NICE technology appraisal guidance 195 (August 2010) for other TNF inhibitors, and the manufacturer provides the 100 mg dose of golimumab at the same price as the 50 mg dose.

www.nice.org.uk/guidance/ta225

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383

Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs).

The response to treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response.

Treatment with another tumour necrosis factor (TNF) - alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/guidance/ta383

Golimumab for treating non-radiographic axial spondyloarthritis (January 2018) NICE TA497

Golimumab is recommended, within its marketing authorisation, as an option for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, nonsteroidal anti-inflammatory drugs.

If patients and their clinicians consider golimumab to be one of a range of suitable treatments, including adalimumab, etanercept and certolizumab pegol, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

Assess the response to golimumab 12 weeks after the start of treatment. Continue treatment only if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value by or 2 or more units, and
- a reduction in the spinal pain visual analogue scale (VAS) score by 2 cm or more.

www.nice.org.uk/guidance/ta497

Infliximab, adalimumab and golimumab for treating moderately-to-severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

Golimumab is an option for treating moderately-to-severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.

Golimumab is recommended only if the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.

Golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

www.nice.org.uk/guidance/ta329

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (July 2012) that golimumab (Simponi®) is accepted for restricted use within NHS Scotland at a dose of 50 mg, alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adults whose disease has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

The Scottish Medicines Consortium has advised (February 2016) that golimumab (Simponi®) is accepted for use within NHS Scotland for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10

Simponi® (Merck Sharp & Dohme Ltd)

Golimumab 100 mg per 1 ml Simponi 50mg/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection £762.97 DT £762.97

Golimumab 50mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £762.97 DT £762.97

Simponi 100mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection £1,525.94 DT £1,525.94

Infliximab

INDICATIONS AND DOSE

Severe active Crohn’s disease

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, then 5 mg/kg after 4 weeks, if condition has responded, then maintenance 5 mg/kg every 8 weeks

Fistulating Crohn’s disease

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, if condition has responded consult product literature for guidance on further doses

Severe active ulcerative colitis

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every
Tuberculosis

▶ CAUTIONS

- Contra-indications. Chemoprophylaxis should ideally be given to contact persons who have previously received adequate treatment for tuberculosis but who were previously not treated adequately. Chemoprophylaxis should be continued until symptoms of tuberculosis develop (e.g., persistent cough, weight loss, and fever).

- Contraindications. Patients with active tuberculosis should not be given prophylaxis until symptoms have resolved and sputum cultures are negative. Prophylaxis should not be given to patients with severe infections or those who are immunosuppressed.

- Precautions. Tuberculosis is highly contagious and can spread to susceptible individuals. Prophylaxis should be given to close contacts of patients with active tuberculosis, especially those who are immunocompromised or have underlying conditions that increase the risk of tuberculosis.

- Side-effects. Side-effects of prophylaxis may include gastrointestinal upset, rash, and fever. Rare side-effects may include hepatitis or pancreatitis.

- Monitoring requirements. Tuberculosis prophylaxis should be monitored regularly to assess for the development of adverse reactions and to ensure compliance with treatment.

- Directions for administration. Prophylaxis should be administered at least 2 hours after the last dose of anti-TB medication. The initial dose should be given after a prolonged period of 16 weeks. The maintenance dose should be given at least every 6 weeks. Patients should be monitored for the development of tuberculosis symptoms.

- Further information. The manufacturer advises prophylactic antypiretics, antihistamines, or hydrocortisone may be administered.

Arthritis

1117

▶ COMMON OR VERY COMMON

- Abscess
- Aplasia
- Arthritis
- Arthralgia
- Chest pain
- Chills
- Constipation
- Decreased appetite
- Depression
- Diarrhoea
- Dizziness
- Dyspepsia
- Eye inflammation
- Fatigue
- Fever
- Gastrointestinal discomfort
- Gastrointestinal disorders
- Haemorrhage
- Headache
- Hepatic disorders
- Hypersensitivity
- Hypertension
- Increased risk of infection
- Infusion related reaction
- Insomnia
- Lymphadenopathy
- Myalgia
- Nausea
- Neutropenia
- Oedema
- Pain
- Palpitations
- Respiratory disorders
- Sensation abnormal
- Seizure
- Sepsis
- Skin reactions
- Vasodilation
- Vertigo

- Rare or very rare

- Agranulocytosis
- Circulatory collapse
- Cyanosis
- Demyelinating disorders
- Granuloma
- Haemolytic anaemia
- Hepatitis B reactivation
- Meningitis
- Pancytopenia
- Pericardial effusion
- Paraneoplastic vasculitis
- Severe cutaneous adverse reactions (SCARS)
- Transverse myelitis
- Vasculitis
- Vasospasm

- Frequency not known

- Dermatomyositis
- Exacerbated hepatosplenic T-cell lymphoma
- Increased risk in inflammatory bowel disease
- Myocardial infarction
- Myocardial ischaemia
- Vision loss

- Further information

- Adverse reactions. Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, transient visual loss, pruritus, urticaria, serum sickness-like reactions, angioedema, anaphylaxis) reported during or within 1–2 hours after infusion (risk greatest during first or second infusion or in patients who discontinue other immunosuppressants). Manufacturer advises prophylactic antypiretics, antihistamines, or hydrocortisone may be administered.


- Side-effects

- Common
- Very common

- Abcess
- Aplasia
- Arthritis
- Arthralgia
- Chest pain
- Chills
- Constipation
- Decreased appetite
- Depression
- Diarrhoea
- Dizziness
- Dyspepsia
- Eye inflammation
- Fatigue
- Fever
- Gastrointestinal discomfort
- Gastrointestinal disorders
- Haemorrhage
- Headache
- Hepatic disorders
- Hypersensitivity
- Hypertension
- Increased risk of infection
- Infusion related reaction
- Insomnia
- Lymphadenopathy
- Myalgia
- Nausea
- Neutropenia
- Oedema
- Pain
- Palpitations
- Respiratory disorders
- Sensation abnormal
- Seizure
- Sepsis
- Skin reactions
- Vasodilation
- Vertigo

- Uncommon
- Anxiety
- Cheilitis
- Cholecyctis
- Confusion
- Drowsiness
- Healing impaired
- Heart failure
- Hypersensitivity
- Lupus-like syndrome
- Lymphocytosis
- Memory loss
- Neoplasms
- Nerve disorders
- Pancreatitis
- Peripheral ischaemia
- Pulmonary oedema
- Seborrhoea
- Seizure
- Syncope
- Thrombocytopenia
- Thrombophlebitis

- Rare or very rare
- Agranulocytosis
- Circulatory collapse
- Cyanosis
- Demyelinating disorders
- Granuloma
- Haemolytic anaemia
- Hepatitis B reactivation
- Meningitis
- Pancytopenia
- Pericardial effusion
- Sarcoïdosis
- Severe cutaneous adverse reactions

- Galen

- Arthritis

- Joint pain
- Joint swelling
- Muscle pain
- Oedema
- Peripheral ischaemia
- Swelling
- Vasospasm

- Frequency not known

- Arthralgia
- Chondritis
- Myalgia
- Myopathy
- Periarteritis
- Periostitis
- Pneumocystis
- Pulmonary fibrosis
- Spondylitis
- Spondylolysis
- Synovitis

- Further information

- Contra-indications. Contra-indications include pregnancy, breastfeeding, and children under the age of 18.

- Precautions. Patients should be monitored regularly for the development of adverse reactions and for signs of infection.

- Contraindications. Prophylaxis should not be given to patients with severe infections or those who are immunosuppressed.

- Side-effects. Side-effects of prophylaxis may include gastrointestinal upset, rash, and fever. Rare side-effects may include hepatitis or pancreatitis.

- Monitoring requirements. Tuberculosis prophylaxis should be monitored regularly to assess for the development of adverse reactions and to ensure compliance with treatment.

- Directions for administration. Prophylaxis should be administered at least 2 hours after the last dose of anti-TB medication. The initial dose should be given after a prolonged period of 16 weeks. The maintenance dose should be given at least every 6 weeks. Patients should be monitored for the development of tuberculosis symptoms.

- Further information. The manufacturer advises prophylactic antypiretics, antihistamines, or hydrocortisone may be administered.
Musculoskeletal system

PRESCRIBING AND DISPENSING INFORMATION
Infliximab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1.

PATIENT AND CARER ADVICE
Tuberculosis
Patients and carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

Blood disorders
Patients and carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Hypersensitivity reactions
Patients and carers should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop.

Alert card
An alert card should be provided.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

Infliximab for plaque psoriasis in adults (January 2008) NICE TA134
Infliximab is recommended for the treatment of very severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) or to photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Infliximab should be withdrawn if the response is not adequate after 10 weeks.

www.nice.org.uk/TA134

Infliximab for acute exacerbations of ulcerative colitis (December 2008) NICE TA163
Infliximab is recommended as an option for the treatment of acute exacerbations of severe ulcerative colitis when treatment with ciclosporin is contra-indicated or inappropriate.

www.nice.org.uk/TA163

Infliximab and adalimumab for Crohn’s disease (May 2010) NICE TA187
Infliximab is recommended for the treatment of severe active Crohn’s disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications. Infliximab should be withdrawn if the response is not adequate after 10 weeks.

www.nice.org.uk/TA187

Infliximab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA187

Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) NICE TA199
Infliximab is recommended for the treatment of active and progressive psoriatic arthritis in adults who have peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination). Infliximab should be discontinued if there is an inadequate response at 12 weeks.

www.nice.org.uk/TA199

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329
Infliximab is an option for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies.

The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen.

Infliximab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

www.nice.org.uk/TA329

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016) NICE TA375
Infliximab, in combination with methotrexate, is recommended as an option for treating rheumatoid arthritis, only if the following criteria are met:

• disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and,
• disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs).

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Patients currently receiving infliximab whose disease does not meet the above criteria should have the option to continue their treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA375

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (February 2016) NICE TA383
Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended as options for treating severe active ankylosing spondylitis in patients whose disease has responded inadequately to, or who are intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs). Infliximab is recommended only if treatment is started with the least expensive infliximab product.

Patients currently receiving infliximab should continue treatment with the same infliximab product until they and their clinician consider it appropriate to stop.

The response to treatment should be assessed 12 weeks after the start of treatment and should only be continued if there is clear evidence of response.

www.getintopharma.com
Treatment with another tumour necrosis factor (TNF) - alpha inhibitor is recommended in those who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or in those whose disease has stopped responding after an initial response.

www.nice.org.uk/TA283

- **MEDICINAL FORMS**  
  There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**  
CAUTIONARY AND ADVISORY LABELS 10

- **Flixabi** (Biogen Idec Ltd)
- **Infliximab 100 mg** Flixabi 100mg powder for concentrate for solution for infusion vials | 1 vial (£377.00 (Hospital only))
- **Inflectra** (Pfizer Ltd)
- **Remicade** (Merck Sharp & Dohme Ltd)
- **Remsima** (Napp Pharmaceuticals Ltd)
- **Zessly** (Sandoz Ltd)
- **Infliximab 100 mg** Inflectra 100mg powder for concentrate for solution for infusion vials | 1 vial (£377.66 (Hospital only))
- **Infliximab 100 mg** Remicade 100mg powder for concentrate for solution for infusion vials | 1 vial (£419.62 (Hospital only))
- **Remsima** (Napp Pharmaceuticals Ltd)
- **Zessly (Sandoz Ltd)**
- **Infliximab 100 mg** Zessly 100mg powder for concentrate for solution for infusion vials | 1 vial (£377.66 (Hospital only))

PHOSPHODIESTERASE TYPE-4 INHIBITORS

**Apremilast**

**DRUG ACTION** Apremilast inhibits the activity of phosphodiesterase type-4 (PDE4) which results in suppression of pro-inflammatory mediator synthesis and promotes anti-inflammatory mediators.

**INDICATIONS AND DOSE**

Active psoriatic arthritis (in combination with disease-modifying antirheumatic drugs or alone) in patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy  
Moderate to severe chronic plaque psoriasis that has not responded to standard systemic treatments or phototherapy, or when these treatments cannot be used because of intolerance or contra-indications

**BY MOUTH**

- **Adult**: Initially 10 mg daily on day 1, then 10 mg twice daily on day 2, then 20 mg in the morning and 20 mg in the evening on day 3, then 20 mg twice daily on day 4, then 20 mg in the morning and 30 mg in the evening on day 5, then maintenance 30 mg twice daily, doses should be taken approximately 12 hours apart; review treatment if no response within 24 weeks of initiation

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (JANUARY 2017): APREMILAST (OTEZLA ®): RISK OF SUICIDAL THOUGHTS AND BEHAVIOUR  
A review of evidence from clinical trials and postmarketing cases has suggested a causal association between apremilast and suicidal thoughts and behaviour.

**CAUTIONS**  
Concomitant use of drugs likely to cause psychiatric symptoms - history of psychiatric illness - low body-weight - consider discontinuation if weight loss is unexplained or clinically significant

**INTERACTIONS**  
Appendix 1: apremilast

**SIDE-EFFECTS**

- **Common or very common** Appetite decreased - back pain - cough - depression - diarrhoea - fatigue - gastrointestinal discomfort - gastrointestinal disorders - headaches - increased risk of infection - insomnia - nausea - vomiting

- **Uncommon** Gastrointestinal haemorrhage - rash - suicidal tendencies - weight decreased

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during treatment.

- **PREGNANCY** Avoid - teratogenic in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid - present in milk in animal studies.

- **RENAL IMPAIRMENT** Dose adjustments: Reduce dose if eGFR less than 30 mL/minute/1.73 m²; consult product literature for initial dose titration.

- **MONITORING REQUIREMENTS**
  - Manufacturer advises monitor body-weight regularly in patients underweight at the start of treatment.
  - Manufacturer advises monitor for psychiatric symptoms (including depression, suicidal ideation and behaviour) - discontinue treatment if new or worsening psychiatric symptoms are identified.

- **PATIENT AND CARER ADVICE**
  - Manufacturer advises patients and carers should be instructed to notify the prescriber of any changes in behaviour or mood, and of any suicidal ideation.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- **Apremilast for treating active psoriatic arthritis (February 2017) NICE TA433**
  - Apremilast, alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is recommended as an option for treating active psoriatic arthritis in adults only if:
    - they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
    - their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination and
    - the manufacturer provides apremilast with the discount agreed in the patient access scheme.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

  www.nice.org.uk/TA433

- **Apremilast for treating moderate to severe plaque psoriasis (November 2016) NICE TA419**
  - Apremilast is recommended as an option for treating chronic plaque psoriasis in patients whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA, or when these treatments are contra-indicated or not tolerated, only if:
    - the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
    - treatment is stopped if the psoriasis has not responded adequately at 16 weeks (defined as a 75% reduction in the PASI score (PASI 75) from when treatment started or a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from start of treatment), and
    - the manufacturer provides apremilast with the discount agreed in the patient access scheme.

  Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their clinician consider it appropriate to stop.

  www.nice.org.uk/TA419

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (June 2015) that apremilast (Otezla ®) is accepted for restricted use within NHS Scotland for the treatment of active psoriatic
musculoskeletal system

arthritis attacks (at least can be used for the symptomatic treatment of frequent gouty heart failure since, unlike NSAIDs, it does not induce toxicity at higher doses, but it is of value in patients with injection can be effective in podagra. [unlicensed indication]. A corticosteroid by intramuscular corticosteroid can be used in acute monoarticular gout resistant to other treatments. Intra-articular injection of a alternative in those who cannot tolerate NSAIDs or who are retention; moreover, it can be given to patients receiving uricosurics are not effective in treating an acute attack and respond adequately to treatment with NSAIDs or to prevent further attacks of gout by correcting the hyperuricaemia. These drugs should never be started during an acute attack; they are usually started 1–2 weeks after the attack has settled. The initiation of treatment may precipitate an acute attack, and therefore an anti-inflammatory analgesic or colchicine should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. However, if an acute attack develops during treatment, then the treatment should continue at the same dosage and the acute attack treated in its own right.

Allopurinol is widely used and is especially useful in patients with renal impairment or urate stones when uricosuric drugs cannot be used; it is not indicated for the treatment of asymptomatic hyperuricaemia. It can cause rashes.

Fexaxostat is licensed for the treatment of chronic hyperuricaemia where urate deposition has already occurred; it is not indicated for patients in whom the rate of urate formation is greatly increased, such as in malignant disease or in Lesch-Nyhan syndrome.

Sulfinpyrazone can be used instead of allopurinol or in conjunction with it in cases that are resistant to treatment. Benzbromarone (available from ‘special-order’ manufacturers or specialist importing companies) is a uricosuric drug that can be used in patients with mild renal impairment.

Crystallisation of urate in the urine can occur with the uricosuric drugs and it is important to ensure an adequate urine output especially in the first few weeks of treatment. As an additional precaution the urine may be rendered alkaline. Aspirin and other salicylates antagonise the uricosuric drugs; they do not antagonise allopurinol but are nevertheless not indicated in gout.

Other drugs used for Hyperuricaemia and gout Naproxen with esomeprazole, p. 1149

ALKALOIDS  PLANT ALKALOIDS

I Colchicine

- INDICATIONS AND DOSE

Acute gout

- BY MOUTH

- Adult: 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days

Short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs

- BY MOUTH

- Adult: 500 micrograms twice daily

Prophylaxis of familial Mediterranean fever (recurrent polyserositis)

- BY MOUTH

- Adult: 0.5–2 mg once daily

DOSE ADJUSTMENTS DUE TO INTERACTIONS

- Manufacturer advises reduce dose by half with concurrent use of moderate inhibitors of CYP3A4.

- Manufacturer advises reduce dose by 75% (to one quarter of usual dose) with concurrent use of potent inhibitors of CYP3A4 or P-glycoprotein inhibitors; avoid concurrent use in patients with hepatic or renal impairment.

- UNLICENSED USE BNF doses may differ from those in the product literature. Use of colchicine for prophylaxis of familial Mediterranean fever (recurrent polyserositis) is an unlicensed indication.

- CONTRA-INDICATIONS Blood disorders

- CAUTIONS Cardiac disease · elderly · gastro-intestinal disease

- INTERACTIONS  Appendix 1: colchicine
Hyperuricaemia and gout

Allopurinol

- **INDICATIONS AND DOSE**
  - Prophylaxis of gout and of uric acid and calcium oxalate renal stones
  - Prophylaxis of hyperuricaemia associated with cancer chemotherapy

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain, diarrhoea, nausea, vomiting
  - Frequency not known: Agranulocytosis, alopecia, bone marrow disorders, gastrointestinal haemorrhage, kidney injury, liver injury, menstrual cycle irregularities, myopathy, nerve disorders, rash, sperm abnormalities, thrombocytopenia
  - **CONTRA-INDICATIONS**
  - XANTHINE OXIDASE INHIBITORS
  - **RENAI IMPAIRMENT**
  - **HEPATIC IMPAIRMENT**
  - **PREGNANCY**
  - **BREAST FEEDING**

- **MEDICINAL FORMS**
  - Tablet
    - Colchicine (Non-proprietary)
    - Colchicine 500 microgram tablets
  - Solution

- **INTERACTIONS**
  - Appendix 1: allopurinol

- **SIDE-EFFECTS**
  - **Common or very common**
  - Rash (discontinue therapy; if rash mild re-introduce cautiously but discontinue immediately if recurrence)
  - **Uncommon**
  - Hypersensitivity, nausea, vomiting
  - **Rare or very rare**
  - Agranulocytosis, alopecia, angina pectoris, angioedema, aplastic anaemia, asthenia, ataxia, bone marrow injuries, cataract, coma, depression, diabetes mellitus, drowsiness, erectile dysfunction, fever, gastrointestinal disorders, bone marrow injuries, haemorrhage, hair colour changes, headache, hepatic disorders, hyperlipidaemia, hypertension, infertility, male maculopathy, malaise, oedema, paraesthesia, paralysis, peripheral neuropathy, severe cutaneous adverse reactions (SCARs), skin reactions, stomatitis, taste altered, thrombocytopenia, vertigo, visual impairment

- **MEDICAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **INDICATIONS AND DOSE**
  - Treatment of chronic hyperuricaemia in gout

- **SIDE-EFFECTS**
  - Common or very common
  - Rash (discontinue therapy; if rash mild re-introduce cautiously but discontinue immediately if recurrence)
  - Uncommon
  - Hypersensitivity, nausea, vomiting
  - Rare or very rare
  - Agranulocytosis, alopecia, angina pectoris, angioedema, aplastic anaemia, asthenia, ataxia, bone marrow injuries, cataract, coma, depression, diabetes mellitus, drowsiness, erectile dysfunction, fever, gastrointestinal disorders, bone marrow injuries, haemorrhage, hair colour changes, headache, hepatic disorders, hyperlipidaemia, hypertension, infertility, male maculopathy, malaise, oedema, paraesthesia, paralysis, peripheral neuropathy, severe cutaneous adverse reactions (SCARs), skin reactions, stomatitis, taste altered, thrombocytopenia, vertigo, visual impairment

- **MEDICAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral different medicines containing the same drug.
Prophylaxis and treatment of acute hyperuricaemia with initial chemotherapy for haematologic malignancies

- BY MOUTH
- Adult: 120 mg once daily, to be started 2 days before start of cytotoxic therapy and continued for 7–9 days, according to chemotherapy duration

IMPORTANT SAFETY INFORMATION

**MHRA/CHM ADVICE: SERIOUS HYPERSensitivity REACTIONS (JUNE 2012)**

There have been rare but serious reports of hypersensitivity reactions, including Stevens-Johnson syndrome and acute anaphylactic shock with febuxostat. Patients should be advised of the signs and symptoms of severe hypersensitivity; febuxostat must be stopped immediately if these occur (early withdrawal is associated with a better prognosis), and must not be restarted in patients who have ever developed a hypersensitivity reaction to febuxostat. Most cases occur during the first month of treatment; a prior history of hypersensitivity to allopurinol and/or renal disease may indicate potential hypersensitivity to febuxostat.

**CONTRA-INDICATIONS** Not a treatment for acute gout but continue if attack develops when already receiving febuxostat, and treat attack separately

**CAUTIONS** Congestive heart failure - ischaemic heart disease - thyroid disorders - transplant recipients

**CAUTIONS, FURTHER INFORMATION** Administer prophylactic NSAID (not aspirin or salicylates) or colchicine for at least 30 days during treatment as indicated.

**INTERACTIONS** → Appendix 1: febuxostat

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea - gout aggravated - headache - hepatic disorders - nausea - oedema - skin reactions


- **Rare or very rare** Alopecia - angioedema - hyperhidrosis - hypersensitivity - musculoskeletal stiffness - nephritis - tubulointerstitial nephritis - nervousness - oral ulceration - pancreatitis - pancytopenia - rhabdomyolysis - severe cutaneous adverse reactions (SCARs) - thirst - thrombocytopenia - tinnitus - vision blurred

**PREGNANCY** Manufacturer advises avoid—limited information available.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

Dose adjustments

Manufacturer advises max. 80 mg daily in mild impairment; no dose information available in moderate to severe impairment.

**RENAL IMPAIRMENT** Use with caution if eGFR less than 30 mL/minute/1.73 m²—no information available.

**PRE-TREATMENT SCREENING** Monitor liver function tests before treatment as indicated.

**MONITORING REQUIREMENTS** Monitor liver function tests periodically during treatment as indicated.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Febuxostat for the management of hyperuricaemia in patients with gout (December 2008) NICE TA164

Febuxostat (Adenuric®) is recommended as an option for the management of chronic hyperuricaemia in gout only for patients who are intolerant of allopurinol or for whom allopurinol is contra-indicated.

For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant discontinuation, or to prevent full dose escalation for optimal effectiveness.

**Scottish Medicines Consortium (SMC) decisions**

SMC No. 637/10 The Scottish Medicines Consortium has advised (September 2010) that febuxostat (Adenuric®) is accepted for restricted use within NHS Scotland for the treatment of chronic hyperuricaemia when treatment with allopurinol is inadequate, not tolerated or contra-indicated.

SMC No. 1153/16 The Scottish Medicines Consortium has advised (June 2016) that febuxostat (Adenuric®) is accepted for restricted use within NHS Scotland for the prevention and treatment of hyperuricaemia in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of tumour lysis syndrome, only when allopurinol is not tolerated or contra-indicated.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Febuxostat (Non-proprietary)**
  - Febuxostat 80 mg: Febuxostat 80mg tablets | 28 tablet [POM]
  - £17.05–£24.36 DT = £24.36
  - Febuxostat 120 mg: Febuxostat 120mg tablets | 28 tablet [POM]
  - £17.05–£24.36 DT = £24.36
  - [A. Menarini Farmaceutica Internazionale SRL]
  - Febuxostat 80 mg: Adenuric 80mg tablets | 28 tablet [POM]
  - £24.36 DT = £24.36
  - Febuxostat 120 mg: Adenuric 120mg tablets | 28 tablet [POM]
  - £24.36 DT = £24.36

3 **Neuromuscular disorders**

**Neuromuscular disorders**

**Drugs that enhance neuromuscular transmission**

Anticholinesterases are used as first-line treatment in *ocular myasthenia gravis* and as an adjunct to immunosuppressant therapy for *generalised myasthenia gravis*.

Corticosteroids are used when anticholinesterases do not control symptoms completely. A second-line immunosuppressant such as azathioprine p. 836 is frequently used to reduce the dose of corticosteroid.

Plasmapheresis or infusion of intravenous immunoglobulin [unlicensed indication] may induce temporary remission in severe relapses, particularly where bulbar or respiratory function is compromised or before thymectomy.

**Anticholinesterases**

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in *myasthenia gravis*. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic crises by causing a depolarising block. This may be difficult to distinguish from a worsening myasthenic state.

Muscarinic side-effects of anticholinesterases include increased sweating, increased salivary and gastric secretions,
increased gastro-intestinal and uterine motility, and bradycardia. These parasympathomimetic effects are antagonised by atropine sulphate p. 1334.

Neostigmine p. 1125 produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an antimuscarinic drug such as atropine sulphate or propantheline bromide p. 86 may be required to prevent colic, excessive salivation, or diarrhoea. In severe disease neostigmine can be given every 2 hours. The maximum that most patients can tolerate is 180 mg daily.

Pyridostigmine bromide p. 1126 is less powerful and slower in action than neostigmine but it has a longer duration of action. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. It is particularly preferred in patients whose muscles are weak on waking. It has a comparatively mild gastrointestinal effect but an antimuscarinic drug may still be required.

Neostigmine is also used to reverse the actions of the non-depolarising neuromuscular blocking drugs.

**Immunosuppressant therapy**

**Corticosteroids** are established as treatment for myasthenia gravis; although they are commonly given on alternate days there is little evidence of benefit over daily administration. Corticosteroid treatment is usually initiated under in-patient supervision and all patients should receive oestrogen prophylaxis.

In *generalised myasthenia gravis* prednisolone p. 678 is given. About 10% of patients experience a transient but very serious worsening of symptoms in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. Smaller doses of corticosteroid are usually required in *ocular myasthenia*. Once clinical remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose.

In *generalised myasthenia gravis* azathioprine is usually started at the same time as the corticosteroid and it allows a lower maintenance dose of the corticosteroid to be used. Ciclosporin p. 838, methotrexate p. 913, or mycophenolate mofetil p. 846 can be used in patients unresponsive or intolerant to other treatments [unlicensed indications].

**Acetylcholine-release enhancers**

Amifampridine p. 1126 is licensed for the symptomatic treatment of Lambert–Eaton myasthenic syndrome (LEMS), a rare disorder of neuromuscular transmission.

Fampridine p. 850 is licensed for the improvement of walking in patients with Multiple sclerosis p. 846 who have a walking disability.

**Skeletal muscle relaxants**

The drugs described are used for the relief of chronic muscle spasm or spasticity associated with Multiple sclerosis p. 848 or other neurological damage; they are not indicated for spasm associated with minor injuries. Baclofen, diazepam, and tizanidine act principally on the central nervous system. Dantrolene has a peripheral site of action; cannabis extract has both a central and a peripheral action. Skeletal muscle relaxants differ in action from the muscle relaxants used in anaesthesia, which block transmission at the neuromuscular junction.

The underlying cause of spasticity should be treated and any aggravating factors (e.g. pressure sores, infection) remedied. Skeletal muscle relaxants are effective in most forms of spasticity except the rare alpha variety. The major disadvantage of treatment with these drugs is that reduction in muscle tone can cause a loss of splinting action of the spastic leg and trunk muscles and sometimes lead to an increase in disability.

Baclofen p. 1128 inhibits transmission at spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia (other adverse events are uncommon).

A cannabis extract p. 1127 containing dronabinol (delta-9-tetrahydrocannabinol) and cannabidiol is licensed as an adjunct treatment for moderate to severe spasticity associated with Multiple sclerosis p. 848 in patients who have not responded adequately to other skeletal muscle relaxants. The dose should be titrated over 2 weeks; response to treatment should be reviewed after 4 weeks and treatment stopped if an adequate response is not achieved.

Danztrolone sodium p. 1346 acts directly on skeletal muscle and produces fewer central adverse effects making it a drug of choice. The dose should be increased slowly. Diazepam p. 343 can also be used. Sedation and occasionally extensor hypotonia are disadvantages. Other benzodiazepines also have muscle-relaxant properties. Muscle-relaxant doses of benzodiazepines are similar to anxiolytic doses.

Tizanidine p. 1129 is an alpha₂-adrenoceptor agonist indicated for spasticity associated with Multiple sclerosis p. 848 or spinal cord injury.

**Other muscle relaxants**

The clinical efficacy of methocarbamol p. 1129 and meprobamate p. 346 as muscle relaxants is not well established, although they have been included in compound analgesic preparations.

**NEUROPROTECTIVE DRUGS**

### Riluzole

**INDICATIONS AND DOSE**

To extend life in patients with amyotrophic lateral sclerosis, initiated by specialist experienced in the management of motor neurone disease

- **BY MOUTH**

**CAUTIONS**

- History of abnormal hepatic function (consult product literature for details) • interstitial lung disease

**SIDE-EFFECTS, FURTHER INFORMATION**

- *Common or very common* Abdominal pain • asthenia • diarrhoea • dizziness • drowsiness • headache • nausea • oral paraesthesia • pain • tachycardia • vomiting

- *Uncommon* Anaemia • angioedema • interstitial lung disease • pancreatitis

- **FREQUENCY NOT KNOWN** Hepatitis • neutropenia

**SIDE-EFFECTS, FURTHER INFORMATION**

- White blood cell counts should be determined in febrile illness; neutropenia requires discontinuation of riluzole.

**PREGNANCY** Avoid—no information available.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid (risk of increased exposure).

**RENAL IMPAIRMENT** Avoid—no information available.

**PATIENT AND CARER ADVICE**

Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever occur.

Driving and skilled tasks Dizziness or vertigo may affect performance of skilled tasks (e.g. driving).

www.getintopharma.com
**3.1 Muscular dystrophy**

**DRUGS FOR NEUROMUSCULAR DISORDERS**

Ataluren

**DRUG ACTION** Ataluren restores the synthesis of dystrophin by allowing ribosomes to read through premature stop codons that cause incomplete dystrophin synthesis in nonsense mutation Duchenne muscular dystrophy.

**INDICATIONS AND DOSE**

Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients (initiated by a specialist)

- **BY MOUTH**
  - Adult: (consult product literature)

**INTERACTIONS** → Appendix 1: ataluren

**SIDE-EFFECTS**

- Common or very common: Appetite decreased - constipation - cough - enuresis - fever - flatulence - gastrointestinal discomfort - haemorrhage - headache - hypertension - hypertriglyceridaemia - nausea - pain - rash erythematous - vomiting - weight decreased

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises discontinue breastfeeding—present in milk in animal studies.

**RENAL IMPAIRMENT** Manufacturer advises close monitoring—safety and efficacy not established.

**MONITORING REQUIREMENTS** Manufacturer advises monitor renal function at least every 6–12 months, and cholesterol and triglyceride concentrations at least annually.

**DIRECTIONS FOR ADMINISTRATION** Manufacturer advises the contents of each sachet should be mixed with at least 30 mL of liquid (water, milk, fruit juice), or 3 tablespoons of semi-solid food (yoghurt or apple sauce).

**PATIENT AND CARER ADVICE** Manufacturer advises patients should maintain adequate hydration during treatment.

Missed doses Manufacturer advises if a morning or midday dose is more than 3 hours late, or an evening dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **Ataluren** for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (July 2016)

NICE HST3

Ataluren, within its marketing authorisation, is recommended for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk, only when:

- the manufacturer provides ataluren with the discount agreed in the patient access scheme, and

- the conditions under which ataluren is made available.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **Ataluren** for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (July 2016)

NICE TA20

Riluzole

Manufacturer advises avoid—seizures, and vomiting.

**TETOS**

**PATIENT AND CARER ADVICE** Manufacturer advises patients should maintain adequate hydration during treatment.

**MEDICATION FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder.

**Oral suspension**

- **Teglatulik** (Martindale Pharmaceuticals Ltd)
  - Riluzole 5 mg per 1 ml Teglatulik 5mg/1ml oral suspension sugar-free $300.00 DT = $100.00

**Tablet**

- **Riluzole** (Non-proprietary)
  - Riluzone 50 mg Riluzole 50mg tablets | 56 tablet $320.00 DT = £12.08
  - **Rilutek** (Sanofi)
  - Riluzole 50 mg Rilutek 50mg tablets | 56 tablet $320.33 DT = £12.08

**SIDE-EFFECTS**

- Common or very common: Skin rash erythematous - hypertonia - hypotonia - increased muscle tone

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
**Nusinersen**

31-Aug-2018

- **DRUG ACTION** Nusinersen is an antisense oligonucleotide that increases the production of survival motor neurone (SMN) protein, thereby helping to compensate for the defect in the SMN1 gene found in 5q spinal muscular atrophy.

- **INDICATIONS AND DOSE**
  - 5q spinal muscular atrophy (initiated by a specialist)
  - **BY INTRATHecal INJECTION**
    - Adult: Initially 12 mg for 4 doses, on days 0, 14, 28 and 63, then 12 mg every 4 months, for advice on missed doses—consult product literature

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: NUSINERSEN (SPINRAZA ™): REPORTS OF COMMUNICATING HYDROCEPHALUS NOT RELATED TO MENINGITIS OR BLEEDING (JULY 2018)

Communicating hydrocephalus not related to meningitis or bleeding has been reported in patients treated with Spinraza™. Patients and caregivers should be informed about the signs and symptoms of hydrocephalus before Spinraza™ is started and should be instructed to seek medical attention in case of: persistent vomiting or headache, unexplained decrease in consciousness, and in children increase in head circumference. Patients with signs and symptoms suggestive of hydrocephalus should be further investigated by a physician with expertise in its management.

- **CAUTIONS** Risk factors for renal toxicity—monitor urine protein (preferably using a first morning urine specimen) - risk factors for thrombocytopenia and coagulation disorders—monitor platelet and coagulation profile before treatment
  - **PREGNANCY** Manufacturer advises avoid—no information available
  - **BREAST FEEDING** Manufacturer advises avoid—no information available.
  - **RENAL IMPAIRMENT** Manufacturer advises close monitoring—safety and efficacy not established
  - **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8 °C); may be stored (in the original carton, protected from light) at or below refrigerator (–2–8 °C); may be stored (in the original carton, protected from light) at or below refrigerator (–2–8 °C)
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **Spinraza** (Biogen Idec Ltd) ▲
  - Nusinersen (as Nusinersen sodium) 2.4 mg per 1 ml
  - Spinraza 12mg/5ml solution for injection vials | 1 vial £75,000.00

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### 3.2 Myasthenia gravis and Lambert-Eaton myasthenic syndrome

#### ANTICHOLINESTERASES

**Anticholinesterases**

- **DRUG ACTION** They prolong the action of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase.
  - **CONTRA-INDICATIONS** Intestinal obstruction - urinary obstruction
  - **CAUTIONS** Arrhythmias - asthma (extreme caution) - atropine or other antidote to muscarinic effects may be necessary (particularly when neostigmine is given by injection) but not given routinely because it may mask signs of overdosage - bradycardia - epilepsy - hyperthyroidism - hypotension - parkinsonism - peptic ulceration - recent myocardial infarction - vagotonia
  - **SIDE-EFFECTS** Abdominal cramps - diarrhoea - excessive tearing - hypersalivation - nausea - vomiting
  - **Overdose** Signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defaecation, involuntary micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.
  - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
  - **BREAST FEEDING** Amount probably too small to be harmful.

**Neostigmine**

*Neostigmine methylsulfate*

- **INDICATIONS AND DOSE**
  - **TREATMENT OF MYASTHENIA GRAVIS**
    - **BY MOUTH**
      - Adult: Initially 15–30 mg, dose repeated at suitable intervals throughout the day, total daily dose 75–300 mg, the maximum that most patients can tolerate is 180 mg daily
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
      - Adult: 1–2.5 mg, dose repeated at suitable intervals throughout the day (usual total daily dose 5–20 mg)
  - **REVERSAL OF NON-DEPOLARISING (COMPETITIVE) NEUROMUSCULAR BLOCKADE**
    - **BY INTRAVENOUS INJECTION**
      - Adult: 2.5 mg (max. per dose 5 mg), repeated if necessary after or with glycopyrronium or atropine, to be given over 1 minute

- **CAUTIONS**
  - With intravenous use glycopyrronium or atropine should also be given when reversing neuromuscular blockade
  - **INTERACTIONS** ▲ Appendix 1: neostigmine
  - **SIDE-EFFECTS**
    - With parenteral use Intestinal hypermotility - muscle spasms
  - **RENAL IMPAIRMENT**
    - Dose adjustments May need dose reduction.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Solution for injection

- **Neostigmine (Non-proprietary)**
  - Neostigmine methylsulfate 2.5 mg per 1 ml
  - Neostigmine 2.5mg/1ml solution for injection ampoules | 10 ampoule Pack £5.45 | £7.72 DT + £6.13
- **Tablet**
  - **Neostigmine (Non-proprietary)**
    - Neostigmine bromide 15 mg
      - Neostigmine 15mg tablets | 140 tablet Pack £120.52 DT + £120.52
Pyridostigmine bromide

**DRUG ACTION** Pyridostigmine bromide has weaker muscarinic action than neostigmine.

**INDICATIONS AND DOSE**

- **Myasthenia gravis**
  - **INITIALLY BY MOUTH**
  - **Adult:** 30–120 mg, doses to be given at suitable intervals throughout day; (by mouth) usual dose 0.3–1.2 g daily in divided doses, it is inadvisable to exceed a total daily dose of 450 mg in order to avoid acetylcholine receptor down-regulation; patients requiring doses exceeding 450 mg daily will usually require input from a specialised neuromuscular service. Immunosuppressant therapy is usually considered if the dose of pyridostigmine exceeds 360 mg daily

- **PRECAUTIONS**
  - Use with caution.
  - **SIDE-EFFECTS** Gastrointestinal hypermotility - muscle cramps - rash
  - **RENAL IMPAIRMENT**
  - **Dose adjustments** Reduce dose; excreted by kidney.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution

- **Tablet**
  - Pyridostigmine bromide (Non-proprietary)
  - Pyridostigmine bromide 60 mg: Pyridostigmine bromide 60mg tablets | 200 tablet (cost) £45.48 DT = £44.30
  - Mestinon (Meda Pharmaceuticals Ltd)
  - Pyridostigmine bromide 60 mg: Mestinon 60mg tablets | 200 tablet (cost) £45.57 DT = £44.30

**CHOLINERGIC RECEPTOR STIMULATING DRUGS**

Amifampridine

**INDICATIONS AND DOSE**

- **Symptomatic treatment of Lambert-Eaton myasthenic syndrome (specialist use only)**
  - **BY MOUTH**
  - **Adult:** Initially 15 mg daily in 3 divided doses, then increased in steps of 5 mg every 4–5 days, increased to up to 60 mg daily in 3–4 divided doses (max. per dose 20 mg); maximum 60 mg per day

- **CONTRA-INDICATIONS** Congenital QT syndromes - epilepsy - uncontrolled asthma

- **CAUTIONS** Non-paraneoplastic form of Lambert- Eaton myasthenic syndrome

- **INTERACTIONS** → Appendix 1: amifampridine

- **SIDE-EFFECTS** Anxiety - arrhythmia - asthenia - asthma - bronchial secretion increased - cough - dizziness - drowsiness - gastrointestinal disorder - headache - movement disorders - palpitations - paraesthesia - Raynaud’s phenomenon - seizure - sleep disorder - vision blurred

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment in men and women.

- **PREGNANCY** Manufacturer advises avoid.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution (risk of increased exposure).

- **Dose adjustments** Manufacturer advises initial dose reduction to 5 mg twice daily in mild impairment, titrate in steps of 5 mg every 7 days.

**SIDE-EFFECTS**

- Abnormal Q-waves - atrial tachyarrhythmia - fibrillation or flutter - complete heart block or any heart block susceptible to evolve to complete heart block - heart failure (with ejection fraction less than 50%) - history of myocardial infarction - sinus node dysfunction - symptomatic coronary artery disease - ventricular tachyarrhythmia

- **CAUTIONS** Cardiac disorders other than those contra-indicated - epilepsy (increased risk of seizures)

- **INTERACTIONS** → Appendix 1: mexiletine

**DRUGS FOR NEUROMUSCULAR DISORDERS**

Mexiteline

**DRUG ACTION** Mexiletine is a sodium channel blocker which reduces the delay of muscle relaxation thereby decreasing muscle stiffness.

**INDICATIONS AND DOSE**

- **Myotonia in non-dystrophic myotonic disorders**
  - **BY MOUTH**
  - **Adult:** 167 mg once daily for at least 1 week, then increased if necessary to 333 mg daily in divided doses for at least 1 week, then increased if necessary to 500 mg daily in divided doses; maintenance 167–500 mg daily; maximum 500 mg per day

- **CONTRA-INDICATIONS** Abnormal Q-waves - atrial tachyarrhythmia - fibrillation or flutter - complete heart block or any heart block susceptible to evolve to complete heart block - heart failure (with ejection fraction less than 50%) - history of myocardial infarction - sinus node dysfunction - symptomatic coronary artery disease - ventricular tachyarrhythmia

- **CAUTIONS** Cardiac disorders other than those contra-indicated - epilepsy (increased risk of seizures)

- **INTERACTIONS** → Appendix 1: mexiletine

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - arrhythmias - asthenia - chest discomfort - drowsiness - headache - hypotension - insomnia - malaise - nausea - pain in extremity - paraesthesia - skin reactions - vasodilatation - vertigo - vision disorders

- **Uncommon** Seizure - speech disorder

- **Rare or very rare** Hepatic disorders - severe cutaneous adverse reactions (SCARs)

- **Frequency not known** Atrioventricular block - circulatory collapse - confusion - diarrhoea - gastrointestinal disorders - hallucination - leucopenia - lupus-like syndrome -
3.4 Nocturnal leg cramps

Nocturnal leg cramps

Quinine salts

Quinine salts p. 619, such as quinine sulfate are effective in reducing the frequency of nocturnal leg cramps by about 25% in ambulatory patients; however, because of potential toxicity, quinine is not recommended for routine treatment and should not be used unless cramps cause regular disruption to sleep. Quinine should only be considered when cramps are very painful or frequent; when other treatable causes of cramp have been excluded; and when non-pharmacological treatments have not worked (e.g. passive stretching exercises). It may take up to 4 weeks for improvement to become apparent; if there is benefit, quinine treatment can be continued. Treatment should be interrupted at intervals of approximately 3 months to assess the need for further quinine treatment. In patients taking quinine long term, a trial discontinuation may be considered. Quinine is toxic in overdose and accidental fatalities have occurred.

3.5 Spasticity

CANNABINOIDS

Cannabis extract

- **INDICATIONS AND DOSE** Adjuvant to moderate to severe spasticity in multiple sclerosis (specialist use only)
  - By buccal administration
  - Adult: (consult product literature)
- **SIDE-EFFECTS**
  - **Common** or very common Appetite abnormal - balance impaired - concentration impaired - constipation - depression - diarrhoea - disorientation - dizziness - drowsiness - dry mouth - dysarthria - euphoric mood - feeling drunk - malaise - memory loss - nausea - oral disorders - perception altered - taste altered - vertigo - vision blurred - vomiting
  - **Uncommon** Abdominal pain upper - delusions - hallucinations - hyperactivity - palpitations - paranoia - pharyngitis - suicidal ideation - syncope - tachycardia - throat irritation - tooth discoloration
- **CONCEPTION AND CONTRACEPTION** Manufacturer recommends effective contraception during and for 3 months after treatment in men and women.
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risks.
- **BREAST FEEDING** Avoid—present in milk.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment (risk of accumulation with chronic dosing)—no information available.
- **RENAL IMPAIRMENT**
  - Monitoring: Manufacturer advises more frequent monitoring in significant renal impairment—possible risk of prolonged or enhanced effect.
  - **MONITORING REQUIREMENTS** Monitor oral mucosa—interrupt treatment if lesions or persistent soreness.
- **PATIENT AND CAREER ADVICE**
  - **Driving and skilled tasks** For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including cannabis, see Drugs and Driving under Guidance on prescribing p. 1.
**1128 Neurumuscular disorders**

**10 Musculoskeletal system**

- **MUSCLE RELAXANTS**

  ### Central Nervously Acting

  **Baclofen**

  **INDICATIONS AND DOSE**

  **Pain of muscle spasm in palliative care**
  - **BY MOUTH**
  - Adult: 5–10 mg 3 times a day
  **Hiccups due to gastric distension in palliative care**
  - **BY MOUTH**
  - Adult: 5 mg twice daily
  **Chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic partial section of spinal cord**
  - **BY MOUTH**
  - Adult: Initially 5 mg 3 times a day, gradually increased; maintenance up to 60 mg daily in divided doses, review treatment if no benefit within 6 weeks of achieving maximum dose; maximum 100 mg per day
  **Severe chronic spasticity unresponsive to oral antispastic drugs (or where side-effects of oral therapy unacceptable) or as alternative to ablative neurosurgical procedures (specialist use only)**
  - **BY INTRATHECAL INJECTION**
  - Adult: Test dose 25–50 micrograms, to be given over at least 1 minute via catheter or lumbar puncture, then increased in steps of 25 micrograms (max. per dose 100 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose-titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis

  **INTERACTIONS**

  → Appendix 1: baclofen

  **SIDE-EFFECTS**

  **GENERAL SIDE-EFFECTS**

  - **Common or very common** Confusion, constipation, depression, diarrhoea, dizziness, drowsiness, dry mouth, euphoric mood, hallucination, headache, hyperhidrosis, hypotension, nausea, paraesthesia, skin reactions, urinary disorders, vision disorders, vomiting
  - **Uncommon** Bradycardia, hypothermia
  - **Rare or very rare** Withdrawal syndrome

  **SPECIFIC SIDE-EFFECTS**

  - **Common or very common**
    - With intrathecal use Anxiety, appetite decreased, asthenia, chills, dyspnoea, fever, hypersalivation, insomnia, neuromuscular dysfunction, oedema, pain, pneumonia, respiratory disorders, seizure, sexual dysfunction
    - With oral use Fatigue, gastrointestinal disorder, muscle weakness, myalgia, respiratory depression, sleep disorders
  - **Uncommon**
    - With intrathecal use Alopecia, deep vein thrombosis, dehydration, flushing, hypertension, hypoglycaemia, ileus, memory loss, pallor, paranoia, suicidal tendencies
  - **Rare or very rare**
    - With oral use Abdominal pain, erectile dysfunction, hepatic function abnormal, taste altered
    - Frequency not known
    - With intrathecal use Scoliosis

  **PREGNANCY**

  Manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies).

  **BREAST FEEDING**

  Present in milk—amount probably too small to be harmful.

  **HEPATIC IMPAIRMENT**

  With oral use Manufacturer advises use with caution—no information available.

  **RENAL IMPAIRMENT**

  Excreted by the kidney.

  **Dose adjustments**

  - With oral use Risk of toxicity—use smaller doses (e.g. 0.5 mg daily by mouth) and if necessary increase dosage interval; if eGFR less than 15 mL/minute/1.73 m² manufacturer advises use by mouth only if potential benefit outweighs risk.

  **TREATMENT CESSATION**

  Avoid abrupt withdrawal (risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions; to minimise risk, discontinue by gradual dose reduction over at least 1–2 weeks (longer if symptoms occur)).

  **PRESCRIBING AND DISPENSING INFORMATION**

  Flavours of oral liquid formulations may include raspberry.

  **Palliative care**

  For further information on the use of baclofen in palliative care, see www.medicinescomplete.com/#content/palliative/baclofen.

  **PATIENT AND CARER ADVICE**

  **Driving and skilled tasks**

  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

  **MUSCLE RELAXANTS**

  **CENTRALLY ACTING**

  **CONTRA-INDICATIONS**

  - With intrathecal use Local infection, systemic infection
  - With oral use Avoid oral route in active peptic ulceration

  **CAUTIONS**

  **GENERAL CAUTIONS**

  - Cerebrovascular disease, diabetes, elderly, epilepsy, history of peptic ulcer, hypertonic bladder sphincter, Parkinson’s disease, psychiatric illness, respiratory impairment

  **SPECIFIC CAUTIONS**

  - With intrathecal use Coagulation disorders, malnutrition (increased risk of post-surgical complications), previous spinal fusion procedure

  **EXCIPIENTS** May contain Propylene glycol

  **Sativex** (Bayer Plc)

  *Test dose 1 dose Sativex oromucosal spray = 270 dose £375.00 DT = £375.00 (DC4-3)*

  **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Spray**

  **MEDICINAL FORMS**

  **Tablet**

  **Baclofen** (Non-proprietary)

  Baclofen 10 mg

  Baclofen 10 mg tablets | 84 tablet £9.99 DT = £1.21

  **Lioresal** (Novartis Pharmaceuticals UK Ltd)

  Baclofen 10 mg

  Lioresal 10 mg tablets | 100 tablet £14.86
Solution for injection
- **Baclofen (Non-proprietary)**
  - Baclofen 50 microgram per 1 ml Baclofen 50mcg/ml solution for injection ampoules | 10 ampoules (POM) £25.00
  - Lioresal (Novartis Pharmaceuticals UK Ltd)
- Baclofen 50 microgram per 1 ml Lioresal Intrathecal 50mcg/ml solution for injection ampoules | 1 ampoule (POM) £3.16

Solution for infusion
- **Baclofen (Non-proprietary)**
  - Baclofen 500 microgram per 1 ml Baclofen 10mg/20ml solution for infusion ampoules | 1 ampoule (POM) £50.00
  - Baclofen 2 mg per 1 ml Baclofen 40mg/20ml solution for infusion ampoules | 10 ampoules (POM) £50.00
  - Lioresal (Novartis Pharmaceuticals UK Ltd)
- Baclofen 500 microgram per 1 ml Lioresal Intrathecal 10mg/20ml solution for infusion ampoules | 1 ampoule (POM) £70.01
  - Baclofen 2 mg per 1 ml Lioresal Intrathecal 10mg/5ml solution for infusion ampoules | 1 ampoule (POM) £4.12

**Oral solution**
- **CAUTIONARY AND ADVISORY LABELS 2, 8, 21**
- **Baclofen (Non-proprietary)**
  - Baclofen 1 mg per 1 ml Baclofen 5mg/5ml oral solution sugar-free | 300 ml (POM) £13.45 DT = £4.12
  - Lioresal (Novartis Pharmaceuticals UK Ltd)
  - Baclofen 1 mg per 1 ml Lioresal 5mg/5ml liquid sugar-free | 300 ml (POM) £10.31 DT = £4.12
  - Lyflex (Chemidex Pharma Ltd)
  - Baclofen 1 mg per 1 ml Lyflex 5mg/5ml oral solution sugar-free | 300 ml (POM) £7.95 DT = £4.12

**Methocarbamol**
- **INDICATIONS AND DOSE**
  - **BY MOUTH**
    - Adult: 1.5 g 4 times a day; reduced to 750 mg 3 times a day if required
    - Elderly: Up to 750 mg 4 times a day, dose may be sufficient

- **CONTRA-INDICATIONS**
  - Brain damage - coma - epilepsy - myasthenia gravis - pre-coma

- **INTERACTIONS**
  - Appendix 1: methocarbamol

- **SIDE-EFFECTS**

- **PREGNANCY**
  - Manufacturer advises caution

- **BREASTFEEDING**
  - Present in milk in animal studies—manufacturer advises caution

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution (risk of increased half-life)

- **DOSE ADJUSTMENTS**
  - Manufacturer advises consider increasing dose interval in chronic impairment

- **RENA1 IMPAIRMENT**
  - Manufacturer advises caution

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

- **LESS SUITABLE FOR PRESCRIBING**
  - Less suitable for prescribing

**Tizanidine**
- **INDICATIONS AND DOSE**
  - **Spasticity associated with multiple sclerosis or spinal cord injury or disease**
    - **BY MOUTH**
      - Adult: Initially 2 mg daily, then increased in steps of 2 mg daily in divided doses, increased at intervals of at least 3–4 days and adjust according to response; usual dose up to 24 mg daily in 3–4 divided doses; maximum 36 mg per day

- **CAUTIONS**
  - Elderly

- **INTERACTIONS**
  - Appendix 1: tizanidine

- **SIDE-EFFECTS**
  - Common or very common: Arrhythmias - dizziness - drowsiness - dry mouth - fatigue - hypotension - rebound hypertension

- **RARE OR VERY RARE**
  - Gastrointestinal disorder - hallucination - hepatic disorders - muscle weakness - nausea - sleep disorders

- **FREQUENCY NOT KNOWN**
  - Abdominal pain - accommodation disorder - anxiety - appetite decreased - confusion - headache - QT interval prolongation - skin reactions - vomiting - withdrawal syndrome

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Treatment should be discontinued if liver enzymes are persistently raised—consult product literature

- **PREGNANCY**
  - Avoid (toxicity in animal studies)

- **BREASTFEEDING**
  - Avoid (present in milk in animal studies)

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution

- **RENA1 IMPAIRMENT**
  - Manufacturer advises caution

- **MONITORING REQUIREMENTS**
  - Monitor liver function monthly for first 4 months for daily doses of 12 mg or higher, and in those who develop unexplained nausea, anorexia or fatigue

- **TREATMENT CESSION**
  - Avoid abrupt withdrawal (risk of rebound hypertension and tachycardia); to minimise risk, discontinue gradually and monitor blood pressure

- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks
  - Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS 2, 8**
    - **Tizanidine (Non-proprietary)**
      - Tizanidine (as Tizanidine hydrochloride) 2 mg Tizanidine 2mg tablets | 120 tablet (POM) £28.89 DT = £3.22
      - Tizanidine (as Tizanidine hydrochloride) 4 mg Tizanidine 4mg tablets | 120 tablet (POM) £40.07 DT = £3.97

www.getintopharma.com
4 Pain and inflammation in musculoskeletal disorders

Low back pain and sciatica 08-Mar-2017

Description of condition
Low back pain is in the lumbosacral area of the back. It can be described as non-specific, mechanical, musculoskeletal or simple (if it is not associated with serious or potentially serious causes). Episodes of back pain do not usually last long, with rapid improvements in pain and disability seen within a few weeks to months.

Sciatica (radicular pain or radiculopathy) is neuropathic leg pain secondary to compressive lumbosacral nerve root pathology.

Non-drug treatment
Exercise programmes, manual therapy, and psychological therapies should be considered for managing low back pain with or without sciatica. Spinal decompression may be considered in patients with sciatica when pain and function has not improved with non-surgical treatment (including drug treatment).

Drug treatment
An oral NSAID (see Non-steroidal anti-inflammatory drugs below) should be considered for managing acute low back pain, taking into consideration the gastrointestinal, cardio-renal and hepatic risks associated with NSAIDs; as well as the need for continued monitoring, and the possible need for gastrointestinal protective treatment (see NSAID-associated ulcers under Peptic ulceration p. 72).

A weak opioid, either alone or with paracetamol p. 444, can be used to manage acute low back pain only if an NSAID is contra-indicated, not tolerated or ineffective (see Opioid analogues under Analgesics p. 442). Paracetamol alone is ineffective for managing low back pain.

Benzodiazepines are sometimes used to manage acute low back pain (particularly in loss of lordosis); however evidence to support their use is very weak.

In patients with chronic low back pain who have had an inadequate response to non-drug treatment, NSAIDs should be considered as first-line therapy. Opioids should be the last treatment option considered and should be considered only in patients for whom other therapies have failed and only if the potential benefits outweigh the risks for individual patients. If indicated, opioids should only be prescribed for a limited period of time. Long term opioid therapy should be avoided.

Selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), tricyclic antidepressants, and antiepileptic drugs should not be offered for managing low back pain.

When non-surgical treatment is ineffective in patients with moderate and severe localised back pain arising from structures supplied by the medial branch nerve, radiofrequency denervation can be considered.

Sciatica
Patients with sciatica may require specific treatment for Neuropathic pain p. 483.

Patients with acute and severe sciatica may benefit from treatment with epidural injections of local anaesthetic and/or corticosteroid.

Useful Resources

Non-steroidal anti-inflammatory drugs 05-Jun-2017

Therapeutic effects
In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol p. 444, but paracetamol is preferred, particularly in the elderly.

In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. Therefore, although paracetamol often gives adequate pain control in osteoarthritis, NSAIDs are more appropriate than paracetamol or the opioid analogues in the inflammatory arthritides (e.g. rheumatoid arthritis) and in some cases of advanced osteoarthritis. NSAIDs can also be of benefit in the less well defined conditions of back pain and soft-tissue disorders.

Choice
Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance to these drugs. About 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another. Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks. If appropriate responses are not obtained within these times, another NSAID should be tried.

NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase; selective inhibition of cyclo-oxygenase-2 is associated with less gastrointestinal intolerance. Several other factors also influence susceptibility to gastrointestinal effects, and a NSAID should be chosen on the basis of the incidence of gastrointestinal and other side-effects.

Ibuprofen p. 1141 is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other non-selective NSAIDs but its anti-inflammatory properties are weaker. It is unsuitable for conditions where inflammation is prominent, such as acute gout. Dextibuprofen p. 1133 is the active enantiomer of ibuprofen. It has similar properties to ibuprofen and is licensed for the relief of mild to moderate pain and inflammation.

Other propionic acid derivatives:
Naproxen p. 1148 is one of the first choices because it combines good efficacy with a low incidence of side-effects (but more than ibuprofen).
Flurbiprofen p. 1140 may be slightly more effective than naproxen, and is associated with slightly more gastrointestinal side-effects than ibuprofen.
Ketoprofen p. 1144 has anti-inflammatory properties similar to ibuprofen and has more side-effects.
Dexketoprofen p. 1134, an isomer of ketoprofen, has been introduced for the short-term relief of mild to moderate pain.
Tiatrofenic acid p. 1152 is as effective as naproxen; it has more side-effects than ibuprofen.

Drugs with properties similar to those of propionic acid derivatives:
Diclofenac sodium p. 1135 and aceclofenac p. 1132 are similar in efficacy to naproxen.
Etodolac p. 1138 is comparable in efficacy to naproxen; it is licensed for symptomatic relief of osteoarthritis and rheumatoid arthritis.
Indomethacin p. 1143 has an action equal to or superior to that of naproxen, but with a high incidence of side-effects
including headache, dizziness, and gastro-intestinal disturbances.

Mefenamic acid p. 1145 has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment.

Meloxicam p. 1146 is licensed for the short-term relief of pain in osteoarthritis and for long-term treatment of rheumatoid arthritis and ankylosing spondylitis.

Nabumetone p. 1147 is comparable in effect to naproxen.

Phenylbutazone is licensed for ankylosing spondylitis, but is not recommended because it is associated with serious side-effects, in particular haematological reactions; it should be used only by a specialist in severe cases where other treatments have been found unsuitable.

Piroxicam p. 1149 is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions.

Sulindac p. 1150 is similar in tolerance to naproxen.

Tenoxicam p. 1151 is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration.

Tolprofen p. 476 is licensed for the treatment of migraine.

Ketorolac trometamol p. 1342 and the selective inhibitor of cyclo-oxygenase-2, parecoxib p. 1342, are licensed for the short-term management of postoperative pain.

The selective inhibitors of cyclo-oxygenase-2, etoricoxib p. 1139 and celecoxib p. 1132, are as effective as non-selective NSAIDs such as diclofenac sodium and naproxen. Although selective inhibitors can cause serious gastro-intestinal events, available evidence appears to indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin.

Celecoxib and etoricoxib are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; etoricoxib is also licensed for the relief of pain from acute gout.

Aspirin p. 121 has been used in high doses to treat rheumatoid arthritis, but other NSAIDs are now preferred.

Dental and orofacial pain
Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include ibuprofen, diclofenac sodium, and diclofenac potassium p. 1135.

Asthma
Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.

NSAIDs and cardiovascular events
All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.

Cyclo-oxygenase-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. Although there are limited data regarding the thrombotic effects of acetylsalicylic acid, treatment advice has been updated in line with diclofenac, based on acetylsalicylic acid’s structural similarity to diclofenac and its metabolism to diclofenac. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib.

Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.

NSAIDs and gastro-intestinal events
All NSAIDs are associated with serious gastro-intestinal toxicity; the risk is higher in the elderly. Evidence on the relative safety of non-selective NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam, ketoprofen, and ketorolac trometamol are associated with the highest risk; indometacin p. 1143, diclofenac, and naproxen p. 1148 are associated with intermediate risk, and ibuprofen p. 1141 with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk). Selective inhibitors of cyclo-oxygenase-2 are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Recommendations are that NSAIDs associated with a low risk (e.g. ibuprofen are generally preferred, to start at the lowest recommended dose) and not to use more than one oral NSAID at a time.

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.

While it is preferable to avoid NSAIDs in patients with active or previous gastro-intestinal ulceration or bleeding, and to withdraw them if gastro-intestinal lesions develop, nevertheless patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness.

Patients at risk of gastro-intestinal ulceration (including the elderly), who need NSAID treatment should receive gastroprotective treatment.

Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia.

NSAIDs and alcohol
Alcohol increases the risk of gastro-intestinal side-effects; this risk is higher in the elderly. Specialist sources recommend that concurrent use need not be avoided with moderate alcohol intake, but greater caution is warranted in those who drink more than the recommended daily limits.

Some cases of acute kidney injury have been attributed to use of NSAIDs and acute excessive alcohol consumption.

Advanced Pharmacy Services
Patients taking NSAIDs may be eligible for the Medicines Use Review service provided by a community pharmacist. For further information, see Advanced Pharmacy Services in Guidance on prescribing p. 1.

Other drugs used for Pain and inflammation in musculoskeletal disorders
Tramadol with dexketoprofen, p. 474
1332 Pain and inflammation in musculoskeletal disorders

ANALGESICS ▶ NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Aceclofenac

- INDICATIONS AND DOSE
  Pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
  ▶ BY MOUTH
  Adult: 100 mg twice daily

- CONTRA-INDICATIONS
  Active gastro-intestinal bleeding - active gastro-intestinal ulceration - cerebrovascular disease - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - ischaemic heart disease - mild heart failure - peripheral arterial disease - severe heart failure

- CAUTIONS
  Allergic disorders - avoid in Acute porphyrias p. 1058 - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - history of cardiac failure - hypertension - left ventricular dysfunction - oedema - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)

- INTERACTIONS ▶ Appendix 1: NSAIDs

- SIDE-EFFECTS
  ▶ Common or very common
  Diarrhoea - dizziness - gastrointestinal discomfort - nausea
  ▶ Uncommon
  Constipation - gastrointestinal disorders - oral disorders - skin reactions - vomiting
  ▶ Rare or very rare
  ▶ Frequency not known
  Acute coronary syndrome - agranulocytosis - asthma - confusion - hallucination - increased risk of arterial thromboembolism - increased risk of ischaemic stroke - malaise - meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - nephritis - tuberculosis - optic neuritis - photochromic reaction - platelet aggregation inhibition - respiratory tract reaction

SIDE-EFFECTS, FURTHER INFORMATION
For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- ALLERGY AND CROSS-SENSITIVITY
  Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION
  Caution — long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY
  Most manufacturers advise avoiding the use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased.

- BREAST FEEDING
  Use with caution during breast-feeding. Manufacturer advises avoid.

- HEPATIC IMPAIRMENT
  Manufacturer advises caution in mild to moderate impairment; avoid in hepatic failure.

- Dose adjustments
  Manufacturer advises consider initial dose reduction to 100 mg daily in mild to moderate impairment.

- RENAL IMPAIRMENT
  Avoid if possible or use with caution; avoid in moderate to severe impairment.

- DOSE ADJUSTMENTS DUE TO INTERACTIONS
  Manufacturer advises reduce dose by half with concurrent use of fluconazole.

Celecoxib

- INDICATIONS AND DOSE
  Pain and inflammation in osteoarthritis
  ▶ BY MOUTH
  Adult: 200 mg daily in 1–2 divided doses, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose
  Pain and inflammation in rheumatoid arthritis
  ▶ BY MOUTH
  Adult: 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose
  Ankylosing spondylitis
  ▶ BY MOUTH
  Adult: 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

DOSE ADJUSTMENTS DUE TO INTERACTIONS
Manufacturer advises reduce dose by half with concurrent use of fluconazole.

- CONTRA-INDICATIONS
  Active gastro-intestinal bleeding - active gastro-intestinal ulceration - cerebrovascular disease - inflammatory bowel disease - ischaemic heart disease - mild to severe heart failure - peripheral arterial disease

- CAUTIONS
  Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - history of cardiac failure - hypertension - left ventricular dysfunction - oedema - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)

- INTERACTIONS ▶ Appendix 1: NSAIDs
Pregnancy

Conception and Contraception

Frequency not known

Side-effects, Further Information

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

Allergy and Cross-sensitivity

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

Contra-indicated in patients with sulfonamide sensitivity.

Conception and Contraception

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

Pregnancy

Avoid (teratogenic in animal studies).

Breast Feeding

Avoid—present in milk in animal studies.

Hepatic Impairment

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

Dose adjustments

Manufacturer advises initial dose reduction of 50% in moderate impairment.

Renal Impairment

Avoid if possible or use with caution. Avoid if eGFR less than 30 mL/minute/1.73 m².

Dose adjustments

The lowest effective dose should be used for the shortest possible duration.

Monitoring

In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

Monitoring Requirements

Monitor blood pressure before and during treatment.

Medicinal Requirements

There can be variation in the licensing of different medicines containing the same drug.

Capsule

Celecoxib (Non-proprietary)

Celecoxib 100 mg

Celecoxib 100 mg capsules | 60 capsule POM £21.55 DT = £2.72

Celecoxib 200 mg

Celecoxib 200 mg capsules | 30 capsule POM £21.55 DT = £1.01

Celebrex (Pfizer Ltd)

Celecoxib 100 mg

Celebrex 100mg capsules | 60 capsule POM £21.55 DT = £2.72

Celecoxib 200 mg

Celebrex 200mg capsules | 30 capsule POM £21.55 DT = £1.01

Dexibuprofen

21-May-2018

indications and dose

Osteoarthritis

By Mouth

Adult: 600–900 mg daily in up to 3 divided doses; increased if necessary up to 1200 mg daily (max. per dose 400 mg)

Dysmenorrhoea

By Mouth

Adult: 600–900 mg daily in up to 3 divided doses (max. per dose 400 mg)

Mild-to-moderate pain

By Mouth

Adult: 600 mg daily in up to 3 divided doses; increased if necessary up to 1200 mg daily (max. per dose 400 mg), higher dose for short-term use for acute pain

Contra-indications

Active gastro-intestinal bleeding—active gastro-intestinal ulceration—history of gastro-intestinal bleeding related to previous NSAID therapy—history of gastro-intestinal perforation related to previous NSAID therapy—history of recurrent gastro-intestinal ulceration (two or more distinct episodes) or history of recurrent gastro-intestinal ulceration (two or more distinct episodes)—severe heart failure

Caution

Allergic disorders—cardiac impairment (NSAIDs may impair renal function)–cerebrovascular disease–coagulation defects–congestive heart failure–connective-tissue disorders–Crohn’s disease (may be exacerbated)–elderly (risk of serious side-effects and fatalities)–ischaemic heart disease–malignant tumours–renal disease–risk factors for cardiovascular events—ulcerative colitis (may be exacerbated)—uncontrolled hypertension

Caution, Further Information

High-dose dexibuprofen–A small increase in cardiovascular risk, similar to the risk associated with cyclo-oxygenase-2 inhibitors and diclofenac, has been reported with high-dose dexibuprofen (≥ 1.2 g daily); use should be avoided in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, congestive heart failure (New York Heart Association classification II–III), and uncontrolled hypertension

Interactions

→ Appendix 1: NSAIDs

Side-effects

Common or very common

Diarrhoea—dizziness—drowsiness—fatigue—gastrointestinal discomfort—headache—nausea—skin reactions—vertigo—vomiting

Uncommon

Angioedema—anxiety—gastrointestinal disorders—haemorrhage—increased risk of infection—insomnia—oral disorders—respiratory disorders—tinnitus—vision blurred—vitreous floaters

Rare or very rare

Agranulocytosis—alopecia—anaemia—asthma—blood disorder—bone marrow disorders—confusion—constipation—depression—fever—granulocytopenia—haemolytic anaemia—hearing impairment—hepatic disorders—hypersensitivity—hypotension—inflammatory bowel disease—irritability—leucopenia—malignant tumours—meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)—nephritis tubulointerstitial—nephrotic syndrome—photosensitivity reaction—psychotic disorder—renal failure (more common in patients with pre-existing renal impairment)—severe cutaneous adverse reactions (SCARs)—shock—tachycardia—thrombocytopenia

Frequency not known

Fluid retention—generalised oedema—glomerulonephritis—increased risk of arterial
Pain and inflammation in musculoskeletal disorders

INDICATIONS AND DOSE

Short-term treatment of mild to moderate pain including dysmenorrhoea

BY MOUTH

Adult: 12.5 mg every 4–6 hours, alternatively 25 mg every 8 hours; maximum 75 mg per day

Elderly: 12.5 mg every 4–6 hours, alternatively 25 mg every 8 hours, initial max. 50 mg; maximum 75 mg daily

CONTRA-INDICATIONS

Active bleeding or bleeding disorders – active or recurrent gastro-intestinal haemorrhage – active or recurrent gastro-intestinal ulcer – chronic dyspepsia – Crohn’s disease – history of NSAID-associated gastro-intestinal bleeding or perforation – known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates – severe dehydration – severe heart failure – ulcerative colitis – varicella infection

CAUTIONS


INTERACTIONS

Appendix 1: NSAIDs

SIDE-EFFECTS

Common or very common Diarrhoea – gastrointestinal discomfort – nausea – vomiting


SIDE-EFFECTS, FURTHER INFORMATION

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID – which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

Caution — long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

BREAST FEEDING

Use with caution during breast-feeding. Present in milk – but risk to infant minimal.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

Dose adjustments

Manufacturer advises initial dose reduction in mild to moderate impairment.

RENAL IMPAIRMENT

Avoid if possible or use with caution. Avoid if eGFR less than 30 mL/minute/1.73 m².

Monitoring

Monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

Dose adjustments

Reduce initial dose.

The lowest effective dose should be used for the shortest possible duration.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

Seractil (Gebro Pharma GmbH)

Dexibuprofen 300 mg Seractil 300mg tablets | 60 tablet [PMS]
£2.47 DT + £5.47

Dexibuprofen (as Dexibuprofen trometamol) 25 mg Keral 25mg tablets | 20 tablet [PMS]
£3.67 | 50 tablet [PMS] £9.18 DT + £9.18

Combinations available: Tramadol with dexketoprofen, p. 474
Pain and inflammation in musculoskeletal disorders

**Diclofenac potassium**

*INDICATIONS AND DOSE*

**Pain and inflammation in rheumatic disease and other musculoskeletal disorders**

- **BY MOUTH**
  - Child 14-17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Acute gout**

- **BY MOUTH**
  - Adult: 75–150 mg daily in 2–3 divided doses

**Postoperative pain**

- **BY MOUTH**
  - Child 9–13 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day
  - Child 14-17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Migraine**

- **BY MOUTH**
  - Adult: 50 mg, to be given at onset of migraine, then 50 mg after 4–6 hours; maximum 200 mg per day

**Fever in ear, nose, or throat infection**

- **BY MOUTH**
  - Child 9–17 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day

**SIDE-EFFECTS**

- **Frequency not known** Hallucination - malaise - optic neuritis

**SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING** Use with caution during breast-feeding. Amount in milk too small to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in severe impairment.

**Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

**Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**PATIENT AND CARER ADVICE**


**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 21
  - **Diclofenac potassium (Non-proprietary)**
    - Diclofenac potassium 25 mg: Diclofenac potassium 25 mg tablets | 28 tablet (PsB) £3.87 DT + £3.87
    - Diclofenac potassium 50 mg: Diclofenac potassium 50 mg tablets | 28 tablet (PsB) £7.41 DT + £7.41
  - **Voltarol Rapid** (Novartis Pharmaceuticals UK Ltd)
    - Diclofenac potassium 50 mg: Voltarol Rapid 50 mg tablets | 30 tablet (PsB) £7.94

**Diclofenac sodium**

*INDICATIONS AND DOSE*

**Pain and inflammation in musculoskeletal disorders**

- **Acute gout**
  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Adult: 75–150 mg daily in 2–3 divided doses
  - **BY RECTUM**
    - Adult: 75–150 mg daily in divided doses

**Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis**

- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 75–150 mg daily in 2–3 divided doses
  - **BY RECTUM**
  - Adult: 75–150 mg daily in divided doses

continued →
Postoperative pain
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 75–150 mg daily in 2–3 divided doses
- **BY RECTUM**
  - Adult: 75–150 mg daily in divided doses

**DILOMAX RETARD®**

**Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
- Adult: **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 capsule once daily

**VOLTAROL®**

**Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
- Adult: **BY MOUTH**
  - Adult: 1 capsule 1–2 times a day

**DILOMAX SR®**

**Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
- Adult: **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 capsule 1–2 times a day

**VOLTAROL® 75MG SR TABLETS**

**Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
- Adult: **BY MOUTH**
  - Adult: 1 tablet 1–2 times a day

**VOLTAROL® EMULGEL**

**Relief of pain in musculoskeletal conditions | Adjunctive treatment in knee or hand osteoarthritis**
- **TO THE SKIN**
  - Adult: Apply 3–4 times a day, therapy should be reviewed after 14 days (or after 28 days for osteoarthritis)

**VOLTAROL® RETARD**

**Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders**
- Adult: **BY MOUTH**
  - Adult: 1 tablet once daily

**VOLTAROL® SOLUTION FOR INJECTION**

**Postoperative pain**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg 1–2 days a time for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

**Acute exacerbations of pain**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg 1–2 times a day for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

**Urinary colic**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 75 mg, then 75 mg after 30 minutes if required

**Acute postoperative pain (in hospital setting)**
- **BY INTRAVENOUS INFUSION**
  - Adult: 75 mg, then 75 mg after 4–6 hours if required for maximum 2 days; maximum 150 mg per day

**Prevention of postoperative pain (in hospital setting)**
- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 25–50 mg, to be given after surgery over 15–60 minutes, then 5 mg/hour for maximum 2 days; maximum 150 mg per day

**CONTRA-INDICATIONS**
- With intravenous use
  - Dehydration
  - History of asthma
  - History of confirmed or suspected cerebrovascular bleeding
  - History of haemorrhagic diathesis
  - Hypoovolaemia
  - Operations with high risk of haemorrhage
- With systemic use
  - Active gastro-intestinal bleeding
  - Active gastro-intestinal ulceration
  - Avoid suppositories in proctitis
  - Cerebrovascular disease
  - History of gastro-intestinal bleeding related to previous NSAID therapy
  - History of gastro-intestinal perforation related to previous NSAID therapy
  - History of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
  - History of recurrent gastro-intestinal ulceration (two or more distinct episodes)
  - Ischaemic heart disease
  - Mild to severe heart failure
  - Peripheral arterial disease

**CAUTIONS**
- With systemic use
  - Allergic disorders
  - Cardiac impairment (NSAIDs may impair renal function)
  - Coagulation defects
  - Connective-tissue disorders
  - Croup’s disease (may be exacerbated)
  - Elderly (risk of serious side-effects and fatalities)
  - History of cardiac failure
  - Hypertension
  - Left ventricular dysfunction
  - Oedema
  - Risk factors for cardiovascular events
  - Ulcerative colitis (may be exacerbated)
- With topical use
  - Avoid contact with eyes
  - Avoid contact with inflamed or broken skin
  - Avoid contact with mucous membranes
  - Not for use with occlusive dressings
  - Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

**INTERACTIONS**
- Appendix 1: NSAIDs

**SIDE-EFFECTS**
- Common or very common
  - With systemic use
    - Appetite decreased
    - Diarrhoea
    - Dizziness
    - Gastrointestinal discomfort
    - Headache
    - Nausea
    - Oedema
    - Rash (discontinue)
    - Skin reactions
    - Vertigo
    - Vomiting
  - With topical use
    - Conjunctivitis
    - Muscle tone increased
    - Oedema
    - Rash (discontinue)
    - Sensation abnormal
    - Skin reactions
    - Skin ulcer

- Uncommon
  - With systemic use
    - Chest pain
    - Heart failure
    - Myocardial infarction
    - Palpitations
  - With topical use
    - Abdominal pain
    - Alopecia
    - Diarrhoea
    - Eye pain
    - Haemorrhage
    - Lacrimation disorder
    - Nausea
    - Seborrhoea

- Rare or very rare
  - With rectal use
    - Ulcerative colitis
    - Aggravated
  - With systemic use
    - Acute kidney injury
    - Agranulocytosis
    - Alopecia
    - Anaemia
    - Angioedema
    - Anxiety
    - Aplastic anaemia
    - Asthma
    - Chest pain
    - Confusion
    - Constipation
    - Depression
    - Drowsiness
    - Dysphoria
    - Erectile dysfunction
    - Fatigue
    - Haemolytic anaemia
    - Haemorrhage
    - Hearing impairment
    - Heart failure
    - Hepatic disorders
    - Hypersensitivity
    - Hypertension
    - Hypotension
    - Irritability
    - Leucopenia
    - Memory loss
    - Meningitis aseptic
    - Patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible
    - Myocardial infarction
    - Nephritis
    - Tubulointerstitial
    - Nephrotic syndrome
    - Oesophageal disorder
    - Oral disorders
    - Palpitations
    - Pancreatitis
    - Photosensitivity reaction
    - Pneumonitis
    - Proteinuria
    - Psychotic disorder
    - Renal papillary necrosis
    - Seizure
    - Sensation abnormal
    - Severe cutaneous adverse reactions (SCARs)
    - Shock
    - Sleep disorders
    - Stroke
    - Taste altered
    - Thrombocytopenia
    - Tinnitus
    - Tremor
    - Vasculitis
    - Vision disorders
- With topical use
  - Acute kidney injury
  - Asthma
  - Hypersensitivity
  - Photosensitivity reaction
  - Rash pustular
- Frequency not known
  - With parenteral use
    - Injection site necrosis

www.getintopharma.com
Pain and inflammation in musculoskeletal disorders

- **PROFESSION SPECIFIC INFORMATION**
  - **Dental practitioners’ formulation**
    - Diclofenac Sodium Tablets may be prescribed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: dispersible tablet, oral suspension, oral solution

- **Modified-release tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 21, 25
    - **Diclofenac 75mg SR** (Dexcel-Pharma Ltd)
    - Diclofenac sodium 75 mg Diclofenac sodium 25 mg gastro-resistant tablets | 28 tablet (POM) £3.56 DT + £8.06
    - Diclofenac sodium 50 mg Diclofenac sodium 50mg gastro-resistant tablets | 28 tablet (POM) £4.97 DT + £1.89 | 84 tablet (POM) £2.48-£15.00
    - Diclofenac sodium 25 mg Diclofenac sodium 25mg gastro-resistant tablets | 28 tablet (POM) £1.77 | 84 tablet (POM) £1.50–£26.97
    - Diclofenac sodium 50 mg Diclofenac sodium 50mg gastro-resistant tablets | 28 tablet (POM) £4.42 | 84 tablet (POM) £8.05
    - Fenactol (Discovery Pharmaceuticals)
      - Diclofenac sodium 50 mg Fenactol 50mg gastro-resistant tablets | 100 tablet (POM) £3.70

- **Suppository**
  - Econac (Advanz Pharma)
    - Diclofenac sodium 100 mg Econac 100mg suppositories | 16 suppository (POM) £3.04 DT + £3.64
    - Voltarol (Novartis Pharmaceuticals UK Ltd)
      - Diclofenac sodium 12.5 mg Voltarol 12.5mg suppositories | 10 suppository (POM) £0.70 DT + £0.70
      - Diclofenac sodium 25 mg Voltarol 25mg suppositories | 10 suppository (POM) £1.24 DT + £1.24
      - Diclofenac sodium 50 mg Voltarol 50mg suppositories | 10 suppository (POM) £2.04 DT + £2.04
    - Diclofenac sodium 100 mg Voltarol 100mg suppositories | 10 suppository (POM) £3.64 DT + £3.64

- **Solution for injection**
  - **EXCIPIENTS:** May contain Benzyl alcohol, propylene glycol
    - Voltarol (Novartis Pharmaceuticals UK Ltd)
      - Diclofenac sodium 25 mg per 1 ml Voltarol 75mg/3ml solution for injection ampoules | 10 ampoule (POM) £9.91 DT = £9.91

- **Modified-release capsule**
  - **CAUTIONARY AND ADVISORY LABELS** 21 (does not apply to Motifene 75 mg), 25
    - EXCIPIENTS: May contain Propylene glycol
      - Diclomax Retard (Galen Ltd)
        - Diclofenac sodium 100 mg Diclomax Retard 100mg capsules | 28 capsule (POM) £8.20 DT + £8.20
      - Diclofenac sodium 75 mg Diclofenac SR 75mg capsules | 56 capsule (POM) £11.40 DT = £11.40
    - Motifene (Daichi Sankyo UK Ltd)
      - Diclofenac sodium 75 mg Motifene 75mg modified-release capsules | 56 capsule (POM) £8.00 DT = £8.00

- With systemic use  Fertility decreased female  • fluid retention  • hallucination  • malaise  • optic neuritis  • platelet aggregation inhibition
- With topical use  Hair colour changes

**SIDE-EFFECTS, FURTHER INFORMATION**
- Topical application of large amounts of diclofenac can result in systemic effects.
- For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 1130

**ALLERGY AND CROSS-SENSITIVITY**
- Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**
- With systemic use  Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**
- With systemic use  Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**
- With systemic use  Use with caution during breast-feeding. Amount in milk too small to be harmful.
- With topical use  Patient packs for topical preparations carry a warning to avoid during breast-feeding.

**HEPATIC IMPAIRMENT**
- With systemic use  Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT**
- With systemic use  Avoid if possible or use with caution. Avoid in severe impairment.
- With intravenous use  Avoid intravenous use if serum creatinine greater than 160 micromol/litre. Contra-indicated in moderate or severe renal impairment.

**Dose adjustments**  • With systemic use  The lowest effective dose should be used for the shortest possible duration.

**Monitoring**  • With systemic use  In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use  For *intravenous infusion* (Voltarol®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute 75 mg with 100–500 mL infusion fluid (previously buffered with 0.5 mL sodium bicarbonate 8.4% solution or with 1 mL sodium bicarbonate 4.2% solution). For intermittent infusion give 25–50 mg over 15–60 minutes or 75 mg over 30–120 minutes. For continuous infusion give at a rate of 5 mg/hour.
  - With topical use  For topical preparations, apply with gentle massage only.

**PRESCRIBING AND DISPENSING INFORMATION**
- With oral use  Voltarol® dispersible tablets are more suitable for short-term use in acute conditions for which treatment required for no more than 3 months (no information on use beyond 3 months).

**PATIENT AND CARER ADVICE**
- For topical preparations, patients and their carers should be advised to wash hands immediately after use.
  - Photosensitivity  Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

www.getintopharma.com
Diclofenac sodium with misoprostol

22-Sep-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, diclofenac sodium p. 1135, misoprostol p. 77.

- **INDICATIONS AND DOSE**

  **ARTHROTEC® 50/200**

  Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis

  - **BY MOUTH**
    - Adult: 1 tablet 2–3 times a day, take with food

  **MISOFEN® 50/200**

  Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis

  - **BY MOUTH**
    - Adult: 1 tablet 2–3 times a day, take with food

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Gastro-resitant tablet**

  **CAUTIONARY AND ADVISORY LABELS** 21, 25

  - **Arthrotec®** (Pfizer Ltd)
    - Misoprostol 200 microgram, Diclofenac sodium 50 mg **Arthrotec 50 gastro-resistant tablets** | 60 tablet [BM] £11.98 DT = £11.98
    - Misoprostol 200 microgram, Diclofenac sodium 75 mg **Arthrotec 75 gastro-resistant tablets** | 60 tablet [BM] £15.83 DT = £15.83
  - **Misofen®** (Morningside Healthcare Ltd)
    - Misoprostol 200 microgram, Diclofenac sodium 50 mg **Misofen 50mg/200microgram gastro-resistant tablets** | 60 tablet [BM] £11.98 DT = £11.98
    - Misoprostol 200 microgram, Diclofenac sodium 75 mg **Misofen 75mg/200microgram gastro-resistant tablets** | 60 tablet [BM] £15.83 DT = £15.83

- **INTERACTIONS** → Appendix 1: NSAIDs


  SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- **ALLERGY AND CROSS-SENSITIVITY** Contra–indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in severe impairment.

  **Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

  **Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Modified-release tablet**

  **CAUTIONARY AND ADVISORY LABELS** 25

  - **Etodolac® (Non-proprietary)**
    - **Etodolac 600 mg** Etodolac 600mg modified-release tablets | 30 tablet [BM] £11.40 DT = £15.50

Etodolac

29-Jun-2016

- **INDICATIONS AND DOSE**

  **Pain and inflammation in rheumatoid arthritis and osteoarthritis**

  - **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
    - Adult: 300–600 mg daily in 1–2 divided doses
  - **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
    - Adult: 600 mg daily

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

  **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

  **INTERACTIONS** → Appendix 1: NSAIDs
**Etoricoxib** 23-Nov-2016

### INDICATIONS AND DOSE

**Pain and inflammation in osteoarthritis**
- **BY MOUTH**
  - Child 16-17 years: 30 mg once daily, increased if necessary to 60 mg once daily
  - Adult: 30 mg once daily, increased if necessary to 60 mg once daily

**Pain and inflammation in rheumatoid arthritis**
- **BY MOUTH**
  - Child 16-17 years: 60 mg once daily, increased if necessary to 90 mg once daily
  - Adult: 60 mg once daily, increased if necessary to 90 mg once daily

**Acute gout**
- **BY MOUTH**
  - Child 16-17 years: 120 mg once daily for maximum 8 days
  - Adult: 120 mg once daily for maximum 8 days

### CONTRA-INDICATIONS
Active gastro-intestinal bleeding - active gastro-intestinal ulceration - cerebrovascular disease - inflammatory bowel disease - ischaemic heart disease - mild to severe heart failure - peripheral arterial disease - uncontrolled hypertension (persistently above 140/90 mmHg)

### CAUTIONS
Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn's disease (may be exacerbated) - dehydration - elderly (risk of serious side-effects and fatalities) - history of cardiac failure - hypertension - left ventricular dysfunction - oedema - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)

### INTERACTIONS
Appendix 1: NSAIDs

### SIDE-EFFECTS
**Common or very common** Arrhythmias - asthenia - bronchospasm - constipation - diarrhea - dizziness - fluid retention - gastrointestinal discomfort - gastrointestinal disorders - headache - hypertension - increased risk of infection - influenza like illness - nausea - oedema - oral ulceration - palpitations - skin reactions - vomiting


**Rare or very rare** Angioedema - confusion - hepatic disorders - muscle complaints - severe cutaneous adverse reactions (SCARs) - shock

### FREQUENCY NOT KNOWN
Nephritis tubulointerstitial - nephropathy

**SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**Pregnancy** Manufacturer advises avoid (teratogenic in animal studies). Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**Breast feeding** Use with caution during breast-feeding. Manufacturer advises avoid—present in milk in animal studies.

**Hepatic impairment** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

**Dose adjustments** Manufacturer advises max. 60 mg once daily in mild impairment; max. 30 mg once daily in moderate impairment.

**Renal impairment** Avoid if possible or use with caution.
  - In adults Avoid if eGFR less than 30 mL/minute/1.73 m².
  - In children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

**Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

**Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**Monitoring requirements** Monitor blood pressure before treatment, 2 weeks after initiation and periodically during treatment.

**Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

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www.getintopharma.com
Felbinac

**DRUG ACTION** Felbinac is an active metabolite of the NSAID fenbufen.

**INDICATIONS AND DOSE** Relief of pain in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

- TO THE SKIN
  - Adult: Apply 2–4 times a day, therapy should be reviewed after 14 days; maximum 25 g per day

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal haemorrhage (two or more distinct episodes) - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

**CAUTIONS** Allergic disorders - avoid contact with eyes - avoid contact with inflamed or broken skin - avoid contact with mucous membranes - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - not for use with occlusive dressings - peripheral arterial disease - risk factors for cardiovascular events - topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported) - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

**INTERACTIONS** → Appendix 1: NSAIDs

**SIDE-EFFECTS** Bronchospasm - gastrointestinal disorder - hypersensitivity - paraesthesia - photosensitivity reaction - skin reactions

**SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 1130.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY** Patient packs for topical preparations carry a warning to avoid during pregnancy.

**BREAST FEEDING** Patient packs for topical preparations carry a warning to avoid during breast-feeding.

**RENAL IMPAIRMENT** Avoid if possible or use with caution. Deterioration in renal function has also been reported after topical use.

**Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

**Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**DIRECTIONS FOR ADMINISTRATION** For topical preparations, apply with gentle massage only.

**PRESCRIBING AND DISPENSING INFORMATION** Caution—topical preparations not generally suitable for children.

**PATIENT AND CARER ADVICE** For topical preparations patients and carers should be advised to wash hands immediately after use.

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Flurbiprofen

**INDICATIONS AND DOSE** Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Migraine | Postoperative analgesia | Mild to moderate pain

- BY MOUTH
  - Child 12-17 years: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions
  - Adult: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions

**Dysmenorrhoea**

- BY MOUTH
  - Child 12-17 years: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day
  - Adult: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

**CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

**INTERACTIONS** → Appendix 1: NSAIDs

**SIDE-EFFECTS** Agranulocytosis - angioedema - aplastic anaemia - asthma - bronchospasm - confusion - constipation - Crohn’s disease - depression - diarrhoea - dizziness - drowsiness - dyspnoea - fatigue - fertility decreased female - gastrointestinal discomfort - gastrointestinal disorders - haemolytic anaemia - haemorrhage - hallucination - headache - heart failure - hepatic disorders - hypersensitivity - hypertension - malaise - meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - nausea - nephritis - tuberculosis - nephropathy - neutropenia - oedema - optic neuritis - oral ulceration - pancreatitis - paraesthesia - photosensitivity reaction - platelet aggregation inhibition - renal failure (more common in patients with pre-existing renal impairment) - respiratory tract reaction - severe cutaneous adverse reactions (SCARs) - skin reactions -

Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

**MEDITINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Gel**
  - Traxam (Advanz Pharma)
    - Felbinac 30 mg per 1 gram Traxam 3% gel | 100 gram POM £8.03 DT = £8.03
  - Foam
    - Traxam (Advanz Pharma)
      - Felbinac 31.7 mg per 1 gram Traxam 3.17% foam | 100 gram POM £8.41 DT = £8.41

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![Image of a page from a book](image-url)
stroke • thrombocytopenia • tinnitus • vertigo • visual impairment • vomiting

SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130.

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment.

Dose adjustments The lowest effective dose should be used for the shortest possible duration.

Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

Flurbiprofen (Non-proprietary)

Flurbiprofen 50 mg Flurbiprofen 100 mg

| Tablet | 100 tablet | POM | £21.30–£35.17 DT | £39.57

| Tablet | 100mg tablets | POM | £38.10–£77.21 DT | £70.78

Ibuprofen

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Mild to moderate pain including dysmenorrhoea | Postoperative analgesia | Migraine | Dental pain

Adult: Initially 300–400 mg 3–4 times a day; increased if necessary up to 600 mg 4 times a day; maintenance 200–400 mg 3 times a day, may be adequate

Increase if necessary to 2.4 g daily in divided doses, dose to be increased only in severe cases

Mild to moderate pain | Pain and inflammation of soft-tissue injuries | Pyrexia with discomfort

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 3–5 years: 50 mg 3 times a day; maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day

Child 6–11 months: 50 mg 3–4 times a day; maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day

Child 1–3 years: 100 mg 3 times a day; maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day

Child 4–6 years: 150 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day

Child 7–9 years: 200 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day; maximum 2.4 g per day

Child 10–11 years: 300 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day; maximum 2.4 g per day

Child 12–17 years: Initially 300–400 mg 3–4 times a day; increased if necessary up to 600 mg 4 times a day; maintenance 200–400 mg 3 times a day, may be adequate

Pain and inflammation

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 12–17 years: 1.6 g once daily, dose preferably taken in the early morning, increased to 2.4 g daily in 2 divided doses, to be increased only in severe cases

Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 3 months–17 years: 30–40 mg/kg daily in 3–4 divided doses; maximum 2.4 g per day

Pain and inflammation in systemic juvenile idiopathic arthritis

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 3 months–17 years: Up to 60 mg/kg daily in 4–6 divided doses; maximum 2.4 g per day

Post-immunisation pyrexia in infants (on doctor’s advice only)

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Child 2–3 months: 50 mg for 1 dose, followed by 50 mg after 6 hours if required

Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

TO THE SKIN

Adult: Apply up to 3 times a day, ibuprofen gel 5% gel to be administered

FENBID FORTE

Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

TO THE SKIN

Adult: Apply up to 4 times a day, therapy should be reviewed after 14 days

IBUGEL FORTE

Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

TO THE SKIN

Adult: Apply up to 3 times a day

UNLICENSED USE

With oral use in children Not licensed for use in children under 3 months or body-weight under 5 kg. Maximum dose for systemic juvenile idiopathic arthritis is unlicensed.

CONTRA-INDICATIONS

With systemic use Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure • varicella infection

CAUTIONS

With systemic use Allergic disorders (in adults) • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • heart
failure · ischaemic heart disease · peripheral arterial disease · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated) · uncontrolled hypertension

With topical use Avoid contact with eyes · avoid contact with inflamed or broken skin · avoid contact with mucous membranes · not for use with occlusive dressings · topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

CAUTIONS, FURTHER INFORMATION

High-dose ibuprofen A small increase in cardiovascular risk, similar to the risk associated with cyclo-oxygenase-2 inhibitors and diclofenac, has been reported with high-dose ibuprofen (> 2.4 g daily); use should be avoided in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, congestive heart failure (New York Heart Association classification II–III), and uncontrolled hypertension.

INTERACTIONS ▶ Appendix 1: NSAIDs

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Uncommon Gastrointestinal discomfort · hypersensitivity · rash (discontinue) · skin reactions

Rare or very rare Angioedema · dyspnoea

Frequency not known Asthma

SPECIFIC SIDE-EFFECTS

Uncommon

With oral use Headache · nausea

Rare or very rare

With oral use Acute kidney injury · agranulocytosis · anaemia · constipation · diarrhoea · gastrointestinal disorders · haemorrhage · leucopenia · liver disorder · meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · oedema · oral ulceration · paronychia · oral papillary necrosis · severe cutaneous adverse reactions (SCARs) · shock · thrombocytopenia · vomiting

Frequency not known

With oral use Crohn’s disease · fertility decreased female · fluid retention · heart failure · hypertension · increased risk of arterial thrombembolism · renal failure (more common in patients with pre-existing renal impairment) · respiratory disorders · respiratory tract reaction

With topical use Bronchospasm · renal impairment · toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-stereoid anti-inflammatory drugs. p. 1130

With topical use Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

Overdose Overdose with ibuprofen may cause nausea, vomiting, epigastric pain, and tinnitus, but more serious toxicity is very uncommon. Charcoal, activated followed by symptomatic measures are indicated if more than 100 mg/kg has been ingested within the preceding hour.

For details on the management of poisoning, see Emergency treatment of poisoning p. 1359.

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

With systemic use in adults Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

BREAST FEEDING

With oral use Use with caution during breast-feeding. Amount too small to be harmful but some manufacturers advise avoid.

With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

HEPATIC IMPAIRMENT

With oral use Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

RENAL IMPAIRMENT

With oral use Avoid if possible or use with caution. Avoid in severe impairment.

With topical use Deterioration in renal function has also been reported after topical use.

Dose adjustments ▶ With oral use The lowest effective dose should be used for the shortest possible duration.

Monitoring ▶ With systemic use In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

DIRECTIONS FOR ADMINISTRATION

With topical use For topical preparations, apply with gentle massage only.

PRESCRIBING AND DISPENSING INFORMATION

With oral use Flavours of syrup may include orange.

PATIENT AND CARER ADVICE

With topical use For topical preparations, patients and their carers should be advised to wash hands immediately after use.

Photosensitivity

With topical use For topical preparations, patients or their carers should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.


PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary

▶ With oral use Ibuprofen Oral Suspension Sugar-free may be prescribed. Ibuprofen Tablets may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY

With topical use Small pack sizes of gel preparations may be available on sale to the public.

With oral use Oral preparations can be sold to the public in certain circumstances.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Effervescent granules

CAUTIONARY AND ADVISORY LABELS 13, 21

ELECTROLYTES: May contain Sodium

Brufen (Mylan)

Ibuprofen 600 mg Brufen 600mg effervescent granules sachets ▶ 20 sachet £6.80 DT + £6.80

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25, 27

Brufen Retard (Mylan)

Ibuprofen 800 mg Brufen Retard 800mg tablets | 56 tablet £10.74 DT + £10.74
<table>
<thead>
<tr>
<th>Tablet CAUTIONARY AND ADVISORY LABELS 21</th>
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<tbody>
<tr>
<td>▶ Ibuprofen (Non-proprietary)</td>
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<tr>
<td>Ibuprofen 200 mg</td>
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<tr>
<td>Ibuprofen 200 mg caplets</td>
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<td>Ibuprofen 400 mg</td>
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<td>Ibuprofen 600 mg tablets coated</td>
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<td>▶ Brufen (Mylan)</td>
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<td>Ibuprofen 400 mg</td>
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<td>▶ Feminax Express (Bayer Plc)</td>
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<tr>
<td>Ibuprofen (as ibuprofen lysine) 200 mg</td>
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<td>▶ Nurofen (Reckitt Benckiser Healthcare (UK) Ltd)</td>
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<td>Ibuprofen 200 mg</td>
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<td>▶ Nurofen Express (Reckitt Benckiser Healthcare (UK) Ltd)</td>
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<tr>
<td>Ibuprofen (as ibuprofen sodium dihydrate) 200 mg</td>
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<tr>
<td>Nurofen Express 256mg caplets</td>
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<tr>
<td>▶ Nurofen Joint &amp; Back Pain Relief (Reckitt Benckiser Healthcare (UK) Ltd)</td>
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<tr>
<td>Ibuprofen (as ibuprofen sodium dihydrate) 200 mg</td>
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<tr>
<td>Nurofen Joint &amp; Back Pain Relief 256mg tablets</td>
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<tr>
<td>Ibuprofen (as ibuprofen sodium dihydrate) 400 mg</td>
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<tr>
<td>▶ Nurofen Migraine Pain (Reckitt Benckiser Healthcare (UK) Ltd)</td>
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<tr>
<td>Ibuprofen (as ibuprofen lysine) 200 mg</td>
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</tbody>
</table>

**Oral suspension** CAUTIONARY AND ADVISORY LABELS 21

| ▶ Ibuprofen (Non-proprietary) |
| Ibuprofen 20 mg per 1 ml | Ibuprofen 100mg/5ml oral suspension sugar free sugar-free | 500 ml (P) £7.15 |
| Ibuprofen 40 mg per 1 ml | Ibuprofen Twelve Plus Pain Relief 200mg/5ml oral suspension sugar-free | 100 ml (P) £4.20 |
| Ibuprofen Seven Plus Pain Relief 200mg/5ml oral suspension sugar-free | 100 ml (P) £4.20 |
| ▶ Brufen (Mylan) |
| Ibuprofen 20 mg per 1 ml | Brufen 100mg/5ml syrup | 500 ml (POD £8.88 DT = £8.88 |

**Modified-release capsule**

| ▶ Nurofen Back Pain SR (Reckitt Benckiser Healthcare (UK) Ltd) |
| Ibuprofen 300 mg | Nurofen Back Pain SR 300mg capsules | 24 capsule (P) £4.52 DP (P) £4.52 |

**Chewable capsule**

| ▶ Nurofen (Reckitt Benckiser Healthcare (UK) Ltd) |
| Ibuprofen 100 mg | Nurofen for Children 100mg chewable capsules | 12 capsule (P) £3.23 |

**Gel**

| ▶ Ibuprofen (Non-proprietary) |
| Ibuprofen 50 mg per 1 gram | Ibuprofen 5% gel | 30 gram (P) £1.13 | 50 gram (P) £1.10 DT = £1.13 | 100 gram (P) £2.26 DT = £2.26 |
| ▶ Fenbid (Advanz Pharma) |
| Ibuprofen 100 mg per 1 gram | Fenbid Forte 10% gel | 100 gram (P) £4.00 DT = £5.79 |
| ▶ Ibutrol (Dermal Laboratories Ltd) |
| Ibuprofen 50 mg per 1 gram | Ibutrol 5% gel | 100 gram (P) £4.87 DT = £2.26 |
| Ibuprofen 100 mg per 1 gram | Ibutrol Forte 10% gel | 100 gram (P) £5.79 DT = £5.79 |
| ▶ Ibutoleve (Dendlon Ltd) |
| Ibuprofen 50 mg per 1 gram | Ibutoleve 5% gel | 30 gram (P) £2.64 | 50 gram (P) £3.70 DT = £1.13 | 100 gram (P) £6.60 DT = £2.26 |

**Phorpain (Advanz Pharma)**

| Ibuprofen 50 mg per 1 gram | Phorpain 9% gel | 100 gram (P) £1.50 DT = £2.26 |

**Capsule**

| ▶ Ibuprofen (Non-proprietary) |
| Ibuprofen 200 mg | Ibuprofen 200mg capsules | 30 capsule (P) £4.53 |
| Flarin (Infrist Healthcare Ltd) |
| Ibuprofen 200 mg | Flarin 200mg capsules | 30 capsule (P) £6.22 DT = £4.53 |
| Nurofen Express (Reckitt Benckiser Healthcare (UK) Ltd) |
| Ibuprofen 200 mg | Nurofen Express 200mg liquid capsules | 30 capsule (P) £4.53 DT = £4.53 |
| Ibuprofen 400 mg | Nurofen Express 400mg liquid capsules | 10 capsule £3.68 | 20 capsule £6.14 DT = £6.14 |

**Oral dispersible tablet**

| ▶ Nurofen Meltlets (Reckitt Benckiser Healthcare (UK) Ltd) |
| Ibuprofen 200 mg | Nurofen Meltlets 200mg tablets sugar-free | 12 tablet (SS) £2.58 DT = £2.58 |

**Indometacin** (Indomethacin)

**INDICATIONS AND DOSE**

**Pain and moderate to severe inflammation in rheumatic disease and other musculoskeletal disorders**

- **By mouth using immediate-release medicines**
  - Adult: 50–200 mg daily in divided doses
- **By rectum**
  - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
- **By mouth using modified-release medicines**
  - Adult: 75 mg 1–2 times a day

**Acute gout**

- **By mouth using immediate-release medicines**
  - Adult: 150–200 mg daily in divided doses
- **By rectum**
  - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
- **By mouth using modified-release medicines**
  - Adult: 75 mg 1–2 times a day

**Dysmenorrhoea**

- **By mouth using immediate-release medicines**
  - Adult: Up to 75 mg daily
- **By rectum**
  - Adult: 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg
- **By mouth using modified-release medicines**
  - Adult: 75 mg daily

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

**CAUTIONS**

**GENERAL CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - epilepsy - heart failure - ischaemic heart disease - parkinsonism - peripheral arterial
Pain and inflammation in musculoskeletal disorders

**SIDE-EFFECTS**

### GENERAL SIDE-EFFECTS

- Agranulocytosis
- Alopecia
- Anaphylactic reaction
- Angioedema
- Anxiety
- Appetite decreased
- Arrhythmias
- Asthma
- Blood disorder
- Bone marrow disorders
- Breast abnormalities
- Chest pain
- Coma
- Confusion
- Congestive heart failure
- Constipation
- Corneal deposits
- Depression
- Diarrhoea
- Disseminated intravascular coagulation
- Dizziness
- Drowsiness
- Dysarthria
- Erythema nodosum
- Eye disorder
- Eye pain
- Fatigue
- Fluid retention
- Fluishing
- Gastrointestinal discomfort
- Gastrointestinal disorders
- Gynaecomastia
- Haemolytic anaemia
- Haemorrhage
- Hallucination
- Headache
- Hearing impairment
- Hepatic disorders
- Hyperglycaemia
- Hyperhidrosis
- Hyperkalaemia
- Hypotension
- Inflammatory bowel disease
- Insomnia
- Leucopenia
- Movement disorders
- Muscle weakness
- Nausea
- Nephritis
- Tubulointerstitial nephritis
- Syndrome
- Oedema
- Oral disorders
- Palpitations
- Pancreatitis
- Paraesthesia
- Peripheral neuropathy
- Photosensitivity reaction
- Platelet aggregation inhibition
- Psychiatric disorders
- Respiratory disorders
- Seizures
- Severe cutaneous adverse reactions (SCARs)
- Skin reactions
- Syncope
- Thrombocytopenia
- Tinnitus
- Urine abnormalities
- Vasculitis
- Vertigo
- Vision disorders
- Vomiting

### SPECIFIC SIDE-EFFECTS

- With oral use: Diarrhoea, malaise, pulmonary oedema, sigmoid lesion perforation.
- With topical use: Photosensitivity.
- With rectal use: Discomfort.
- With systemic use: Active gastro-intestinal bleeding, active gastro-intestinal ulceration, history of gastro-intestinal bleeding, history of gastro-intestinal perforation, history of gastro-intestinal ulceration, severe heart failure.

### ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

### CONCEPTION AND CONTRACEPTION

Caution—Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

### PREGNANCY

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

### BREAST FEEDING

Amount probably too small to be harmful—manufacturers advise avoid. Use with caution during breast-feeding.

### HEPATIC IMPAIRMENT

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

### RENAL IMPAIRMENT

Avoid if possible or use with caution. Avoid in severe impairment.

### Dose adjustments

The lowest effective dose should be used for the shortest possible duration.

### Monitoring

In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

### MONITORING REQUIREMENTS

During prolonged therapy ophthalmic and blood examinations particularly advisable.

### PATIENT AND CARER ADVICE

- Driving and skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving).

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

### Suppository

- Indocid (Asgen Pharma Trading Ltd)
- Indometacin 100 mg Indocid 100mg suppositories | 10 suppository (PZN) £17.61 DT = £17.61

### Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 21

- Berlind Retard (Tillomed Laboratories Ltd)
- Indometacin 75 mg Berlind 75 Retard capsules | 100 capsule (PZN) £8.65 DT = £8.65

### Capsule

CAUTIONARY AND ADVISORY LABELS 21

- Indometacin (Non-proprietary)
- Indometacin 25 mg Indometacin 25mg capsules | 28 capsule (PZN) £1.03 DT = £1.00
- Indometacin 50 mg Indometacin 50mg capsules | 28 capsule (PZN) £1.33 DT = £1.33

### Ketoprofen

15-May-2018

### INDICATIONS AND DOSE

Pain and mild inflammation in rheumatic disease and musculoskeletal conditions | Dysmenorrhoea | Acute gout

#### By mouth

- Adult: 100–200 mg once daily

### Relief of pain in rheumatic disease and musculoskeletal conditions

#### To the skin

- Adult: Apply 2–4 times a day for up to 7 days, ketoprofen 2.5% gel to be administered; maximum 15 g per day

### POWERGEL

#### Relief of pain in musculoskeletal conditions | Adjunctive treatment in knee or hand osteoarthritis

#### To the skin

- Adult: Apply 2–3 times a day for up to max. 10 days

### CONTRA-INDICATIONS

- With systemic use: Active gastro-intestinal bleeding, active gastro-intestinal ulceration, history of gastro-intestinal bleeding, history of gastro-intestinal perforation, history of gastro-intestinal ulceration, severe heart failure

### CAUTIONS

- With systemic use: Allergic disorders, cardiac impairment (NSAIDs may impair renal function), cerebrovascular disease, coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), heart failure, ischaemic heart disease, peripheral arterial disease, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated), uncontrolled hypertension.

- With topical use: Avoid contact with eyes; avoid contact with inflamed or broken skin; avoid contact with mucous membranes, not for use with occlusive dressings, topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

### INTERACTIONS

#### Appendix 1: NSAIDs

### SIDE-EFFECTS

#### GENERAL SIDE-EFFECTS

- Uncommon Diarrhoea, paraesthesia, skin reactions
- Rare or very rare Hypersensitivity, photosensitivity reaction
- Frequency not known Angioedema

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**SPECIFIC SIDE-EFFECTS**

- **Common or very common**
  - With oral use: Gastrointestinal discomfort, nausea, vomiting
  - With systemic use: Constipation, dizziness, drowsiness, fatigue, gastrointestinal disorders, headache, oedema, rash (discontinue)

- **Uncommon**
  - With oral use: Asthma, haemorrhagic anaemia, hepatic disorders, pancreatitis, shock, stomatitis, tinnitus, vision disorders, weight increased
  - With topical use: Renal impairment

- **Frequency not known**
  - With oral use: Frequency not known
  - With topical use: Frequency not known

**SIDE-EFFECTS, FURTHER INFORMATION**

Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 1130

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONCEPTION**

- With systemic use: Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

- With systemic use: Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possible persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
  - With topical use: Patient packs for topical preparations carry a warning to avoid during pregnancy.

**BREAST FEEDING**

- With systemic use: Use with caution during breast-feeding. Amount probably too small to be harmful but manufacturers advise avoid.
  - With topical use: Patient packs for topical preparations carry a warning to avoid during breast-feeding.

**HEPATIC IMPAIRMENT**

- With systemic use: Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.
  - With topical use: Manufacturer advises caution.

**RENAL IMPAIRMENT**

- With systemic use: Avoid if possible or use with caution. Avoid in severe impairment.
  - With topical use: Deterioration in renal function has also been reported after topical use.

**Dose adjustments**

- With systemic use: The lowest effective dose should be used for the shortest possible duration.

**Monitoring**

- With systemic use: In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**DIRECTIONS FOR ADMINISTRATION**

- With topical use: For topical preparations apply with gentle massage only.

**PRESCRIBING AND DISPENSING INFORMATION**

- With topical use: Caution—topical preparations not generally suitable for children.
  - With oral use: Flavours of oral liquid formulations may include strawberry.

**PATIENT AND CARER ADVICE**

- With topical use: For topical preparations, patients and their carers should be advised to wash hands immediately after use.

**Photosensitivity**

- With topical use: Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity. Patients should be advised not to expose area treated to sunbeds or sunlight (even on a bright but cloudy day) during, and for two weeks after stopping treatment; treated areas should be protected with clothing.

**EXCEPTIONS TO LEGAL CATEGORY**

- With topical use: Smaller pack sizes of gel preparations may be available on sale to the public.

**MEDICAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: gel

**Modified-release capsule**

**CAUTIONARY AND ADVISORY LABELS 21, 25**

- Larafen CR (Ennogen Pharma Ltd)
  - Ketoprofen 200 mg Larafen CR 200mg capsules | 28 capsule
  - £19.08 DT = £23.85
- Oruvail (Sanofi)
  - Ketoprofen 100 mg Oruvail 100 modified-release capsules | 56 capsule
  - £23.93 DT = £23.93
  - Ketoprofen 200 mg Oruvail 200 modified-release capsules | 28 capsule
  - £23.85 DT = £23.85
  - Valket Retard (Tillomed Laboratories Ltd)
  - Ketoprofen 200 mg Valket 200 Retard capsules | 28 capsule
  - £10.70 DT = £23.85

**Gel**

**CAUTIONARY AND ADVISORY LABELS 11**

- EXCIPIENTS: May contain Ethanol, fragrances
  - Ketoprofen (Non-proprietary)
    - Ketoprofen 25 mg per 1 gram Ketoprofen 2.5% gel | 50 gram
    - £6.34 DT = £6.34 | 100 gram
    - £10.68 DT = £10.68
  - Oruvail (Sanofi)
    - Ketoprofen 25 mg per 1 gram Oruvail 2.5% gel | 100 gram
    - £6.84 DT = £6.84
  - Powergel (A. Menarini Farmaceutica Internazionale SRL)
    - Ketoprofen 25 mg per 1 gram Powergel 2.5% gel | 50 gram
    - £3.06 DT = £3.06 | 100 gram
    - £5.89 DT = £5.89
  - Tiloket (Tillomed Laboratories Ltd)
    - Ketoprofen 25 mg per 1 gram Tiloket 2.5% gel | 50 gram
    - £3.00 DT = £3.00 | 100 gram
    - £6.00 DT = £6.00

**Mefenamic acid**

**INDICATIONS AND DOSE**

**Pain and inflammation in rheumatoid arthritis and osteoarthritis**

**Postoperative pain**

- **Mild to moderate pain**
  - **BY MOUTH**
    - Adult: 500 mg 3 times a day

continued →

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Acute pain including dysmenorrhea | Menorrhagia

- BY MOUTH
- Child 12-17 years: 500 mg 3 times a day
- Adult: 500 mg 3 times a day

- CONTRA-INDICATIONS Active gastro-intestinal bleeding, active gastro-intestinal ulceration, history of gastro-intestinal bleeding related to previous NSAID therapy, history of gastro-intestinal perforation related to previous NSAID therapy, history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes), history of recurrent gastro-intestinal ulceration (two or more distinct episodes), inflammatory bowel disease, severe heart failure.

- CAUTIONS Acute porphyrias p. 1058; allergic disorders - cardiac impairment (NSAIDs may impair renal function), cerebrovascular disease, coagulation defects, connective tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), epilepsy, heart failure, ischaemic heart disease, peripheral arterial disease, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated), uncontrolled hypertension.

- INTERACTIONS → Appendix 1: NSAIDs

- SIDE-EFFECTS Agranulocytosis, anaemia, angioedema, appetite decreased - asthma, bone marrow disorders - confusion - constipation, Crohn’s disease - depression, diarrhoea (discontinue), disseminated intravascular coagulation - dizziness - drowsiness - dyspnoea - dysuria - ear pain - eosinophilia - eye irritation - fatigue - fertility decreased female - gastrointestinal discomfort, gastrointestinal disorders, glomerulonephritis - glucose tolerance impaired - haemolytic anaemia - haemorrhage, hallucination - headache - heart failure - hepatic disorders - hyperphosphataemia, hyperkalaemia, hyperpotassemia - hyperkoalaemia, hypothyroidism - insomina, leucopenia - malaise - meningitis aseptic (patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible), multi organ failure, nausea - nephritis acute interstitial - nephrotic syndrome - nervousness - neutropenia - oedema - optic neuritis - oral ulceration - palpitations, pancreatitis, paraesthesia - photosensitivity reaction - proteinuria - rash (discontinue) - renal failure (more common in patients with pre-existing renal impairment), renal failure non-oliguric - renal papillary necrosis, respiratory disorders, seizure - sepsis, severe cutaneous adverse reactions (SCARs) - skin reactions - thrombocytopenia - tinnitus - vertigo - vision disorders - vomiting.

SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

Overdose Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent, require treatment. For details on the management of poisoning, see Emergency treatment of poisoning p. 1359, in particular, Convulsions.

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- BREAST FEEDING Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

- HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment.

- Dose adjustments The lowest effective dose should be used for the shortest possible duration.

- Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Oral suspension

CAUTIONARY AND ADVISORY LABELS 21 EXCPIENTS: May contain Ethanol

- Mefenamic acid (Non-proprietary)

Mefenamic acid 10 mg per 1 ml Mefenamic acid 50mg/5ml oral suspension | 125 ml ▶ £17.00 DT + £17.00

Tablet

CAUTIONARY AND ADVISORY LABELS 21

- Mefenamic acid (Non-proprietary)

Mefenamic acid 500 mg Mefenamic acid 500mg tablets | 28 tablet ▶ £60.00 DT + £26.77 | 84 tablet ▶ £92.71-£170.00

- Ponstan (Chemixde Pharma Ltd)

Mefenamic acid 500 mg Ponstan Forte 500mg tablets | 100 tablet ▶ £15.72

Capsule

CAUTIONARY AND ADVISORY LABELS 21

- Mefenamic acid (Non-proprietary)

Mefenamic acid 250 mg Mefenamic acid 250mg capsules | 100 capsule ▶ £60.10 DT + £22.89

- Ponstan (Chemixde Pharma Ltd)

Mefenamic acid 250 mg Ponstan 250mg capsules | 100 capsule ▶ £18.17 DT + £22.89

Meloxicam

INDICATIONS AND DOSE

Exacerbation of osteoarthritis (short-term)

- BY MOUTH

Child 12-17 years: 7.5 mg once daily, then increased if necessary up to 15 mg once daily

Adult: 7.5 mg once daily, then increased if necessary up to 15 mg once daily

Pain and inflammation in rheumatic disease | Ankylosing spondylitis

- BY MOUTH

Child 16-17 years: 15 mg once daily, then reduced to 7.5 mg once daily if required

Adult: 15 mg once daily, then reduced to 7.5 mg once daily if required

Elderly: 7.5 mg once daily

Relief of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in children intolerant to other NSAIDs

- BY MOUTH

Child 12-17 years (body-weight up to 50 kg): 7.5 mg once daily

Child 12-17 years (body-weight 50 kg and above): 15 mg once daily

UNLICENSED USE Not licensed for use in children under 16 years.

CONTRA-INDICATIONS Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy, history of gastro-intestinal perforation related to previous NSAID therapy, history of recurrent gastro-intestinal...
haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

- **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- **INTERACTIONS** → Appendix 1: NSAIDs

- **SIDE-EFFECTS**

  - **Common or very common** Constipation - diarrhoea - gastrointestinal discomfort - gastrointestinal disorders - headache - nausea - vomiting

  - **Uncommon** Anaemia - angioedema - burping - dizziness - drowsiness - electrolyte imbalance - fluid retention - flushing - haemorrhage - hepatic disorders - hypersensitivity - oedema - skin reactions - stomatitis - vertigo

  - **Rare or very rare** Acute kidney injury - asthma - conjunctivitis - leucopenia - mood altered - nighttime - palpitations - severe cutaneous adverse reactions (SCARs) - thrombocytopenia - tinnitus - vision disorders

  - **Frequency not known** Agranulocytosis - confusion - decreased fertility - decreased female - heart failure - increased risk of arterial thromboembolism - nephritis tubulointerstitial - nephritic syndrome - photosensitivity reaction - renal necrosis

- **SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID - which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution — long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possible persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Present in milk in animal studies — manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution.

  - In adults Avoid if eGFR less than 25 mL/minute/1.73 m².

  - In children Avoid if estimated glomerular filtration rate less than 25 mL/minute/1.73 m².

- **Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

- **Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  - **Orodispersible tablet**

    - Meloxicam (Non-proprietary)

      - Meloxicam 7.5 mg Meloxicam 7.5mg orodispersible tablets sugar free - 30 tablet (PST) £25.50 DT = £25.50

      - Meloxicam 15 mg Meloxicam 15mg orodispersible tablets sugar free - 30 tablet (PST) £25.50 DT = £25.50

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID — which includes those in whom attacks of
CONTRA-INDICATIONS

1. Hepatic impairment
   - May deteriorate, possibly leading to renal failure.
   - Sodium and water retention may occur and renal function may be delayed and duration may increase.

2. Breast feeding
   - Use with caution during breast-feeding.
   - Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

3. Renal impairment
   - Avoided if possible or use with caution. Avoid in severe impairment.
   - Dose adjustments: The lowest effective dose should be used for the shortest possible duration.
   - Monitoring: In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21
- Nabumetone (Non-proprietary)
  - Nabumetone 500 mg: Nabumetone 500 mg tablets | 56 tablet PGR £20.00 DT + £6.90
- Reiflex (Meda Pharmaceuticals Ltd)
  - Nabumetone 500 mg: Reiflex 500 mg tablets | 60 tablet PGR £6.18

Naproxen

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease
- By mouth
  - Adult: 0.5–1 g daily in 1–2 divided doses

Pain and inflammation in musculoskeletal disorders

Dysmenorrhoea
- By mouth
  - Adult: Initially 500 mg, then 250 mg every 6–8 hours as required, maximum dose after the first day 1.25 g daily

Acute gout
- By mouth
  - Adult: Initially 750 mg, then 250 mg every 8 hours until attack has passed

CONTRA-INDICATIONS

Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

CAUTIONS

- Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

INTERACTIONS

Appendix 1: NSAIDs

SIDE-EFFECTS


SIDE-EFFECTS, FURTHER INFORMATION

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

ALLERGY AND CROSS-SENSITIVITY

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCESSION AND CONTRACEPTION

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

BREAST FEEDING

Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

RENAL IMPAIRMENT

Avoided if possible or use with caution. Avoid in severe impairment.

Dose adjustments: The lowest effective dose should be used for the shortest possible duration.

Monitoring: In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) decisions

SMC No. 1154/16

The Scottish Medicines Consortium has advised (June 2016) that naproxen effervescent tablets (Stirlescent®) are accepted for restricted use within NHS Scotland for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, dysmenorrhoea and acute gout in adults unable to swallow naproxen tablets.

EXCEPTIONS TO LEGAL CATEGORY

Can be sold to the public for the treatment of primary dysmenorrhoea in women aged 15–50 years subject to max. single dose of 500 mg, max. daily dose of 750 mg for max. 3 days, and a max. pack size of 9 × 250 mg tablets.
## Pain and inflammation in musculoskeletal disorders

### Piroxicam

#### INDICATIONS AND DOSE

**Rheumatoid arthritis (initiated by a specialist)**
- **Osteoarthritis (initiated by a specialist)**
- **Ankylosing spondylitis (initiated by a specialist)**

- **By mouth**
  - Adult: Up to 20 mg once daily

**Pain relief in musculoskeletal conditions**
- **Treatment in knee or hand osteoarthritis (adjunct)**

- **To the skin**
  - Adult: Apply 3–4 times a day, 0.5% gel to be applied; review treatment after 4 weeks

### IMPORTANT SAFETY INFORMATION

**CHMP ADVICE—PIROXICAM (JUNE 2007)**

- With systemic use
  - The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastrointestinal side effects and serious skin reactions. The CHMP has advised that:
    - Piroxicam should be initiated only by physicians experienced in treating inflammatory or degenerative rheumatic diseases
    - Piroxicam should not be used as first-line treatment
    - In adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
    - Piroxicam dose should not exceed 20 mg daily
    - Piroxicam should no longer be used for the treatment of acute painful and inflammatory conditions
    - Treatment should be reviewed 2 weeks after initiating piroxicam, and periodically thereafter
    - Concomitant administration of a gastro-protective agent should be considered.

Topical preparations containing piroxicam are not affected by these restrictions.

### CONTRA-INDICATIONS

- With systemic use
  - Active gastro-intestinal bleeding · active gastro-intestinal ulceration · history of gastro-intestinal bleeding · history of gastro-intestinal perforation · history of gastro-intestinal ulceration · inflammatory bowel disease · severe heart failure

### CAUTIONS

- With systemic use
  - Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · cerebrovascular disease · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · elderly (risk of serious side-effects and fatalities) · heart failure · ischaemic heart disease · peripheral arterial disease · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated) · uncontrolled hypertension

- With topical use
  - Avoid contact with eyes · avoid contact with inflamed or broken skin · avoid contact with mucous membranes · not for use with occlusive dressings · topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

### INTERACTIONS

- Appendix 1: NSAIDs

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### Naproxen with esomeprazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, naproxen p. 1148, esomeprazole p. 78.

#### INDICATIONS AND DOSE

Patients requiring naproxen for osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, who are at risk of NSAID-associated duodenal or gastric ulcer and when treatment with lower doses of naproxen or other NSAIDs ineffective

- **By mouth**
  - Adult: 500/20 mg twice daily, dose expressed as x/y mg naproxen/esomeprazole

#### INTERACTIONS

- Appendix 1: NSAIDs · proton pump inhibitors

#### PRESCRIBING AND DISPENSING INFORMATION

Naproxen component is gastro-resistant.
Piroxicam (Non-proprietary)

Piroxicam 5 mg per 1 gram

- Piroxicam 5 mg per 1 gram
- Piroxicam 0.5% gel
- 60 gram Pote £3.50 DT + £1.67
- 100 gram Pote £4.80
- 112 gram Pote £5.25 DT + £3.12

Feldene (Pfizer Ltd)

- Piroxicam 5 mg per 1 gram
- Piroxicam 0.9% gel
- 60 gram Pote £6.00 DT + £1.67
- 112 gram Pote £9.41 DT + £3.12

Alopecia

- Alopecia
- Angioedema
- Aplastic anaemia
- Confusion
- Depression
- Embolism
- Thrombosis
- Eye irritation
- Eye swelling
- Fertility decreased
- Fluid retention
- Haemolytic anaemia
- Haemorrhage
- Hallucination
- Hearing impairment
- Heart failure
- Hepatic disorders
- Hypersensitivity
- Hypertension
- Malaise
- Mood altered
- Nervousness
- Onycholysis
- Parasthesia
- Sleep disorders
- Vasculitis

SIDE-EFFECTS, FURTHER INFORMATION

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs, p. 1130

Topical application of large amounts can result in systemic effects.

ALLERGY AND CROSS-SENSITIVITY

- Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

- With systemic use Caution—Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY

- Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
- With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

BREAST FEEDING

- With systemic use Use with caution during breast-feeding. Amount too small to be harmful.
- With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

HEPATIC IMPAIRMENT

- With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAL IMPAIRMENT

- With systemic use Avoid if possible or use with caution.
- With topical use Deterioration in renal function has also been reported after topical use.

Dose adjustments

- With systemic use The lowest effective dose should be used for the shortest possible duration.
- Monitoring

- With systemic use In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

DIRECTIONS FOR ADMINISTRATION

- Piroxicam orodispersible tablets can be taken by placing on the tongue and allowing to dissolve or by swallowing.
- With topical use For topical preparations apply with gentle massage only.

PRESCRIBING AND DISPENSING INFORMATION

- With topical use Caution—Topical preparations not generally suitable for children.
- PATIENT AND CARER ADVICE

- With topical use Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

LESS SUITABLE FOR PRESCRIBING

- With oral use Piroxicam is less suitable for prescribing.

MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

ORODISPERSIBLE TABLET

CAUTIONARY AND ADVISORY LABELS

- 10, 21 EXCIPIENTS: May contain Aspartame
- Feldene Melt (Pfizer Ltd)
- Piroxicam 20 mg Feldene Melt 20 mg tablets sugar-free
- 30 tablet Pote £10.53 DT + £10.53

GEL

- EXCIPIENTS: May contain Benzyl alcohol, propylene glycol
- Piroxicam (Non-proprietary)
- Piroxicam 5 mg per 1 gram Piroxicam 0.5% gel
- 60 gram Pote £3.50 DT + £1.67
- 100 gram Pote £4.80
- 112 gram Pote £5.25 DT + £3.12

Feldene (Pfizer Ltd)

- Piroxicam 5 mg per 1 gram Feldene 0.9% gel
- 60 gram Pote £6.00 DT + £1.67
- 112 gram Pote £9.41 DT + £3.12

CAPSULE

CAUTIONARY AND ADVISORY LABELS

- 21 EXCIPIENTS: May contain Aspartame
- Piroxicam (Non-proprietary)
- Piroxicam 10 mg Piroxicam 10 mg capsules
- 56 capsule Pote £16.82 DT + £4.90
- Piroxicam 20 mg Piroxicam 20 mg capsules
- 28 capsule Pote £19.76 DT + £4.47

Feldene (Pfizer Ltd)

- Piroxicam 10 mg Feldene 10 mg capsules
- 30 capsule Pote £3.86
- Piroxicam 20 mg Feldene 20 mg capsules
- 30 capsule Pote £7.71

Sulindac

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Acute gout

BY MOUTH

- Adult: 200 mg twice daily for maximum duration
- 7–10 days in peri-articular disorders, dose may be reduced according to response; acute gout should respond within 7 days; maximum 400 mg per day

CONTRA-INDICATIONS

- Active gastro-intestinal bleeding—active gastro-intestinal ulceration—history of gastro-intestinal bleeding related to previous NSAID therapy
- History of gastro-intestinal perforation related to previous NSAID therapy
- History of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)—history of recurrent gastro-intestinal ulceration (two or more distinct episodes)—severe heart failure

CAUTIONS

- Allergic disorders—cardiac impairment (NSAIDs may impair renal function)—cerebrovascular disease—coagulation defects—connective-tissue disorders—Crohn’s disease (may be exacerbated)—elderly (risk of serious side-effects and fatalities)—ensure adequate hydration—heart

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failure • history of renal stones • ischaemic heart disease • peripheral arterial disease • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension

**INTERACTIONS** → Appendix 1: NSAIDs

**SIDE-EFFECTS**

- Acute psychosis • agranulocytosis • alopecia • angioedema • appetite decreased • arrhythmia • asthenia • asthma • bone marrow disorders • cholecystitis • confusion • constipation • Crohn’s disease aggravated • depression • diarrhea • dizziness • drowsiness • dyspnoea • dysuria • eye disorder • fever • gastrointestinal discomfort • gastrointestinal disorders • gynaecomastia • haemolytic anaemia • haemorrhage • hallucination • headache • hearing loss • heart failure • hepatic disorders • hyperglycaemia • hyperhidrosis • hyperkalaemia • hypersensitivity • hypertensive • increased risk of arterial thromboembolism • increased risk of infection • insomnia • leucopenia • malaise • meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • mucosal abnormalities • muscle weakness • nausea • nephritis tubulointerstitial • nephrotic syndrome • nerve disorders • nervousness • neutropenia • oedema • oral disorders • palpitations • pancreatitis • paraesthesia • photosensitivity reaction • psychiatric disorder • renal impairment • respiratory disorders • seizure • severe cutaneous adverse reactions (SCARs) • skin reactions • syncope • taste altered • thrombocytopenia • tinnitus • urine abnormalities • urine discoulouration • vertigo • vision disorders • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**

Use with caution during breast-feeding.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

**RENA IMPAIRMENT**

Avoid if possible or use with caution. Avoid in severe impairment.

**Dose adjustments**

The lowest effective dose should be used for the shortest possible duration.

**Monitoring**

In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVICE LABELS</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulindac (Non-proprietary)</td>
<td>Sulindac 100 mg</td>
<td>56 tablet</td>
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<tr>
<td>Sulindac 200 mg</td>
<td>56 tablet (PBM)</td>
<td>£96.00</td>
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</tbody>
</table>

**INDICATIONS AND DOSE**

**Pain and inflammation in rheumatic disease**

**BY MOUTH**

- Adult: 20 mg once daily
- By intravenous injection, or by intramuscular injection

**Pain and inflammation in acute musculoskeletal disorders**

**BY MOUTH**

- Adult: 20 mg once daily for 7 days; maximum duration of treatment 14 days (including treatment by intravenous or intramuscular injection)
- By intravenous injection, or by intramuscular injection

- Adult: 20 mg once daily as initial treatment for 1–2 days if oral administration not possible

**CONTRA-INDICATIONS**

Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastrointestinal bleeding related to previous NSAID therapy • history of gastrointestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure

**CAUTIONS**

Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • heart failure • ischaemic heart disease • peripheral arterial disease • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension

**INTERACTIONS** → Appendix 1: NSAIDs

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Constipation • Crohn’s disease aggravated • diarrhea • gastrointestinal discomfort • gastrointestinal disorders • haemorrhage • headache • nausea • vomiting
- Uncommon Fatigue • oedema • skin reactions
- Rare or very rare Asthma • bronchospasm • depression • dyspnoea • hyperglycaemia • nervousness • palpitations • pancreatitis • severe cutaneous adverse reactions (SCARs) • sleep disorders • vertigo • weight changes
- Frequency not known Agranulocytosis • alopecia • anaemia • angioedema • aplastic anaemia • confusion • eosinophilia • fertility decreased female • haemolytic anaemia • hallucination • heart failure • hepatic disorders • hypersensitivity • hypertension • leucopenia • malaise • nail disorder • nephritis tubulointerstitial • nephropathy • paraesthesia • photosensitivity reaction • platelet aggregation inhibition • purpura non-thrombocytopenic • renal failure (more common in patients with pre-existing renal impairment) • thrombocytopenia • tinnitus • vasculitis • vision disorders

**SPECIFIC SIDE-EFFECTS**

- Common or very common
- With oral use: Dizziness • dry mouth • oral disorders
- Rare or very rare
- With oral use: Embolism and thrombosis • metabolic disorder
- Frequency not known
- With oral use: Drowsiness • eye irritation • eye swelling
- With parenteral use: Appetite decreased • increased risk of arterial thromboembolism • increased risk of ischaemic stroke • increased risk of myocardial infarction • meningitis aseptic (patients with connective-tissue disorders such as
systemic lupus erythematosus may be especially susceptible).- neutropenia - oral ulceration

SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- BREAST FEEDING Use with caution during breast-feeding. Present in milk in animal studies.

- HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment.

- RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment.

Dose adjustments The lowest effective dose should be used for the shortest possible duration.

Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

- Tenoxicam (Non-proprietary)
  - Tenoxicam 20 mg Tenoxicam 20mg powder and solvent for solution for injection vials | 1 vial £3.98

Tablet

CAUTIONARY AND ADVISORY LABELS 21

- Mobiflex (Meda Pharmaceuticals Ltd)
  - Tenoxicam 20 mg Mobiflex 20mg tablets | 30 tablet £13.42

### Tiaprofenic acid

#### INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders

- BY MOUTH
  - Adult: 300 mg twice daily

#### IMPORTANT SAFETY INFORMATION

CSM ADVICE

Following reports of severe cystitis the CSM has recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and should be stopped if urinary symptoms develop.

Patients should be advised to stop taking tiaprofenic acid and to report to their doctor promptly if they develop urinary-tract symptoms (such as increased frequency, nocturia, urgency, pain on urinating, or blood in urine).

- CONTRA-INDICATIONS Active bladder disease (or symptoms) - active gastro-intestinal bleeding - active gastro-intestinal ulceration - active prostate disease (or symptoms) - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - history of recurrent urinary-tract disorders (if urinary symptoms develop discontinue immediately and perform urine tests and culture) - severe heart failure

- CAUTIONS Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- INTERACTIONS ▶ Appendix 1: NSAIDs

- SIDE-EFFECTS Agranulocytosis - alopexia - anaemia - angioedema - aplastic anaemia - appetite decreased - asthma - bladder pain - bronchospasm - confusion - constipation - Crohn’s disease aggravated - cystitis - depression - diarrhoea - dizziness - drowsiness - dyspnoea - fatigue - fertility decreased female - fluid retention - gastrointestinal discomfort - gastrointestinal disorders - haemolytic anaemia - haemorrhage - hallucination - headache - heart failure - hepatic disorders - hypersensitivity - hypertension - increased risk of arterial thromboembolism - malaise - meningitis aseptic (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - nausea - nephritis tubulointerstitial - nephropathy - neutropenia - oedema - optic neuritis - oral ulceration - pancreatitis - paraesthesia - photosensitivity reaction - renal failure (more common in patients with pre-existing renal impairment) - severe cutaneous adverse reactions (SCARs) - skin reactions - sodium retention - thrombocytopenia - tinnitus - urinary disorders - urinary tract infection - vertigo - visual impairment - vomiting

SIDE-EFFECTS, FURTHER INFORMATION For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- BREAST FEEDING Use with caution during breast-feeding. Amount too small to be harmful.

- HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

Dose adjustments Reduce dose in mild or moderate impairment.

- RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment.

Dose adjustments Reduce dose in mild or moderate impairment. The lowest effective dose should be used for the shortest possible duration.

Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
**Soft tissue and joint disorders**

5 Local inflammation of joints and soft tissue

Other drugs used for Local inflammation of joints and soft tissue

Betamethasone, p. 674

**CORTICOSTEROIDS**

Corticosteroids, inflammatory disorders

Systemic corticosteroids

Short-term treatment with corticosteroids can help to rapidly decrease inflammatory symptoms of rheumatoid arthritis. Long-term treatment in patients with established rheumatoid arthritis should only be continued after evaluating the risks and all other treatments have been considered.

*Polyarthritis nodosa* and *polymyositis* are usually treated with corticosteroids.

Systemic lupus erythematosus is treated with corticosteroids when necessary using a similar dosage regimen to that for polyarthritis nodosa and polymyositis. Patients with pleurisy, pericarditis, or other systemic manifestations will respond to corticosteroids. It may then be possible to reduce the dosage; alternate-day treatment is sometimes adequate, and the drug may be gradually withdrawn. In some mild cases corticosteroid treatment may be stopped after a few months. Many mild cases of systemic lupus erythematosus do not require corticosteroid treatment. Alternative treatment with non-steroidal anti-inflammatory drugs, and possibly chloroquine p. 616 or hydroxychloroquine sulfate p. 1095, should be considered.

Ankylosing spondylitis should not be treated with long-term corticosteroids; rarely, pulse doses may be needed and may be useful in extremely active disease that does not respond to conventional treatment.

Local corticosteroid injections

Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, particularly in rheumatoid arthritis, they are given by intra-articular injection to relieve pain, increase mobility, and reduce deformity in one or a few joints; they can also provide symptomatic relief while waiting for disease-modifying antirheumatic drugs (DMARDs) to take effect. Full aseptic precautions are essential; infected areas should be avoided. Occasionally an acute inflammatory reaction develops after an intra-articular or soft-tissue injection of a corticosteroid. This may be a reaction to the microcrystalline suspension of the corticosteroid used, but must be distinguished from sepsis introduced into the injection site.

Smaller amounts of corticosteroids may also be injected directly into soft tissues for the relief of inflammation in conditions such as tennis or golfer’s elbow or compression neuropathies. In tendinitis, injections should be made into the tendon sheath and not directly into the tendon (due to the absence of a true tendon sheath and a high risk of rupture, the Achilles tendon should not be injected).

Hydrocortisone p. 1154 acetate or one of the synthetic analogues is generally used for local injection. Intra-articular corticosteroid injections can cause flushing and may affect the hyaline cartilage. Each joint should not usually be treated more than 4 times in one year.

Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions.

**Dexamethasone**

**DRUG ACTION** Dexamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity.

**INDICATIONS AND DOSE**

Local inflammation of joints

- **BY INTRA-ARTICULAR INJECTION**
  - Adult: 0.3–3.3 mg, where appropriate, dose may be repeated at intervals of 3–21 days according to response, dose given according to size—consult product literature

Local inflammation of soft tissues

- **BY LOCAL INFILTRATION**
  - Adult: 1.7–5 mg, dose given according to size—consult product literature, where appropriate may be repeated at intervals of 3–21 days, use the 3.3 mg/mL injection preparation for this dose

**INTERACTIONS**

- Appendix 1: corticosteroids

**PREGNANCY** Dexamethasone readily crosses the placenta.

**PRESCRIBING AND DISPENSING INFORMATION**

Dexamethasone 3.8 mg/mL Injection has replaced dexamethasone 4 mg/mL Injection. All dosage recommendations for intravenous, intramuscular, intrarticular use or local infiltration; are given in units of dexamethasone base.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Surgam** (Sanofi)
  - Tiapropholic acid 300 mg Surgam 300mg tablets | 56 tablet PSH £14.95 DT = £14.95

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www.getintopharma.com
Hydrocortisone

**DRUG ACTION** Hydrocortisone has equal glucocorticoid and mineralocorticoid activity.

**INDICATIONS AND DOSE**

**HYDROCORTISTAB®**

Local inflammation of joints and soft-tissues

- **BY INTRA-ARTICULAR INJECTION**
- Adult: 5–50 mg, select dose according to size of patient and joint; where appropriate dose may be repeated at intervals of 21 days. Not more than 3 joints should be treated on any one day, for details consult product literature

**INTERACTIONS** → Appendix 1; corticosteroids

**SIDE-EFFECTS** Myocardial rupture (following recent myocardial infarction)

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Suspension for injection**
  - **Hydrocortisab** (Advanz Pharma)
    - Hydrocortisone acetate 25 mg per 1 ml
    - Hydrocortisab 25mg/1ml suspension for injection ampoules | 10 ampoule [P ] £68.72 DT = £68.72

**Methylprednisolone with lidocaine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, methylprednisolone above, lidocaine hydrochloride p. 103.

**INDICATIONS AND DOSE**

Local inflammation of joints

- **BY INTRA-ARTICULAR INJECTION**
- Adult: 4–80 mg, dose adjusted according to size; where appropriate may be repeated at intervals of 7–35 days, for details consult product literature

**INTERACTIONS** → Appendix 1: antiarrhythmics - corticosteroids

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Suspension for injection**
  - **Depo-Medrone with Lidocaine** (Pfizer Ltd)
    - Lidocaine hydrochloride 10 mg per 1 ml
    - Methylprednisolone acetate 40 mg per 1 ml
    - Depo-Medrone with Lidocaine suspension for injection 2ml vials | 1 vial [P ] £7.06 DT = £7.06 | 10 vial [P ] £70.13
    - Depo-Medrone with Lidocaine suspension for injection 1ml vials | 1 vial [P ] £3.94 DT = £3.94 | 10 vial [P ] £38.88

**Prednisolone**

**DRUG ACTION** Prednisolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects.

**INDICATIONS AND DOSE**

**DELTASTAB®**

Local inflammation of joints

- **BY INTRA-ARTICULAR INJECTION**
- Adult: 4–80 mg, select dose according to size; not more than 3 joints should be treated on any one day; where appropriate may be repeated when relapse occurs, for details consult product literature

**INTERACTIONS** → Appendix 1: corticosteroids


**PATIENT AND CARER ADVICE** Patient counselling is advised for methylprednisolone tablets and injections (steroid card).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Depo-Medrone** (Pfizer Ltd)
  - Methylprednisolone acetate 40 mg per 1 ml
  - Depo-Medrone 40mg/2ml suspension for injection vials | 1 vial [P ] £3.44 DT = £3.44 | 10 vial [P ] £34.04
  - Depo-Medrone 80mg/2ml suspension for injection vials | 1 vial [P ] £6.18 DT = £6.18 | 10 vial [P ] £61.39
  - Depo-Medrone 120mg/3ml suspension for injection vials | 1 vial [P ] £8.96 DT = £8.96 | 10 vial [P ] £88.81

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**

Prednisolone has been confused with propranolol; care must be taken to ensure the correct drug is prescribed and dispensed.

- **INTERACTIONS** → Appendix 1: corticosteroids

- **SIDE-EFFECTS** Diarrhoea - dizziness - hiccups - Kaposi’s sarcoma - myocardial rupture (following recent myocardial infarction) - scleroderma renal crisis - vomiting

- **PREGNANCY** As it crosses the placenta 88% of prednisolone is inactivated.

- **BREAST FEEDING** Prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Deltastab** (Advanz Pharma)
  - Prednisolone acetate 25 mg per 1 ml
  - Deltastab 25mg/1ml suspension for injection ampoules | 10 ampoule [P ] £68.72
**Triamcinolone acetonide**

**Drug Action** Triamcinolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effect.

**Indications and Dose**

**Adcortyl**<sup>®</sup> Intra-Articular/Intradermal

Local inflammation of joints and soft tissues

- **By Intra-Articular Injection**
  - Adults: 2.5–15 mg, adjusted according to size (for larger doses use *Kenalog*<sup>®</sup>). Where appropriate dose may be repeated when relapse occurs, for details consult product literature.

- **By Intradermal Injection**
  - Adults: 2–3 mg, max. 5 mg at any one site (total max. 30 mg). Where appropriate may be repeated at intervals of 1–2 weeks, for details consult product literature

**Kenalog**<sup>®</sup> Vials

Local inflammation of joints and soft tissues

- **By Intra-Articular Injection**
  - Adults: 5–40 mg (max. per dose 80 mg), for further details consult product literature, select dose according to size. For doses below 5 mg use *Adcortyl*<sup>®</sup> Intra-articular/Intradermal injection, where appropriate dose may be repeated when relapse occurs.

**Interactions** → Appendix 1: corticosteroids

**Patient and Carer Advice** Patient counselling is advised for triamcinolone acetonide injection (steroid card).

**Medicinal Forms** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for Injection**

**Cautionary and Advisory Labels.** 10

- *Adcortyl Intra-articular / Intradermal* (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Triamcinolone acetonide 10 mg per 1 ml *Adcortyl Intra-articular / Intradermal* 50mg/5ml suspension for injection vials | 1 vial £3.63
  - Adcortyl Intra-articular / Intradermal 20mg/1ml suspension for injection ampoules | 5 ampoule £4.47 DT + £4.47
  - *Kenalog* (Bristol-Myers-Squibb Pharmaceuticals Ltd)
  - Triamcinolone acetonide 40 mg per 1 ml *Kenalog Intra-articular / Intramuscular* 40mg/1ml suspension for injection vials | 5 vial £7.45 DT + £7.45

**Triamcinolone hexacetonide**

**Drug Action** Triamcinolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects.

**Indications and Dose**

Local inflammation of joints and soft-tissues (for details, consult product literature)

- **By Intra-Articular Injection**
  - Adults: 2–20 mg, adjusted according to size of joint, no more than 2 joints should be treated on any one day, where appropriate, may be repeated at intervals of 3–4 weeks

- **By Peri-Articular Injection**
  - Adults: 10–20 mg, adjusted according to size of joint, no more than 2 joints should be treated on any one day

**Contra-Indications** Consult product literature

**Cautions** Consult product literature

**Interactions** → Appendix 1: corticosteroids

**Side-Effects** Protein catabolism

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**5.2 Soft tissue disorders**

**Extravasation**

Local guidelines for the management of extravasation should be followed where they exist or specialist advice is sought.

Extravasation injury follows leakage of drugs or intravenous fluids from the veins or inadvertent administration into the subcutaneous or subdermal tissue. It must be dealt with promptly to prevent tissue necrosis.

Acidic or alkaline preparations and those with an osmolarity greater than that of plasma can cause extravasation injury; excipients including alcohol and polyethylene glycol have also been implicated. Cytotoxic drugs commonly cause extravasation injury. In addition, certain patients such as the very young and the elderly are at increased risk. Those receiving anticoagulants are more likely to lose blood into surrounding tissues if extravasation occurs, while those receiving sedatives or analgesics may not notice the early signs or symptoms of extravasation.

**Extravasation Prevention**

Precautions should be taken to avoid extravasation; ideally, drugs likely to cause extravasation injury should be given through a central line and patients receiving repeated doses of hazardous drugs peripherally should have the cannula rested at regular intervals. Attention should be paid to the manufacturers’ recommendations for administration.

Placing a glyceryl trinitrate p. patch distal to the cannula may improve the patency of the vessel in patients with small veins or in those whose veins are prone to collapse.

Patients should be asked to report any pain or burning at the site of injection immediately.

**Extravasation Management**

If extravasation is suspected the infusion should be stopped immediately but the cannula should not be removed until after an attempt has been made to aspirate the area (through the cannula) in order to remove as much of the drug as possible. Aspiration is sometimes possible if the extravasation presents with a raised bleb or blister at the injection site and is surrounded by hardened tissue, but it is often unsuccessful if the tissue is soft or soggy.

**Corticosteroids** are usually given to treat inflammation, although there is little evidence to support their use in extravasation. Hydrocortisone p. 675 or dexamethasone p. 675 can be given either locally by subcutaneous injection or intravenously at a site distant from the injury.

**Antihistamines** and **analgesics** may be required for symptom relief.

The management of extravasation beyond these measures is not well standardised and calls for specialist advice. Treatment depends on the nature of the offending substance; one approach is to localise and neutralise the substance whereas another is to spread and dilute it.

The first method may be appropriate following extravasation of vesicant drugs and involves administration...
of an antidote (if available) and the application of cold compresses 3–4 times a day (consult specialist literature for details of specific antidotes). Spreading and diluting the offending substance involves infiltrating the area with physiological saline, applying warm compresses, elevating the affected limb, and administering hyaluronidase p. physiological saline, applying warm compresses, elevating

Enzymes used in soft-tissue disorders
Collagenase
Collagenase below are proteolytic enzymes that are derived from the fermentation of Clostridium histolyticum and have the ability to break down collagen. A preparation containing a mixture of two collagenases is licensed for the treatment of Dupuytren’s contracture; the preparation should be injected into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint.

Hyaluronidase
Hyaluronidase is used to render the tissues more readily permeable to injected fluids, e.g. for introduction of fluids by subcutaneous infusion (termed hypodermoclysis).

Rubefacients
Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method that itself produces irritation of the skin. Topical rubefactive preparations may contain nicotinate and salicylate compounds, essential oils, capsicum, and camphor. The evidence available does not support the use of topical rubefacients in acute or chronic musculoskeletal pain.

Topical NSAIDs
The use of a NSAID by mouth is effective for relieving musculoskeletal pain. Topical NSAIDs (e.g. felbinic p. 1140, ibuprofen p. 1141, ketoprofen p. 1144, and piroxicam p. 1149 may provide some relief of pain in musculoskeletal conditions; they can be considered as an adjunctive treatment in knee or hand osteoarthritis.

Capsaicin
A preparation containing capsaicin 0.025% p. 483 can be considered as an adjunct in hand or knee osteoarthritis. It may need to be used for 1–2 weeks before pain is relieved. A capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia after lesions have healed, and for the relief of painful diabetic neuropathy.

A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients.

ENZYMES

Collagenase

DIRECTIONS FOR ADMINISTRATION
Reconstitution and injected volumes vary with site of injection—consult product literature.

Monitoring Requirements
Manufacturer advises monitor patients for at least 30 minutes after injection—risk of severe allergic reaction.

Directions for Administration
Reconstitution and injected volumes vary with site of injection—consult product literature.

National Funding/Access Decisions
NICE decisions
Collagenase clostridium histolyticum for treating Dupuytren’s contracture (July 2017) NICE TA459

Peyronie’s disease (specialist use only)

BY INTRALESIONAL INJECTION
Adult: 580 micrograms, then 580 micrograms after 1–3 days, doses to be administered into the Peyronie’s plaque; if more than one plaque is present, only the plaque causing the deformity should be injected, a treatment course consists of a maximum of 4 treatment cycles, administered at intervals of approximately 6 weeks. Each treatment cycle consists of 2 injections and 1 penile modelling procedure; the modelling procedure is performed 1–3 days after the second injection of each treatment cycle

Contra-Indications
Avoid injecting into other structures containing collagen (e.g. tendons, nerves, blood vessels, urethra and corpora cavernosa)—risk of injury

Caution
Coagulation disorders—use of anticoagulants

Side-Effects
Common or very common
– Abdominal pain
– Anxiety
– Breast abnormalities
– Dizziness
– Fatigue
– Headache
– Hypersensitivity
– Hypotension
– Insomnia
– Irritability
– Ligation
– Limb discomfort
– Limb injury
– Local swelling
– Malignancy
– Monoplegia
– Muscle weakness
– Musculoskeletal discomfort
– Symptome
– Tongue disorders
– Thrombocytopenia
– Tremor
– Vomiting
– Wound complications

Pregnancy
Manufacturer advises avoid.

Breast Feeding
Manufacturer advises caution—no information available.

Coagulation disorders
Use of anticoagulants

Risk of injury

Disease

Functional problems and metacarpophalangeal joint contracture of 30° to 60° and proximal interphalangeal joint contracture of less than 30° or first web contracture) plus up to 2 affected joints, and

Percutaneous needle fasciotomy is not considered appropriate, but limited fasciectomy is considered appropriate by the treating hand surgeon, and

The choice of treatment (collagenase clostridium histolyticum or limited fasciectomy) is made on an individual basis after discussion between the responsible hand surgeon and the patient about the risks and benefits of the treatments available, and

One injection is given per treatment session by a hand surgeon in an outpatient setting. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding.

Enzymes used in soft-tissue disorders

Collagenase
Collagenase below are proteolytic enzymes that are derived from the fermentation of Clostridium histolyticum and have the ability to break down collagen. A preparation containing a mixture of two collagenases is licensed for the treatment of Dupuytren’s contracture; the preparation should be injected into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint.

Hyaluronidase
Hyaluronidase is used to render the tissues more readily permeable to injected fluids, e.g. for introduction of fluids by subcutaneous infusion (termed hypodermoclysis).

Rubefacients
Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method that itself produces irritation of the skin. Topical rubefactive preparations may contain nicotinate and salicylate compounds, essential oils, capsicum, and camphor. The evidence available does not support the use of topical rubefacients in acute or chronic musculoskeletal pain.

Topical NSAIDs
The use of a NSAID by mouth is effective for relieving musculoskeletal pain. Topical NSAIDs (e.g. felbinic p. 1140, ibuprofen p. 1141, ketoprofen p. 1144, and piroxicam p. 1149 may provide some relief of pain in musculoskeletal conditions; they can be considered as an adjunctive treatment in knee or hand osteoarthritis.

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A preparation containing capsaicin 0.025% p. 483 can be considered as an adjunct in hand or knee osteoarthritis. It may need to be used for 1–2 weeks before pain is relieved. A capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia after lesions have healed, and for the relief of painful diabetic neuropathy.

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ENZYMES

Collagenase

DIRECTIONS FOR ADMINISTRATION
Reconstitution and injected volumes vary with site of injection—consult product literature.

Monitoring Requirements
Manufacturer advises monitor patients for at least 30 minutes after injection—risk of severe allergic reaction.

DIRECTIONS FOR ADMINISTRATION
Reconstitution and injected volumes vary with site of injection—consult product literature.

NATIONAL FUNDING/ACCESS DECISIONS
NICE decisions
Collagenase clostridium histolyticum for treating Dupuytren’s contracture (July 2017) NICE TA459

For people not taking part in the ongoing clinical trial (HTA-15-102/04), collagenase clostridium histolyticum (Xiapex®) is recommended as an option for treating Dupuytren’s contracture with a palpable cord in patients only if the following apply:

• There is evidence of moderate disease (functional problems and metacarpophalangeal joint contracture of 30° to 60° and proximal interphalangeal joint contracture of less than 30° or first web contracture) plus up to 2 affected joints, and

• Percutaneous needle fasciotomy is not considered appropriate, but limited fasciectomy is considered appropriate by the treating hand surgeon, and

• The choice of treatment (collagenase clostridium histolyticum or limited fasciectomy) is made on an individual basis after discussion between the responsible hand surgeon and the patient about the risks and benefits of the treatments available, and

• One injection is given per treatment session by a hand surgeon in an outpatient setting. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding.

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arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta459

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- **Xiapex** (Swedish Orphan Biovitrum Ltd)
  - Collagenase clostridium histolyticum 900 microgram
  - Xiapex 0.9mg powder and solvent for solution for injection vials | 1 vial £572.00

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### Hyaluronidase

**INDICATIONS AND DOSE**

- **Enhance permeation of subcutaneous or intramuscular injections**
  - By subcutaneous injection, or by intramuscular injection
  - Adult: 1500 units, to be dissolved directly into the solution to be injected (ensure compatibility)

- **Enhance permeation of local anaesthetics**
  - By local infiltration
  - Adult: 1500 units, to be mixed with the local anaesthetic solution

- **Enhance permeation of ophthalmic local anaesthetic**
  - To the eye
  - Adult: 15 units/mL, to be mixed with the local anaesthetic solution

**Hypodermoclysis**

- By subcutaneous injection
  - Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride injection, administered before start of 500–1000 mL infusion fluid

**Extravasation**

- By local infiltration
  - Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area as soon as possible after extravasation

**Haematoma**

- By local infiltration
  - Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area

**CONTRA-INDICATIONS** Avoid sites where infection is present - avoid sites where malignancy is present - do not apply direct to cornea - not for anaesthesia in unexplained premature labour - not for intravenous administration - not to be used to enhance the absorption and dispersion of dopamine and/or alpha-adrenoceptor agonists - not to be used to reduce swelling of bites - not to be used to reduce swelling of stings

**CAUTIONS** Elderly (control speed and total volume and avoid overhydration especially in renal impairment)

**SIDE-EFFECTS** Oedema - periocular oedema

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- **Hyaluronidase (Non-proprietary)**
  - Hyaluronidase 1500 unit
  - Hyaluronidase 1.500 unit powder for solution for injection ampoules | 10 ampoule £136.55

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Chapter 11
Eye

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Eye

Eye treatment: drug administration
Drugs are most commonly administered to the eye by topical application as eye drops or eye ointments. When a higher drug concentration is required within the eye, a local injection may be necessary. Eye-drop dispenser devices are available to aid the instillation of eye drops from plastic bottles and some are prescribable on the NHS (consult Drug Tariff—see Appliances and Reagents). Product-specific devices may be supplied by manufacturers—consult individual manufacturers for information. They are particularly useful for the elderly, visually impaired, arthritic, or otherwise physically limited patients.

Eye drops and eye ointments
Eye drops are generally instilled into the pocket formed by gently pulling down the lower eyelid and keeping the eye closed for as long as possible after application; one drop is all that is needed. Instillation of more than one drop should be discouraged because it may increase systemic side-effects. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye-drop preparations are used at the same time of day, dilution and overflow may occur when one immediately follows the other. The patient should therefore leave an interval of at least 5 minutes between the two; the interval should be extended when eye drops with a prolonged contact time, such as gels and suspensions, are used. Eye ointment should be applied after drops.

Systemic effects may arise from absorption of drugs into the general circulation from conjunctival vessels or from the nasal mucosa after the excess preparation has drained down through the tear ducts. The extent of systemic absorption following ocular administration is highly variable; nasal drainage of drugs is associated with eye drops much more often than with eye ointments. Pressure on the lacrimal punctum for at least a minute after applying eye drops reduces nasolacrimal drainage and therefore decreases systemic absorption from the nasal mucosa.

After using eye drops or eye ointments, patients should be warned not to drive or perform other skilled tasks until vision is clear.

Also see warnings relating to eye drops and contact lenses.

Eye lotions
These are solutions for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first-aid treatment. Sterile sodium chloride 0.9% solution p. 1169 is usually used. Clean water will suffice in an emergency.

Other preparations administered to the eye
Subconjunctival injection may be used to administer anti-infective drugs, mydriatics, or corticosteroids for conditions not responding to topical therapy; intracameral and intravitreal routes can also be used to administer certain drugs, for example antibacterials. These injections should only be used under specialist supervision.

Drugs such as antimicrobials and corticosteroids may be administered systemically to treat susceptible eye conditions.

Ophthalmic Specials
Certain eye drops, e.g. amphotericin p. 593, ceftazidime p. 528, cefuroxime p. 1171, colistimethate sodium p. 556, desferrioxamine mesilate p. 1028, dexamethasone p. 1162, gentamicin p. 1171, and vancomycin p. 534 can be prepared aseptically from material supplied for injection.

The Royal College of Ophthalmologists and the UK Ophthalmic Pharmacy Group have produced the Ophthalmic Specials Guidance to help prescribers and pharmacists manage and restrict the use of unlicensed eye preparations. ‘Specials’ should only be prescribed in situations where a licensed product is not suitable for a patient’s needs. The Ophthalmic Specials Guidance can be accessed on the Royal College of Ophthalmologists website (www.rcophth.ac.uk).

The guidance will be reviewed every six months to ensure the most accurate and up-to-date information is available.

Preservatives and sensitisers
Information on preservatives and substances identified as skin sensitisers is provided under Excipients statements in preparation entries. Very rarely, cases of corneal calcification have been reported with the use of phosphate-containing eye drops in patients with significantly damaged corneas—consult product literature for further information.

Eye preparations: control of microbial contamination
Preparations for the eye should be sterile when issued. Care should be taken to avoid contamination of the contents during use.

Eye drops in multiple-application containers for domiciliary use should not be used for more than 4 weeks after first opening (unless otherwise stated by the manufacturer).
Multiple application eye drops for use in hospital wards are normally discarded 1 week after first opening—local practice may vary. Individual containers should be provided for each patient. A separate container should be supplied for each eye only if there are special concerns about contamination. Containers used before an eye operation should be discarded at the time of the operation and fresh containers supplied postoperatively. A fresh supply should also be provided upon discharge from hospital; in specialist ophthalmology units, it may be acceptable to issue containers that have been dispensed to the patient on the day of discharge.

In out-patient departments single-application containers should be used; if multiple-application containers are used, they should be discarded after single patient use within one clinical session.

In eye surgery single-application containers should be used if possible; if a multiple-application container is used, it should be discarded after single use. Preparations used during intra-ocular procedures and others that may penetrate into the anterior chamber must be isotonic and without preservatives and buffered if necessary to a neutral pH. Specially formulated fluids should be used for intra-ocular surgery; intravenous infusion preparations are not usually suitable for this purpose (Hartmann’s solution may be used in some ocular surgery). For all surgical procedures, a previously unopened container is used for each patient.

**Contact lenses**

For cosmetic reasons many people prefer to wear contact lenses rather than spectacles; contact lenses are also sometimes required for medical indications. Visual defects are corrected by either rigid (‘hard’ or gas permeable) lenses or soft (hydrogel or silicone hydrogel—in adults only) lenses; soft lenses are the most popular type, because they are initially the most comfortable, but they may not give the best vision. Lens should usually be worn for a specified number of hours each day and removed for sleeping. The risk of infectious and non-infectious keratitis is increased by extended continuous contact lens wear, which is not recommended, except when medically indicated.

Contact lenses require meticulous care. Poor compliance with directions for use, and with daily cleaning and disinfection, can result in complications including ulcerative keratitis or conjunctivitis. One-day disposable lenses, which are worn only once and therefore require no disinfection or cleaning, are becoming increasingly popular.

*Acanthamoeba keratitis*, a painful and sight-threatening condition, is associated with ineffective lens cleaning and disinfection, the use of contaminated lens cases, or tap water coming into contact with the lenses. The condition is especially associated with the use of soft lenses (including frequently replaced lenses) and should be treated by specialists.

**Contact lenses and drug treatment**

Special care is required in prescribing eye preparations for contact lens users. Some drugs and preservatives in eye preparations can accumulate in hydrogel lenses and may induce toxic and adverse reactions. Therefore, unless medically indicated, the lenses should be removed before instillation of the eye preparation and not worn during the period of treatment. Alternatively, unpreserved drops can be used. Eye drops may, however, be instilled while patients are wearing rigid corneal contact lenses. Treatment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

Many drugs given systemically can also have adverse effects on contact lens wear. These include oral contraceptives (particularly those with a higher oestrogen content), drugs which reduce blink rate (e.g. anxiolytics, hypnotics, antihistamines, and muscle relaxants), drugs which reduce lacrimation (e.g. antihistamines, antimuscarinics, phenothiazines and related drugs, some beta-blockers, diuretics, and tricyclic antidepressants), and drugs which increase lacrimation (including ephedrine hydrochloride p. 272 and hyaluronate sodium hydrochloride p. 180). Other drugs that may affect contact lens wear are isotretinoin p. 1270 (can cause conjunctival inflammation), aspirin p. 121 (salicylic acid appears in tears and can be absorbed by contact lenses—leading to irritation), and rifampicin p. 582 and sulfasalazine p. 44 (can discolor lenses).

## 1 Allergic and inflammatory eye conditions

### Eye, allergy and inflammation

**Corticosteroids**

Corticosteroids administered locally to the eye or given by mouth are effective for treating anterior segment inflammation, including that which results from surgery. *Topical corticosteroids* are applied frequently for the first 24–48 hours; once inflammation is controlled, the frequency of application is reduced. They should normally only be used under expert supervision; three main dangers are associated with their use:

- a ‘red eye’, when the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye.
- Bacterial, fungal, and amoebic infections pose a similar hazard;
- ‘steroid glaucoma’ can follow the use of corticosteroid eye preparations in susceptible individuals;
- a ‘steroid cataract’ can follow prolonged use.

Combination products containing a corticosteroid with an anti-infective drug are sometimes used after ocular surgery to reduce inflammation and prevent infection; use of combination products is otherwise rarely justified.

**Systemic corticosteroids** may be useful for ocular conditions. The risk of producing a ‘steroid cataract’ increases with the dose and duration of corticosteroid use.

**Intravitreal corticosteroids**

An intravitreal implant containing dexamethasone p. 1162 (Ozurdex®) is licensed for the treatment of adults with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion; it is also licensed for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

An intravitreal implant containing fluocinolone acetonide p. 1192 (Iluvien®) is licensed for the treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies. It should be administered by specialists experienced in the use of intravitreal injections.

**Eye care, other anti-inflammatory preparations**

Other preparations used for the topical treatment of inflammation and allergic conjunctivitis include antihistamines, lodoxamide p. 1161, and sodium cromoglicate p. 1161.

Eye drops containing antihistamines, such as antazoline (with xylometazoline hydrochloride p. 1203 as Otivine-Antisin®), azelastine hydrochloride p. 1160, epinastine hydrochloride p. 1160, ketotifen p. 1160, and olopatadine p. 1161, can be used for allergic conjunctivitis. Sodium cromoglicate (sodium cromoglycate) and nedocromil sodium eye drops p. 1161 can be useful for vernal
keratoconjunctivitis and other allergic forms of conjunctivitis.

Lodoxamide eye drops are used for severe keratitis in patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Ciclosporin p. 1165 is licensed for severe keratitis in patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Ceneegermin p. 1165 is licensed for moderate to severe neurotrophic keratitis.

### 11.1 Allergic conjunctivitis

#### Other drugs used for Allergic conjunctivitis

Diclofenac sodium p. 1178

#### Antihistamines

##### Antazoline with xylometazoline

- **INDICATIONS AND DOSE**
  - **Allergic conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply 2–3 times a day for maximum 7 days
    - Adult: Apply 2–3 times a day for maximum 7 days
  - **SIDE-EFFECTS**
    - Drowsiness
    - Eye irritation
    - Headache
    - Hypersensitivity
    - Nasal irritation
    - Rhinitis
    - Taste altered
    - Visual impairment
  - **INTERACTIONS**
    - Appendix 1: antihistamines, non-sedating
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - Otrivine Antistin (Thea Pharmaceuticals Ltd)
      - Antazoline sulfate 5 mg per 1 ml
      - **Optilast (Meda Pharmaceuticals Ltd)**
      - Azelastine hydrochloride 500 microgram per 1 ml

##### Epinastine hydrochloride

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply twice daily for maximum 8 weeks
    - Adult: Apply twice daily for maximum 8 weeks
  - **SIDE-EFFECTS**
    - Common or very common: Eye irritation
    - Uncommon: Taste bitter (if applied incorrectly)
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - *Relestat* (Allergan Ltd)
      - Epinastine hydrochloride 500 microgram per 1 ml

##### Ketotifen

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 3-17 years: Apply twice daily
    - Adult: Apply twice daily
  - **INTERACTIONS**
    - Appendix 1: antihistamines, sedating
  - **SIDE-EFFECTS**
    - Common or very common: Eye discomfort
    - Uncommon: Dry eye
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - *Ketofall* (Scope Ophthalmics Ltd)
      - *Ketotifen* (as Ketotifen fumarate) 250 microgram per 1 ml

##### Azelastine hydrochloride

- **INDICATIONS AND DOSE**
  - **Seasonal allergic conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply twice daily, increased if necessary to 4 times a day
    - Adult: Apply twice daily, increased if necessary to 4 times a day
  - **Perennial conjunctivitis**
    - **TO THE EYE**
    - Child 12-17 years: Apply twice daily, increased if necessary to 4 times a day for maximum duration of treatment 6 weeks
    - Adult: Apply twice daily, increased if necessary to 4 times a day, maximum duration of treatment 6 weeks
  - **SIDE-EFFECTS**
    - Common: Eye irritation
    - Uncommon: Taste bitter (if applied incorrectly)
  - **INTERACTIONS**
    - Appendix 1: antihistamines, non-sedating
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **EXCIPIENTS:** May contain Benzalkonium chloride
**Olopatadine**

**INDICATIONS AND DOSE**

- **Seasonal allergic conjunctivitis**
  - **TO THE EYE**
  - Child 3–17 years: Apply twice daily for maximum 4 months
  - Adult: Apply twice daily for maximum 4 months

**SIDE-EFFECTS**

- **Common or very common** Asthenia - dry eye - eye discomfort - headache - nasal dryness - taste altered
- **Uncommon** Dizziness - eye disorders - eye inflammation - increased risk of infection - numbness - skin reactions - vision disorders
- **Frequency not known** Drowsiness - dyspnœa - malaise - nausea - vomiting

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**
  
  **EXCIPIENTS:** May contain Benzalkonium chloride
  
  Olopatadine (as Olopatadine hydrochloride) 1 mg per 1 ml
  
  **Olopatadine**

**MAST-CELL STABILISERS**

**Lodoxamide**

**INDICATIONS AND DOSE**

- **Allergic conjunctivitis**
  - **TO THE EYE**
  - Child 4–17 years: Apply 4 times a day, improvement of symptoms may sometimes require treatment for up to 4 weeks
  - Adult: Apply 4 times a day, improvement of symptoms may sometimes require treatment for up to 4 weeks

**SIDE-EFFECTS**

- **Common or very common** Dry eye - eye discomfort - eye disorders - vision disorders
- **Uncommon** Corneal deposits - dizziness - eye inflammation - headache - nausea
- **Rare or very rare** Nasal complaints - rash - taste altered

**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**
  
  **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
  
  Alomide (Novartis Pharmaceuticals UK Ltd)
  
  Lodoxamide (as Lodoxamide trometamol) 1 mg per 1 ml
  
  **Lodoxamide**

**Nedocromil sodium**

**INDICATIONS AND DOSE**

- **Seasonal and perennial conjunctivitis**
  - **TO THE EYE**
  - Child 6–17 years: Apply twice daily, increased if necessary to 4 times a day, max. 12 weeks duration of treatment for seasonal allergic conjunctivitis
  - Adult: Apply twice daily, increased if necessary to 4 times a day, max. 12 weeks duration of treatment for seasonal allergic conjunctivitis

  **Seasonal keratoconjunctivitis**
  
  **TO THE EYE**
  
  Child 6–17 years: Apply 4 times a day
  
  Adult: Apply 4 times a day

**SIDE-EFFECTS**

- **Common or very common** Eye discomfort - eye strain - taste altered

**MEDICINAL FORMS**

- No licensed medicines listed.

**Sodium cromoglicate**

(Sodium cromoglicate)

**INDICATIONS AND DOSE**

- **Seasonal allergic conjunctivitis**
  - **TO THE EYE**
  - Child: Apply 4 times a day
  - Adult: Apply 4 times a day

**SIDE-EFFECTS**

- **Eye stinging**

**EXCEPTIONS TO LEGAL CATEGORY**

- Sodium cromoglicate 2% eye drops can be sold to the public (in max. pack size of 10 mL) for treatment of acute seasonal and perennial allergic conjunctivitis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

  **Eye drops**
  
  **Sodium cromoglicate**
  
  Sodium cromoglicate 20 mg per 1 ml
  
  **Opatanol**

**1.2 Inflammatory eye conditions**

**Other drugs used for inflammatory eye conditions**

Adalimumab, p. 1108

**ANALGESICS > NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Nepafenac**

**INDICATIONS AND DOSE**

- **Prophylaxis and treatment of postoperative pain and inflammation associated with cataract surgery**
  - **TO THE EYE**
  - Child: Apply 4 times a day
  - Adult: (consult product literature)

**SIDE-EFFECTS**

- **Common or very common** Eye discomfort - eye disorders - eye inflammation
- **Uncommon** Allergic dermatitis - corneal deposits - dizziness - dry eye - headache - nausea
- **Rare or very rare** Allergic conjunctivitis - dry eye - eye disorders - eye inflammation - headache - nasal dryness - taste altered

**MEDICATION FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**
  
  **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate, sodium metabisulphite, sodium chloride, water
  
  Nepafenac (Novartis Pharmaceuticals UK Ltd)
  
  Nepafenac (as Nepafenac sodium) 0.2% eye drops | 10 ml
  
  **Nepafenac**

**Scottish Medicines Consortium (SMC) decisions**

- The Scottish Medicines Consortium (SMC) has advised (May 2017) that nepafenac (Nevanac®) 3 mg/mL eye drops are accepted for use within NHS Scotland for the reduction in risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

www.getintopharma.com
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**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

**EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate

- Nevanac (Novartis Pharmaceuticals UK Ltd)
  - Nevanac 1 mg per 1 ml Nevanac 1mg/ml eye drops | 5 ml 
    - £14.92 DT + £14.92
  - Nevanac 3 mg per 1 ml Nevanac 3mg/ml eye drops | 3 ml 
    - £14.92 DT + £14.92

**CORTICOSTEROIDS**

**Betamethasone**

**DRUG ACTION** Betamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity.

**INDICATIONS AND DOSE**

**Local treatment of inflammation (short-term)**

- **TO THE EYE USING EYE DROP**
  - Child: Apply every 1–2 hours until controlled then reduce frequency
  - Adult: Apply every 1–2 hours until controlled then reduce frequency

- **TO THE EYE USING EYE OINTMENT**
  - Child: Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops
  - Adult: Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops

**INTERACTIONS**

**SIDE-EFFECTS** Vision disorders

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Ear/eye/nose drops solution**

**EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate

- Betnesol (RPH Pharmaceuticals AB)
  - Betnesol sodium phosphate 1 mg per 1 ml Betnesol 0.1% eye/ear/nose drops | 10 ml 
    - £2.32 DT + £2.32
  - Vistanethasone (Martindale Pharmaceuticals Ltd)
  - Vistanethasone sodium phosphate 1 mg per 1 ml Vistanethasone 0.1% eye/ear/nose drops | 5 ml 
    - £1.02 | 10 ml 
    - £1.16 DT + £2.32

**Eye treatment**

- **Betamethasone (Non-proprietary)**
  - Betamethasone sodium phosphate 1 mg per 1 gram Betamethasone 0.1% eye ointment | 3 gram 
    - £3.48 DT + £4.11

**Combinations available:** *Betamethasone with neomycin*, p. 1164

**Dexamethasone**

**DRUG ACTION** Dexamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity.

**INDICATIONS AND DOSE**

**Local treatment of inflammation (short-term)**

- **TO THE EYE USING EYE DROP**
  - Child: Apply 4–6 times a day
  - Adult: Apply every 30–60 minutes until controlled, then reduced to 4–6 times a day

**Short term local treatment of inflammation (severe conditions)**

- **TO THE EYE USING EYE DROP**
  - Child: Apply every 30–60 minutes until controlled, reduce frequency when control achieved

**INTERACTIONS**

**SIDE-EFFECTS**

**UNLICENSED USE** Maxidex ® not licensed for use in children under 2 years. Dropodex ® not licensed for use in children.

**CONTRA-INDICATIONS**

- With intravitreal use Active ocular herpes simplex - active or suspected ocular infection - active or suspected periorcular infection - rupture of the posterior lens capsule in patients with aphakia, iris or transscleral fixated intra-ocular lens or anterior chamber intra-ocular lens - uncontrolled advanced glaucoma

- With intravitreal use history of ocular viral infection (including herpes simplex) - posterior capsule tear or iris defect (risk of implant migration into the anterior chamber which may cause corneal oedema and, in persistent severe cases, the need for corneal transplantation) - retinal vein occlusion with significant retinal ischaemia

**PREGNANCY** Dexamethasone readily crosses the placenta.

- With intravitreal use in adults Manufacturer advises avoid unless potential benefit outweighs risk — no information available.

**BREAST FEEDING**

- With intravitreal use in adults. Manufacturer advises avoid unless potential benefit outweighs risk — no information available.

**MONITORING REQUIREMENTS**

- With intravitreal use in adults. Monitor intra-ocular pressure and for signs of ocular infection. In patients with posterior capsule tear or iris defect monitor for implant migration to allow for; early diagnosis and management.

**PRESCRIBING AND DISPENSING INFORMATION**

- When used by eye Although multi-dose dexamethasone eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion (July 2011) NICE TA229

  - With intravitreal use in adults Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion. Dexamethasone intravitreal implant is also recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:

Macular oedema following either branch retinal vein occlusion or central retinal vein occlusion (specialist use only) | Visual impairment due to diabetic macular oedema in adults who are pseudophakic, or who are insufficiently responsive to, or unsuitable for non-corticosteroid therapy (specialist use only) | For the treatment of inflammation of the posterior segment of the eye presenting as non-infectious uveitis (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: 700 micrograms, to be administered into the affected eye, concurrent administration to both eyes not recommended. For further information on pre-treatment, administration and repeat dosing, consult product literature
treatment with laser photoocoagulation has not been beneficial, or

treatment with laser photoocoagulation is not considered suitable because of the extent of macular haemorrhage.

www.nice.org.uk/TA229

Dexamethasone intravitreal implant for treating diabetic macular oedema (July 2015) NICE TA349

With intravitreal use in adults Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular oedema only if:

- the implant is to be used in an eye with an intraocular (pseudophakic) lens and
- the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable.

www.nice.org.uk/TA349

Adalimumab and dexamethasone for treating non-infectious uveitis (July 2017) NICE TA460

With intravitreal use in adults Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in patients, only if there is:

- active disease (that is, current inflammation in the eye), and
- worsening vision with a risk of blindness. Patients currently receiving dexamethasone whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA460

Scottish Medicines Consortium (SMC) decisions

With intravitreal use in adults The Scottish Medicines Consortium has advised (June 2012) that dexamethasone intravitreal implant (Ozurdex®) is accepted for restricted use within NHS Scotland for the treatment of patients with macular oedema following central retinal vein occlusion, and in patients with branch retinal vein occlusion who are not clinically suitable for laser treatment, including patients with dense macular haemorrhage, or patients who have received and failed on previous laser treatment.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

Eye drops

EXCipients: May contain Benzalkonium chloride, disodium edetate, polyacrylates

> Dexafree (Thea Pharmaceuticals Ltd)
  Dexamethasone sodium phosphate 1 mg per 1 ml Dexafree 1mg/ml eye drops 0.4ml unit dose | 30 unit dose (POD) £9.79

> Dropodex (Rayner Pharmaceuticals Ltd)
  Dexamethasone sodium phosphate 1 mg per 1 ml Dropodex 0.1% eye drops 0.4ml unit dose | 20 unit dose (POD) £10.48 DT + £10.48

> Eysylux (Aspire Pharma Ltd)
  Dexamethasone 1 mg per 1 ml Eytsylux 1mg/ml eye drops | 6 ml (POD) £9.75 DT + £9.75

> Maxidex (Novartis Pharmaceuticals UK Ltd)
  Dexamethasone 1 mg per 1 ml Maxidex 0.1% eye drops | 5 ml (POD) £1.42 DT + £1.42 | 10 ml (POD) £2.80 DT + £2.80

Implant

> Ozurdex (Allergan Ltd)
  Dexamethasone 700 microgram Ozurdex 700microgram intravitreal implant in applicator | 1 device (POD) £870.00 (Hospital only)

Combinations available: Dexamethasone with framycetin sulfate and gramicidin, p. 1164 - Dexamethasone with hyromellose, neomycin and polymyxin B sulfate, p. 1164 - Dexamethasone with tobramycin, p. 1164

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**1164  Allergic and inflammatory eye conditions**

**CORTICOSTEROIDS › CORTICOSTEROID COMBINATIONS WITH ANTI-INFECTIVES**

### Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1162, neomycin sulfate p. 520.

#### INDICATIONS AND DOSE

Local treatment of eye inflammation and bacterial infection (short-term)
- TO THE EYE USING EYE DROP
  - Adult: Apply up to 6 times a day

**POTENCY**
- Betamethasone (as valerate) 0.1% with neomycin cream and ointment: potent.

#### INTERACTIONS

Appendix 1: corticosteroids • neomycin

#### LESS SUITABLE FOR PRESCRIBING

Betamethasone with neomycin eye-drops are less suitable for prescribing.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Ear/eye/nose drops solution**
  - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
  - **Betnesol-N** (RPN Pharmaceuticals AB)
    - Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml Betnesol-N ear/eye/nose drops | 10 ml [POD] £2.39 DT + £2.39

### Dexamethasone with framycetin sulfate and gramicidin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1162, framycetin sulfate p. 1195.

#### INDICATIONS AND DOSE

Local treatment of inflammation (short-term)
- TO THE EYE USING EYE DROP
  - Child: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency
  - Adult: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency

#### CAUTIONS

Avoid prolonged use

#### INTERACTIONS

Appendix 1: corticosteroids

#### LESS SUITABLE FOR PRESCRIBING

Sofradex® is less suitable for prescribing.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Ear/eye drops solution**
  - **EXCIPIENTS:** May contain Polysorbates
    - **Sofradex** (Sanofis)
      - Gramicidin 50 microgram per 1 ml, Dexamethasone (as Dexamethasone sodium metasulfobenzoate) 500 microgram per 1 ml, Framycetin sulfate 5 mg per 1 ml Sofradex ear/eye drops | 8 ml [POD] £1.50

### Dexamethasone with hyromellose, neomycin and polymyxin B sulfate

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1162, neomycin sulfate p. 520.

#### INDICATIONS AND DOSE

Local treatment of inflammation (short-term)
- TO THE EYE USING EYE DROP
  - Adult: Apply every 30–60 minutes until controlled, then reduced to 4–6 times a day

Local treatment of inflammation (short-term)
- TO THE EYE USING EYE OINTMENT
  - Adult: Apply 3–4 times a day, alternatively, apply at night when used with eye drops

#### INTERACTIONS

Appendix 1: aminoglycosides • corticosteroids

#### LESS SUITABLE FOR PRESCRIBING

Dexamethasone with neomycin and polymyxin B sulfate is less suitable for prescribing.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **EXCIPIENTS:** May contain Benzalkonium chloride, polysorbates
    - **Maxitol** (Novartis Pharmaceuticals UK Ltd)
      - Dexamethasone 1 mg per 1 gram, Neomycin (as Neomycin sulfate) 3500 unit per 1 gram, Polymyxin B sulfate 6000 unit per 1 gram Maxitol eye ointment | 3.5 gram [POD] £1.44

- **Eye drops**
  - **EXCIPIENTS:** May contain Benzalkonium chloride, polysorbates
    - **Maxitol** (Novartis Pharmaceuticals UK Ltd)
      - Dexamethasone 1 mg per 1 ml, Hyromellose 5 mg per 1 ml, Neomycin (as Neomycin sulfate) 3500 unit per 1 ml, Polymyxin B sulfate 6000 unit per 1 ml Maxitol eye drops | 5 ml [POD] £1.68

### Dexamethasone with tobramycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 1162, tobramycin p. 1171.

#### INDICATIONS AND DOSE

Local treatment of inflammation (short-term)
- TO THE EYE

#### INTERACTIONS

Appendix 1: aminoglycosides

#### LESS SUITABLE FOR PRESCRIBING

Dexamethasone with tobramycin eye-drops are less suitable for prescribing.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
    - **Tobradex** (Novartis Pharmaceuticals UK Ltd)
      - Dexamethasone 1 mg per 1 ml, Tobramycin 3 mg per 1 ml Tobradex 3mg/ml / 1mg/ml eye drops | 5 ml [POD] £5.37 DT + £5.37

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IMMUNOSUPPRESSANTS > CALCINEURIN INHIBITORS AND RELATED DRUGS

**Ciclosporin (Cyclosporin)**

- **DRUG ACTION** Ciclosporin inhibits production and release of lymphokines, thereby suppressing cell-mediated immune response.

- **INDICATIONS AND DOSE**

  **IKERVIS ®**

  **Severe keratitis in dry eye disease that has not responded to treatment with tear substitutes (initiated by a specialist)**

  - **TO THE EYE**
  - **Adults:** Apply 1 drop once daily, to be applied to the affected eye(s) at bedtime, review treatment at least every 6 months

- **CONTRA-INDICATIONS** Active or suspected ocular or peri-ocular infection

- **CAUTIONS** Glaucoma—limited information available; history of ocular herpes—no information available

- **INTERACTIONS** → Appendix: ciclosporin

- **SIDE-EFFECTS**
  - **Common or very common** Eye discomfort · eye disorders · eye inflammation · vision blurred
  - **Uncommon** Eye deposit · increased risk of infection

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available

- **BREAST FEEDING**
  - Manufacturer advises avoid—limited information.

- **DIRECTIONS FOR ADMINISTRATION**
  - Manufacturer advises keep eyes closed for 2 minutes after using eye drops to increase local drug action and reduce systemic absorption.

- **PATIENT AND CARER ADVICE**
  - **Driving and skilled tasks** Manufacturer advises patients and carers should be counselled on how to perform driving and performance of skilled tasks—increased risk of blurred vision.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE decisions**

  - Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears (December 2015)
  - NICE TA369

  Ciclosporin (Ikervis ®) is recommended as an option, within its marketing authorisation, for treating severe keratitis in patients with dry eye disease that has not improved despite treatment with tear substitutes.

  www.nice.org.uk/guidance/ta369

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**

  - **Ikervis** (Santen UK Ltd)
    - Ciclosporin 1 mg per 1 ml Ikervis 0.1% eye drops 0.3ml unit dose | 30 unit dose (POD) £72.00 DT = £72.00

- NERVE GROWTH FACTORS

  **Cenegermin**

  - **DRUG ACTION** Cenegermin is a recombinant form of human nerve growth factor which allows restoration of corneal integrity; endogenous human nerve growth factor is involved in the differentiation and maintenance of neurons.

  - **INDICATIONS AND DOSE**

    **Moderate or severe neurotrophic keratitis (specialist use only)**

    - **TO THE EYE**
    - **Adult:** Apply 1 drop 6 times a day, to be applied every 2 hours, starting in the morning and completing within 12 hours; treatment should be continued for 8 weeks

  - **CONTRA-INDICATIONS**

    - Eye infection—resolve before initiating treatment (if an infection occurs during treatment, cenegermin should be suspended until infection resolution) · patients requiring immediate corneal surgery (assess for risk of corneal melting or impending perforation before initiating treatment)

  - **CAUTIONS**

    - Ocular cancer—manufacturer recommends monitor for cancer progression before and after treatment

  - **SIDE-EFFECTS**

    - **Common or very common** Eye disorders · eye inflammation · eye pain · headache · photophobia
    - **Uncommon** Corneal abscess

  - **PREGNANCY** Manufacturer advises avoid—no information available.

  - **BREAST FEEDING** Manufacturer advises avoid—no information available.

  - **DIRECTIONS FOR ADMINISTRATION**

    - Manufacturer advises that other topical ophthalmic preparations should be administered at least 15 minutes before or after use.

  - **HANDLING AND STORAGE**

    - For information on storage of cenegermin, consult product literature.

  - **PATIENT AND CARER ADVICE**

    - Manufacturer advises patients and carers should be counselled on how to administer cenegermin eye drops.

  - **NATIONAL FUNDING/ACCESS DECISIONS**

    **NICE decisions**

    - Cenegermin for treating neurotrophic keratitis (July 2018)
    - NICE TA532

    Cenegermin (Oxervate ®) is not recommended, within its marketing authorisation, for treating moderate or severe neurotrophic keratitis in adults. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

    www.nice.org.uk/guidance/ta532

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**

  - **Oxervate** (Dompe UK Ltd)
  - Cenegermin 20 microgram per 1 ml Oxervate 20micrograms/ml eye drops preservative free | 1 ml (POD) (Hospital only)
1166 Dry eye conditions

1.2a Anterior uveitis

**ANTIMUSCARINICS**

**Antimuscarinics (eye)**

**CAUTIONS** Children under 3 months owing to the possible association between cyclopentolate and the development of amblyopia - darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. Mydriasis can precipitate acute angle-closure glaucoma (usually in those aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber) (in adults) - mydriasis can precipitate acute angle-closure glaucoma (usually in those who are predisposed to the condition because of a shallow anterior chamber) (in children) - neonates at increased risk of systemic toxicity (in neonates)

**SIDE-EFFECTS** Dizziness, photophobia, skin reactions, tachycardia

**PATIENT AND CARER ADVICE** Patients may not be able to undertake skilled tasks until vision clears after mydriasis.

**Atropine sulfate**

**INDICATIONS AND DOSE**

**Cycloplegia**

- Adult: (consult product literature)

**Anterior uveitis**

- Adult: (consult product literature)

**INTERACTIONS** → Appendix 1: atropine

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION** Systemic side-effects can occur, particularly in children and the elderly.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose cyclopentolate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

**EXCIPIENTS:** May contain Benzalkonium chloride

- Cyclopentolate hydrochloride (Bausch & Lomb UK Ltd)
  - Cyclopentolate hydrochloride 5 mg per 1 ml Minims cyclopentolate hydrochloride 0.5% eye drops 0.5ml unit dose | 20 unit dose £11.41 DT = £11.41
  - Cyclopentolate hydrochloride 10 mg per 1 ml Minims cyclopentolate hydrochloride 1% eye drops 0.5ml unit dose | 20 unit dose £11.68 DT = £11.68
  - Mydrilate (Intrapharm Laboratories Ltd)
  - Cyclopentolate hydrochloride 5 mg per 1 ml Mydrilate 0.5% solution | 5 ml £8.08 DT = £8.08
  - Cyclopentolate hydrochloride 10 mg per 1 ml Mydrilate 1% solution | 5 ml £8.08 DT = £8.08

**Homatropine hydrobromide**

**INDICATIONS AND DOSE**

**Anterior uveitis**

- Adult: (consult product literature)

**INTERACTIONS** → Appendix 1: homatropine

**MEDICINAL FORMS** Forms available from special-order manufacturers include: eye drops

2 Dry eye conditions

**Dry eye**

**Tear deficiency, ocular lubricants, and astringents**

Chronic soreness of the eyes associated with reduced or abnormal tear secretion (e.g. in Sjögren’s syndrome) often responds to tear replacement therapy or pilocarpine p. 1183 given by mouth in adults. The severity of the condition and patient preference will often guide the choice of preparation.

Hypromellose p. 1168 is the traditional choice of treatment for tear deficiency. It may need to be instilled frequently (e.g. hourly) for adequate relief. Ocular surface mucin is often abnormal in tear deficiency and the combination of hypromellose with a mucolytic such as acetylcysteine p. 1167 can be helpful.

The ability of carboxomers to cling to the eye surface may help reduce frequency of application to 4 times daily.
Polyvinyl alcohol p. 1168 increases the persistence of the tear film and is useful when the ocular surface mucin is reduced.

Sodium hyaluronate eye drops p. 1169, with or without trehalose, are also used in the management of tear deficiency.

Sodium chloride 0.9% drops p. 1169 are sometimes useful in tear deficiency, and can be used as ‘comfort drops’ by contact lens wearers, and to facilitate lens removal. They are also used to irrigate the eye. Special presentations of sodium chloride 0.9% and other irrigation solutions are used routinely for intra-ocular surgery. Sodium chloride 0.5% eye drops are used for the short-term treatment of corneal oedema in adults.

Eye ointments containing a paraffin can be used to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion. They may cause temporary visual disturbance and are best suited for application before sleep. Ointments should not be used during contact lens wear.

**Ocular Lubricants**

### Acetylcysteine

**INDICATIONS AND DOSE**

- **Tear deficiency** / **Impaired or abnormal mucus production**
  - TO THE EYE
  - Adult: Apply 3–4 times a day

**SIDE-EFFECTS**

Eye discomfort · eye redness

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- **Ilube** (Rayner Pharmaceuticals Ltd)
  - Acetylcysteine 50 mg per 1 ml Ilube 5% eye drops | 10 ml £16.90

**CARBOMERS**

(Polyacrylic acid)

**INDICATIONS AND DOSE**

- **Dry eyes including keratoconjunctivitis sicca, unstable tear film**
  - TO THE EYE
  - Child: Apply 3–4 times a day or when required
  - Adult: Apply 3–4 times a day or when required

**UNLICENSED USE**

- In children Some preparations not licensed for use in children.

**PRESCRIBING AND DISPENSING INFORMATION**

Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaerythritol.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye gel**
  - EXCIPIENTS: May contain Benzalkonium chloride, cetrimide, disodium edetate
  - **Blephagel** (Thea Pharmaceuticals Ltd)
    - Carbomer 3.6 mg per 1 gram Blephagel 0.36% eye gel preservative free | 30 gram £7.53
  - **Liquivisc** (Thea Pharmaceuticals Ltd)
    - Carbomer 974P 2.5 mg per 1 gram Liquivisc 0.25% eye gel | 10 gram £4.50
  - **Eye drops**
    - **Gelfears** (Bausch & Lomb UK Ltd)
      - Carbomer 980 2 mg per 1 gram Gelfears 0.2% gel | 10 gram £2.80

**Hydroxyethylcellulose**

**INDICATIONS AND DOSE**

- **Tear deficiency**
  - TO THE EYE
  - Child: Apply as required
  - Adult: Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose hydroxyethylcellulose eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **Artificial tears** (Bausch & Lomb UK Ltd)
    - Hydroxyethylcellulose 4.4 mg per 1 ml Minims artificial tears
    - 0.44% eye drops 0.5ml unit dose | 20 unit dose £9.33

- **Viscotears** (Bausch & Lomb UK Ltd)
  - Carbomer 980 2 mg per 1 gram Viscotears 2mg/g liquid gel
    - 10 gram £1.59
    - Viscotears 2mg/g eye gel 0.6ml unit dose | 30 unit dose £5.42

**Carmellose sodium**

**INDICATIONS AND DOSE**

- **Dry eye conditions**
  - TO THE EYE
  - Child: Apply as required
  - Adult: Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**

Some preparations are contained units which are resealable and may be used for up to 12 hours.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **Carmellose sodium** (Non-proprietary)
    - Carmellose 0.5% eye drops | 10 ml £7.49
    - Evolve Carmellose 0.5% eye drops preservative free | 10 ml £4.99
  - **Carmellose sodium 5 mg per 1 ml**
    - Carmellose 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £5.75 DT = £4.80
    - **PF Drops** Carmellose 0.5% eye drops preservative free | 10 ml £7.49
    - PF Drops Carmellose 1% eye drops preservative free | 10 ml £7.49
  - **Carmize** (Aspire Pharma Ltd)
    - Carmize 1% eye drops | 10 ml £8.49
    - Carmize 0.5% eye drops | 10 ml £7.49
  - **Cellusan** (Allergan Ltd)
    - Cellusan 1% eye drops preservative free | 10 ml £4.80
    - Cellusan Light 0.5% eye drops preservative free | 10 ml £4.80
  - **Celluvisc** (Alcon Ltd)
    - Celluvisc 1% eye drops 0.4ml unit dose | 30 unit dose £3.00 DT = £2.00 | 60 unit dose £10.99
  - **Carmellose sodium 5 mg per 1 ml**
    - Celluvisc 0.5% eye drops 0.4ml unit dose | 30 unit dose £4.80 DT = £4.80
    - Ocu-Lube Carmellose 1% eye drops preservative free | 10 ml £9.73
    - **Ocu-Lube Carmellose 0.5% eye drops** preservative free | 10 ml £7.49
    - **Optive-Lique** (Essential-Healthcare Ltd)
      - Optive-Lique 0.5% eye drops | 10 ml £3.73
      - Optive-Lique Forte 1% eye drops | 10 ml £3.97
    - **Optive** (Allergan Ltd)
      - Optive 0.5% eye drops | 10 ml £7.49
      - **Optive Plus** (Allergan Ltd)
        - Optive Plus 0.5% eye drops | 10 ml £7.49
      - **Tearvis** (Sai-Meds Ltd)
        - Tearvis 1% eye drops | 10 ml £8.49
        - Tearvis 0.5% eye drops | 10 ml £7.49
Hydroxypropyl guar with polyethylene glycol and propylene glycol

(Formulated as an ocular lubricant)

**INDICATIONS AND DOSE**

**Dry eye conditions**

- TO THE EYE
- Child: Apply as required
- Adult: Apply as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Gel eye drops**
  - Systane Gel eye drops (Alcon Eye Care Ltd)
  - Systane Gel eye drops | 10 ml £7.49

**Hypermellose**

**INDICATIONS AND DOSE**

- **Tear deficiency**
  - TO THE EYE
  - Child: Apply as required
  - Adult: Apply as required

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose hypermellose eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

- **Eye drops**
  - **Excipients**: May contain Benzalkonium chloride, disodium edetate
  - Hypermellose (Non-proprietary)
    - Hypermellose 3 mg per 1 ml
    - Hypermellose 0.3% eye drops
      - preserved free | 10 ml £5.75
      - preserved 0.3% eye drops | 10 ml [P] £1.21 DT = £1.45 | 10 ml £0.99 DT = £1.45
    - Artelac (Bausch & Lomb UK Ltd)
      - Hypermellose 3.2 mg per 1 ml
      - Artelac Single Dose Unit 0.32% eye drops
        - 5 ml unit dose [P] £16.95 DT = £16.95 | 60 unit dose [P] £32.85
      - Artelac 0.32% eye drops | 10 ml [P] £4.99 DT = £4.99
    - Hydromoor (Rayner Pharmaceuticals Ltd)
      - Hydromoor 0.3% eye drops 0.4ml unit dose
        - preservative free | 30 unit dose [P] £35.75
    - Hypermellose (Aspire Pharma Ltd)
      - Hypermellose 3 mg per 1 ml
      - PF Drops Hypermellose 0.3% eye drops
        - preservative free | 10 ml £5.75
    - Hypronol (Ennogen Healthcare Ltd)
      - Hypronol 3 mg per 1 ml
      - Hypronol 0.3% eye drops preservative free
        - 10 ml £4.55
    - Isopto Plain (Alcon Eye Care Ltd)
      - Hypronol 5 mg per 1 ml
      - Isopto Plain 0.5% eye drops
        - 10 ml [P] £0.81 DT = £0.81
    - Tear-Lac (Scope Ophthalmics Ltd)
      - Hypronol 3 mg per 1 ml
      - Tear-Lac Hypronol 0.3% eye drops
        - preservative free | 10 ml £5.80
    - Xaloin Hydrate (Visufarma UK Ltd)
      - Hypronol 3 mg per 1 ml
      - Xaloin Hydrate 0.3% eye drops
        - preservative free | 10 ml £4.69

Hypromellose with dextran 70

The properties listed below are those particular to the combination only. For the properties of the components please consider, hypermellose above.

**INDICATIONS AND DOSE**

- **Tear deficiency**
  - TO THE EYE
  - Child: Apply as required
  - Adult: Apply as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - **Excipients**: May contain Benzalkonium chloride, disodium edetate
  - Tears Naturale (Alcon Eye Care Ltd)
    - Dextran 70 1 mg per 1 ml, Hypermellose 3 mg per 1 ml
      - Tears Naturale eye drops | 15 ml [P] £3.89 DT = £1.89
      - Tears Naturale eye drops 0.4ml unit dose | 28 unit dose [P] £13.26 DT = £13.26

Liquid paraffin with white soft paraffin and wool alcohols

**INDICATIONS AND DOSE**

- **Dry eye conditions**
  - TO THE EYE
  - Child: Apply as required, best suited for application before sleep
  - Adult: Apply as required, best suited for application before sleep

**PATIENT AND CARER ADVICE**

May cause temporary visual disturbance. Should not be used during contact lens wear.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye ointment**
  - Lacri-Lube (Allergan Ltd)
    - Wool alcohols 2 per gram, Liquid paraffin 425 mg per 1 gram, White soft paraffin 573 mg per 1 gram
      - Lacri-lube eye ointment | 3.5 gram [P] £3.01 | 5 gram [P] £3.98

Paraffin, yellow, soft

**INDICATIONS AND DOSE**

- **Eye surface lubrication**
  - TO THE EYE
  - Child: Apply every 2 hours as required
  - Adult: Apply every 2 hours as required

**PATIENT AND CARER ADVICE**

Ophthalmic preparations may cause temporary visual disturbance. Should not be used during contact lens wear.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Eye ointment**
  - Paraffin, yellow, soft (Non-proprietary)
    - Liquid paraffin 100 mg per 1 gram, Wool fat 100 mg per 1 gram, Yellow soft paraffin 800 mg per 1 gram
      - Simple eye ointment | 4 gram [P] £18.57 DT = £18.57

Polyvinyl alcohol

**INDICATIONS AND DOSE**

- **Tear deficiency**
  - TO THE EYE
  - Child: Apply as required
  - Adult: Apply as required

www.getintopharma.com
**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose polyvinyl alcohol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

- **EXCipients:** May contain benzalkonium chloride, disodium edetate
- **Liquifilm Tears** (Allergan Ltd)
  - Polyvinyl alcohol 14 mg per 1 ml
  - Liquidfilm Tears 1.4% eye drops | 15 ml £1.93
  - Liquidfilm Tears 1.4% eye drops 0.4ml unit dose preservative free | 30 unit dose £0.35
- **Refresh Ophthalmic** (Allergan Ltd)
  - Polyvinyl alcohol 14 mg per 1 ml
  - Refresh Ophthalmic 1.4% eye drops | 30 unit dose £2.25
- **Sno Tears** (Bausch & Lomb UK Ltd)
  - Polyvinyl alcohol 14 mg per 1 ml
  - Sno Tears 1.4% eye drops | 10 ml £1.06

**INDICATIONS AND DOSE**

**Dry eye conditions**

- **Adult:** Apply as required, use 0.9% eye preparations
- **Child:** Apply as required, use 0.9% eye preparations

**Sodium chloride**

**INDICATIONS AND DOSE**

**Tear deficiency | Ocular lubricants and astringents | Irrigation, including first-aid removal of harmful substances | Intra-ocular or topical irrigation during surgical procedures**

- **TO THE EYE**
- **Adult:** Use 5% eye preparations (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose sodium chloride eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, eye ointment

**Eye drops**

- **Sodium chloride (Non-proprietary)**
  - Sodium chloride 50 mg per 1 ml
  - Sodium chloride 5% eye drops | 10 ml £25.25

- **Oemstra (Ennogen Healthcare Ltd)**
  - Sodium chloride 50 mg per 1 ml
  - Hypersal 5% eye drops | 10 ml £25.25

**Sodium hyaluronate**

**INDICATIONS AND DOSE**

**Dry eye conditions**

- **TO THE EYE**
- **Adult:** Apply as required

**PRESCRIBING AND DISPENSING INFORMATION** Some preparations are contained in units which are resealable and may be used for up to 12 hours. Although multi-dose sodium hyaluronate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Eye drops

- **Artelac Rebalance** (Bausch & Lomb UK Ltd)
  - Artelac Rebalance 0.15% eye drops | 10 ml £4.00

- **Artelac Splash** (Bausch & Lomb UK Ltd)
  - Artelac Splash 0.2% eye drops 0.5ml unit dose | 30 unit dose £0.70
  - 60 unit dose £1.20

- **Blink Intensive** (AMO UK Ltd)
  - Blink Intensive Tears 0.2% eye drops 0.4ml unit dose | 20 unit dose £2.97
  - Blink Intensive Tears 0.2% eye drops | 10 ml £2.97

- **Clinitas** (Alltacor Ltd)
  - Clinitas Multi 0.4% eye drops preservative free | 10 ml £6.99
  - Clinitas 0.4% eye drops 0.5ml unit dose | 30 unit dose £5.70

- **Evolve HA** (Medicom Healthcare Ltd)
  - Evolve HA 0.2% eye drops preservative free | 10 ml £5.99
  - Hy-Opt (Alissa Healthcare Research Ltd)
  - Hy-Opt 0.1% eye drops preservative free | 10 ml £8.50
  - Hy-Opt 0.2% eye drops preservative free | 10 ml £9.50

- **Hyabak** (Thea Pharmaceuticals Ltd)
  - Hyabak 0.15% eye drops preservative free | 10 ml £7.99

- **Hycosan** (Scope Ophthalmics Ltd)
  - Hycosan Extra 0.2% eye drops | 1.5 ml
  - Hycosan 0.1% eye drops | 7.5 ml

- **Hydromed** (Farmigea S.P.A.)
  - Hydromed 0.2% eye drops preservative free | 10 ml £5.60
  - Hydromed 0.2% eye drops 0.5ml unit dose preservative free | 30 unit dose £5.60

- **Hylo-Comod** (Scope Ophthalmics Ltd)
  - Hylo-Comod 0.1% eye drops preservative free | 10 ml £8.50
  - Hylo-Forté 0.2% eye drops preservative free | 10 ml £9.50

- **Hylo-Fresh** (Scope Ophthalmics Ltd)
  - Hylo-Fresh 0.03% eye drops preservative free | 10 ml £4.95

- **Lubristil** (Rayner Pharmaceuticals Ltd)
  - Lubristil 0.15% eye drops 0.3ml unit dose preservative free | 20 unit dose £4.99

- **Ocu-Lube HA** (Sai-Meds Ltd)
  - Ocu-Lube HA 0.1% eye drops preservative free | 10 ml £8.00

- **OcuSan** (Agepha Pharma S.r.o.)
  - OcuSan 0.2% eye drops 0.5ml unit dose | 20 unit dose £5.41

- **Optive Fusion** (Allergan Ltd)
  - Optive Fusion 0.1% eye drops | 10 ml £7.49
Eye infections

Eye, infections

Most acute superficial eye infections can be treated topically. Blepharitis and conjunctivitis are often caused by staphylococci; keratitis and endophthalmitis may be bacterial, viral, or fungal.

Bacterial blepharitis is treated by application of an antibacterial eye ointment to the conjunctival sac or to the lid margins. Systemic treatment may occasionally be required and is usually undertaken after culturing organisms from the lid margin and determining their antimicrobial sensitivity; antibiotics such as the tetracyclines given for 3 months or longer may be appropriate.

Sodium hyaluronate and trehalose

21-Nov-2017

**INDICATIONS AND DOSE**

Dry eye conditions

- TO THE EYE
- Adult: Apply 1 drop 4–6 times a day

**PRESCRIBING AND DISPENSING INFORMATION** Sodium hyaluronate and trehalose preparations do not contain preservatives; multi-dose preparation can be used for up to 3 months.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - Thealoz Duo (Thea Pharmaceuticals Ltd)
  - Thealoz Duo eye drops preservative free | 10 ml £8.99
  - Thealoz Duo UD eye drops 0.4ml unit dose preservative free | 30 unit dose £6.99

**Soybean oil**

**INDICATIONS AND DOSE**

Dry eye conditions

- TO THE EYE
- Child: Apply up to 4 times a day
- Adult: Apply up to 4 times a day

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - Emustil (Rayner Pharmaceuticals Ltd)
  - Emustil eye drops 0.3ml unit dose preservative free | 20 unit dose £6.22

3 Eye infections

Antibacterials for eye infections

Bacterial eye infections are generally treated topically with eye drops and eye ointments. Systemic administration is sometimes appropriate in blepharitis.

Chloramphenicol p. 1173 has a broad spectrum of activity and is the drug of choice for superficial eye infections. Chloramphenicol eye drops are well tolerated and the recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia is not well founded.

Other antibacterials with a broad spectrum of activity include the quinolones, ciprofloxacin p. 1172, levofloxacin p. 1172, moxifloxacin p. 1172, and ofloxacin p. 1172; the aminoglycosides, gentamicin p. 1171 and tobramycin p. 1171 are also active against a wide variety of bacteria. Gentamicin, tobramycin, quinolones (except moxifloxacin), and polymyxin B are effective for infections caused by *Pseudomonas aeruginosa*.

Ciprofloxacin eye drops are licensed for corneal ulcers; intensive application (especially in the first 2 days) is required throughout the day and night.

Azithromycin eye drops p. 1171 are licensed for trachomatous conjunctivitis caused by *Chlamydia trachomatis* and for purulent bacterial conjunctivitis. *Trachoma* which results from chronic infection with *Chlamydia trachomatis* can be treated with azithromycin by mouth [unlicensed indication].

Fusidic acid is useful for staphylococcal infections. Propamidine isethionate p. 1173 is of little value in bacterial infections but is used by specialists to treat the rare, but potentially sight-threatening, condition of *actinomycetoma keratitis* [unlicensed indication].

Cefuroxime p. 1171 can be administered by intracameral injection for the prophylaxis of endophthalmitis following cataract surgery.

**With corticosteroids**

Many antibacterial preparations also incorporate a corticosteroid but such mixtures should not be used unless a patient is under close specialist supervision. In particular they should not be prescribed for undiagnosed ‘red eye’ which is sometimes caused by the herpes simplex virus and may be difficult to diagnose.

Administration

Frequency of application depends on the severity of the infection and the potential for irreversible ocular damage; antibacterial eye preparations are usually administered as follows:

- **Eye drops**, apply 1 drop at least every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing.
- **Eye ointment**, apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

Antifungals for eye infections

Fungal infections of the cornea are rare but can occur after agricultural injuries, especially in hot and humid climates. Orbital mycosis is rarer, and when it occurs it is usually because of direct spread of infection from the paranasal sinuses. Increasing age, debility, or immunosuppression can
encourage fungal proliferation. The spread of infection through blood occasionally produces metastatic endophthalmitis.

Many different fungi are capable of producing ocular infection; they can be identified by appropriate laboratory procedures.

Antifungal preparations for the eye are not generally available. Treatment will normally be carried out at specialist centres, but requests for information about supplies of preparations not available commercially should be addressed to the Strategic Health Authority (or equivalent in Scotland or Northern Ireland), or to Moorfields Eye Hospital, 162 City Road, London EC1V 2PD (tel. (020) 7253 3411) or www.moorfields.nhs.uk.

Antivirals for eye infections

Herpes simplex infections producing, for example, dendritic corneal ulcers can be treated with aciclovir p. 1174 or ganciclovir p. 1174. Aciclovir eye ointment is used in combination with systemic treatment for ophthalmic zoster.

Slow-release ocular implants containing ganciclovir (available on a named-patient basis from specialist importing companies) may be inserted surgically to treat immediate sight-threatening CMV retinitis. Local treatments do not protect against systemic infection or infection in the other eye. See systemic treatment of CMV retinitis.

3.1 Bacterial eye infection

ANTIBACTERIALS > AMINOGLYCOSIDES

Gentamicin

- INDICATIONS AND DOSE

  Bacterial eye infections

  ➤ TO THE EYE

  ➤ Child: Apply 1 drop at least every 2 hours in severe infection, reduce frequency as infection is controlled and continue for 48 hours after healing, frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient

  ➤ Adult: Apply 1 drop at least every 2 hours, reduce frequency as infection is controlled and continue for 48 hours after healing, frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient

  ➤ INTERACTIONS ➔ Appendix 1: aminoglycosides

  ➤ PRESCRIBING AND DISPENSING INFORMATION

  Eye drops may be sourced as a manufactured special or from specialist importing companies.

- MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug. Forms available from specialist importing companies include:

  Ear/eye drops solution

  EXCipients: May contain benzalkonium chloride

  ➤ Gentamicin (Non-proprietary) Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml

  0.3% ear/eye drops | 10 ml

  £2.63 DT = £2.47

Tobramycin

- INDICATIONS AND DOSE

  Local treatment of infections

  ➤ TO THE EYE

  ➤ Child 1–17 years: Apply twice daily for 6–8 days

Bacterial eye infection 1171

Qty

Adult: Apply twice daily for 6–8 days

Local treatment of infections (severe infection)

➤ TO THE EYE

➤ Child 1–17 years: Apply 4 times a day for first day, then apply twice daily for 5–7 days

➤ Adult: Apply 4 times a day for first day, then apply twice daily for 5–7 days

➤ INTERACTIONS ➔ Appendix 1: aminoglycosides

➤ MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug.

  Powder for solution for injection

  ➤ Aprokam (Thea Pharmaceuticals Ltd) Cefuroxime (as Cefuroxime sodium) 50 mg Aprokam 50 mg powder for solution for injection vials | 10 vial

  £49.95

ANTIBACTERIALS > MACROLIDES

Azithromycin

- INDICATIONS AND DOSE

  Trachomatous conjunctivitis caused by Chlamydia trachomatis Purulent bacterial conjunctivitis

  ➤ TO THE EYE

  ➤ Child: Apply twice daily for 3 days, review if no improvement after 3 days of treatment

  ➤ Adult: Apply twice daily for 3 days, review if no improvement after 3 days of treatment

  ➤ INTERACTIONS ➔ Appendix 1: macrolides
### Ciprofloxacin > QUINOLONES

**INDICATIONS AND DOSE**

**Superficial bacterial eye infection**
- **Child:** Apply 4 times a day for maximum duration of treatment 21 days
- **Adult:** Apply 4 times a day for maximum duration of treatment 21 days
- **TO THE EYE USING EYE OINTMENT**
  - **Child 1-17 years:** Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
  - **Adult:** Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
- **SUPERFICIAL BACTERIAL EYE INFECTION (SEVERE INFECTION)**
  - **TO THE EYE USING EYE DROP**
  - **Child:** Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days
  - **Adult:** Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days
- **Corneal ulcer**
  - **TO THE EYE USING EYE DROP**
  - **Child:** Apply every 15 minutes for 6 hours, then apply every 30 minutes for the remainder of day 1, then apply every 1 hour on day 2, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night
  - **Adult:** Apply every 15 minutes for 6 hours, then apply every 30 minutes for the remainder of day 1, then apply every 1 hour on day 2, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night
- **TO THE EYE USING EYE OINTMENT**
  - **Child 1-17 years:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night
  - **Adult:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night

**SIDE-EFFECTS**
- **UNLICENSED USE** Eye ointment not licensed for use in children under 1 year.
- **INTERACTIONS** → Appendix 1: quinolones
- **SIDE-EFFECTS**
  - **Rare or very rare** Ear pain
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises caution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Eye drops**
  - **Exipients:** May contain Benzalkonium chloride
  - **Ciloxan (Novartis Pharmaceuticals UK Ltd)**
    - Ciprofloxacin (as Ciprofloxacin hydrochloride) 3 mg per 1 ml
  - **Ciloxan 0.3% eye drops | 5 ml [FCA] £4.70 DT + £4.70**

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### Levofloxacin

**INDICATIONS AND DOSE**

**Local treatment of eye infections**
- **TO THE EYE**
  - **Child 1-17 years:** Apply every 2 hours for first 2 days, to be applied maximum 8 times a day, then apply 4 times a day for 3 days
  - **Adult:** Apply every 2 hours for first 2 days, to be applied maximum 8 times a day, then apply 4 times a day for 3 days
- **INTERACTIONS** → Appendix 1: quinolones
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Although multi-dose levofloxacin eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **Exipients:** May contain Benzalkonium chloride
    - **Levofloxacin (Non-proprietary)**
      - Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
        - Levofloxacin 5mg/ml eye drops | 5 ml [FCA] £6.95 DT + £6.95
      - **Ofatux (Santen UK Ltd)**
        - Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
          - Ofatux 5mg/ml eye drops 0.3ml unit dose | 30 unit dose [FCA] £17.95 DT + £17.95
          - Ofatux 5mg/ml eye drops | 5 ml [FCA] £6.95 DT + £6.95

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### Moxifloxacin

**INDICATIONS AND DOSE**

**Local treatment of infections**
- **TO THE EYE**
  - **Child:** Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days
  - **Adult:** Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days
- **INTERACTIONS** → Appendix 1: quinolones
- **SIDE-EFFECTS**
- **UNLICENSED USE** Eye ointment not licensed for use in children under 1 year.
- **INTERACTIONS** → Appendix 1: quinolones
- **SIDE-EFFECTS**
  - **Rare or very rare** Conjunctival haemorrhage
  - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises caution.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Eye drops**
  - **Moxivig (Novartis Pharmaceuticals UK Ltd)**
    - Moxifloxacin (as Moxifloxacin hydrochloride) 5 mg per 1 ml
      - Moxivig 0.5% eye drops | 5 ml [FCA] £9.80 DT + £9.80

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www.getintopharma.com
**Chloramphenicol**

**DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

**Superficial eye infections**

- **TO THE EYE USING EYE DROP**
  - Child: Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient
  - Adult: Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient

- **TO THE EYE USING EYE OINTMENT**
  - Child: Apply daily, to be applied at night (if eye drops used during the day), alternatively apply 3–4 times a day, if ointment used alone
  - Adult: Apply daily, to be applied at night (if eye drops used during the day), alternatively apply 3–4 times a day, if ointment used alone

**INTERACTIONS**

- **Appendix 1: chloramphenicol**
- **SIDE-EFFECTS** Angioedema • bone marrow disorders • eye stinging • fever • paraesthesia • skin reactions
- **PREGNANCY** Avoid unless essential—no information on topical use but risk of “neonatal grey-baby syndrome” with oral use in third trimester.
- **BREAST FEEDING** Avoid unless essential—*theoretical* risk of bone–marrow toxicity.
- **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose chloramphenicol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**SIDE-EFFECTS**

- **UNLICENSED USE** Not licensed for *Acanthamoeba keratitis* infections.
- **SIDE-EFFECTS** Eye discomfort • vision blurred
- **PREGNANCY** Manufacturer advises avoid unless essential—no information available.

**EXCEPTIONS TO LEGAL CATEGORY** Chloramphenicol 0.5% eye drops (in max. pack size 10 mL) and 1% eye ointment (in max. pack size 4 g) can be sold to the public for treatment of acute bacterial conjunctivitis in adults and children over 2 years; max. duration of treatment 5 days.
3.2 Viral eye infection  
3.2a Ophthalmic herpes simplex

### ANTIVIRALS > NUCLEOSIDE ANALOGUES

#### Aciclovir  
(Acyclovir)

- **INDICATIONS AND DOSE**  
  Herpes simplex infection (local treatment)  
  - TO THE EYE USING EYE OINTMENT  
  - Child: Apply 1 centimetre times a day continue for at least 3 days after complete healing  
  - Adult: Apply 1 centimetre times a day continue for at least 3 days after complete healing

- **INTERACTIONS**  
  → Appendix 1: aciclovir

- **SIDE-EFFECTS**
  - Common or very common: Eye inflammation - eye pain

- **PATIENT AND CARER ADVICE**  
  Medicines for Children leaflet: Aciclovir eye ointment for herpes simplex infections www.medicinesforchildren.org.uk/aciclovir-eye-ointment-herpes-simplex-infection-0

- **MEDICINAL FORMS**  
  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye ointment**
    - Zovirax (GlaxoSmithKline UK Ltd)  
      Aciclovir 30 mg per 1 gram  
      Zovirax 3% ophthalmic ointment  
      4.5 gram  
      £3.34 DT = £3.34

- **Ganciclovir**  
  31-May-2018

- **INDICATIONS AND DOSE**  
  Acute herpetic keratitis  
  - TO THE EYE  
  - Adult: Apply 5 times a day until healing complete, then apply 3 times a day for a further 7 days, treatment does not usually exceed 21 days

  - **INTERACTIONS**  
    → Appendix 1: ganciclovir

  - **SIDE-EFFECTS**
    - Common or very common: Eye stinging - punctate keratitis

  - **ALLERGY AND CROSS-SENSITIVITY**  
    Contra-indicated in patents hypersensitive to valganciclovir, aciclovir, or valaciclovir.

  - **CONCEPTION AND CONTRACEPTION**  
    As teratogenicity and impaired fertility observed in animal studies with oral and intravenous ganciclovir, manufacturer advises women of childbearing potential should use effective contraception during treatment; men with partners of childbearing

### Eye procedures

#### 4 Eye procedures

### Nucleoside analogues

#### Mydriatics and cycloplegics

**Overview**  
Antimuscarinics dilate the pupil and paralyse the ciliary muscle; they vary in potency and duration of action.

- Short-acting, relatively weak mydriatics, such as tropicamide 0.5% below (action lasts for 4–6 hours), facilitate the examination of the fundus of the eye. Longer-acting options include cyclopentolate hydrochloride 1% p. 1166 (action up to 24 hours) or atropine sulfate p. 1166 (action up to 7 days).

- Phenylephrine hydrochloride p. 1175 is used for mydriasis in diagnostic or therapeutic procedures; mydriasis occurs within 60–90 minutes and lasts up to 5–7 hours.

Mydriatics and cycloplegics are used in the treatment of anterior uveitis, usually as an adjunct to corticosteroids. Atropine sulfate is used in anterior uveitis mainly to prevent posterior synechiae and to relieve ciliary spasm; cyclopentolate hydrochloride or homatropine hydrobromide p. 1166 (action up to 3 days) can also be used and may be preferred because they have a shorter duration of action.

#### Other drugs used for Eye procedures

- Apraclonidine, p. 1187

### Antimuscarinics

#### Tropicamide

- **INDICATIONS AND DOSE**  
  Fundoscopy  
  - TO THE EYE  
  - Child: 0.5% eye drops to be applied 20 minutes before examination  
  - Adult: (consult product literature)

- **INTERACTIONS**  
  → Appendix 1: tropicamide

- **SIDE-EFFECTS**  
  Eye erythema - eye irritation (on prolonged administration) - eye pain - headache - hypotension - nausea - syncope - vision blurred

- **PRESCRIBING AND DISPENSING INFORMATION**  
  Although multi-dose tropicamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**  
  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye drops**
    - EXCIPIENTS: May contain Benzalkonium chloride, edetic acid (edta)  
      Mydriacyl (Alcon Eye Care Ltd)  
      Tropicamide 10 mg per 1 ml  
      Mydriacyl 1% eye drops  
      5 ml  
      £1.60
MIOTICS > PARASYMPATHOMIMETICS

Acetylcholine chloride

INICATIONS AND DOSE
Cataract surgery | Penetrating keratoplasty | Iridectomy | Anterior segment surgery requiring rapid complete miosis

TO THE EYE
Adult: (consult product literature)

CAUTIONS
- Asthma • gastro-intestinal spasm • heart failure • hyperthyroidism • parkinsonism • peptic ulcer • urinary-tract obstruction
- SIDE-EFFECTS
  - Bradycardia • corneal decompensation • corneal oedema • dyspnoea • flushing • hyperhidrosis • hypotension
- PREGNANCY
  - Avoid unless potential benefit outweighs risk—no information available.
- BREAST FEEDING
  - Avoid unless potential benefit outweighs risk—no information available.

ME DI C INAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
- Irrigation
  - Miochol-E (Bausch & Lomb UK Ltd)
  - Acetylcholine chloride 20 mg
  - Miochol-E 20mg powder and solvent for solution for intraocular irrigation vials | 1 vial (P00) £7.28
  - Miphetil (Farmitalia Zambon Ltd)
  - Acetylcholine chloride 20 mg
  - Miphetil 20mg powder and solvent for solution for intraocular irrigation ampoules | 6 ampoules (P00) €43.68
  - (Hospital only)

SYMPATHOMIMETICS > VASOCONSTRICTOR

Phenylephrine hydrochloride

INICATIONS AND DOSE
Mydriasis
- TO THE EYE
- Child: Apply 1 drop, to be administered before procedure, a drop of proxymetacaine topical anaesthetic may be applied to the eye a few minutes before using phenylephrine to prevent stinging
- Adult: Apply 1 drop, to be administered before procedure, then apply 1 drop after 60 minutes if required, a drop of topical anaesthetic may be applied to the eye a few minutes before using phenylephrine to prevent stinging

CONTRA-INDICATIONS
- 10% strength eye drops in children • 10% strength eye drops in elderly • aneurysms • cardiovascular disease • hypertension • thyrotoxicosis

CAUTIONS
- Asthma • cerebral arteriosclerosis (in adults) • corneal epithelial damage • darkly pigmented iris is more resistant to pupillary dilation and caution should be exercised to avoid overdosage • diabetes (avoid eye drops in long-standing diabetes) • mydriasis can precipitate acute angle-closure glaucoma in a few patients, usually over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber • mydriasis can precipitate acute angle-closure glaucoma in the very few children who are predisposed to the condition because of a shallow anterior chamber • ocular hyperaemia • susceptibility to angle-closure glaucoma

INTERACTIONS
- Appendix 1: sympathomimetics, vasoconstrictor
- SIDE-EFFECTS
  - Arrhythmias • conjunctivitis allergic • eye discomfort • hypertension • myocardial infarction (usually after use of 10% strength in patients with pre-existing
cardiovascular disease) • palpitations • periorbital pallor (in children) • vision disorders

- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** Use only if potential benefit outweighs risk—no information available.
- **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose phenylephrine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
- **PATIENT AND CARER ADVICE** Driving and skilled tasks Patients should be warned not to undertake skilled tasks (e.g. driving) until vision clears after mydriasis.

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

#### Eye drops
- May contain Disodium edetate, sodium metabisulphite
- **Phenylephrine hydrochloride** (Baush & Lomb UK Ltd)
  - Phenylephrine hydrochloride 25 mg per 1 ml Minims
  - Phenylephrine hydrochloride 2.5% eye drops 0.5ml unit dose | 20 unit dose £11.87
  - Phenylephrine hydrochloride 100 mg per 1 ml Minims
  - Phenylephrine hydrochloride 10% eye drops 0.5ml unit dose | 20 unit dose £11.87

#### Tropicamide with phenylephrine

The properties listed below are those particular to the combination only. For the properties of the components please consider, phenylephrine hydrochloride p. 1175, tropicamide p. 1174.

### INDICATIONS AND DOSE
- Pre-operative mydriasis | Diagnostic procedures when monotherapy insufficient
  - **TO THE EYE**
  - Adult: One insert to be applied into the lower conjunctival sac up to max. 2 hrs before procedure; remove insert within 30 minutes of satisfactory mydriasis, and within 2 hours of application

### INTERACTIONS
- Appendix 1: antiarrhythmics • sympathomimetics, vasoconstrictor • tropicamide

### DIRECTIONS FOR ADMINISTRATION
- Patients with severe dry eyes may require a drop of saline to improve insert tolerance.

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

#### Ophthalmic insert
- **Mydristar** (Thea Pharmaceuticals Ltd)
  - Tropicamide 28 mg, Phenylephrine hydrochloride 5.4 mg Mydristar 5.4mg/0.28mg ophthalmic inserts | 20 insert £84.00

#### Tropicamide with phenylephrine and lidocaine

**INDICATIONS AND DOSE**
- Mydriasis and intraocular anaesthesia during cataract surgery
  - **BY INTRACAMERAL INJECTION**
  - Adult: 0.2 mL for 1 dose, to be injected slowly at the start of the surgical procedure

#### DOSE EQUIVALENCE AND CONVERSION
- Each 0.2 mL dose of Mydristar® solution for injection contains 0.04 mg of tropicamide, 0.62 mg of phenylephrine hydrochloride and 2 mg of lidocaine hydrochloride.

**CONTRA-INDICATIONS**
- Cataract surgery combined with vitrectomy • history of acute, narrow-angle glaucoma • shallow anterior chamber

**CAUTIONS**
- Conditions where systemic exposure to phenylephrine or lidocaine could be harmful (consult product literature) • risk of floppy iris syndrome (consult product literature)

**INTERACTIONS**
- Appendix 1: antiarrhythmics • sympathomimetics, vasoconstrictor • tropicamide

**SIDE-EFFECTS**
- Uncommon: Headache • hyperaemia • hypertension • keratitis

**ALLERGY AND CROSS-SENSITIVITY**
- Contra-indicated in patients with known hypersensitivity to amide-type anaesthetics or atropine derivatives.

**PREGNANCY**
- Manufacturer advises avoid (systemic uptake after administration cannot be excluded)—insufficient data available for phenylephrine and tropicamide in pregnancy; lidocaine crosses the placenta but is not known to be harmful in animal studies.

**BREAST FEEDING**
- Manufacturer advises avoid—no data available for phenylephrine or tropicamide; lidocaine present in milk in small amount.

**PRE-TREATMENT SCREENING**
- Manufacturer advises patients must have demonstrated, at a previous visit, a satisfactory pupil dilatation with topical mydriatic treatment.

**PATIENT AND CARER ADVICE**
- Driving and skilled tasks
- Manufacturer advises patients should be counselled about the effects on driving and driving tasks.

**4.1 Post-operative pain and inflammation**

### Eye, surgical and peri-operative drug use

**Ocular peri-operative drugs**
- Ocular drugs commonly used for the preparation of the eye for surgery, drugs that are injected into the anterior chamber of the eye (intracameral use), is used for the prophylaxis of endophthalmitis after cataract surgery.

- Non-steroidal anti-inflammatory eye drops such as diclofenac sodium p. 1178, flurbiprofen p. 1178, ketorolac trometamol p. 1178, and nepafenac p. 1161, are used for the prophylaxis and treatment of inflammation, pain, and other symptoms associated with ocular surgery or laser treatment of the eye. Bromfenac p. 1178 is used for the treatment of postoperative inflammation following cataract surgery.

- Non-steroidal anti-inflammatory eye drops such as diclofenac sodium p. 1178, flurbiprofen p. 1178, ketorolac trometamol p. 1178, and nepafenac p. 1161, are used for the prophylaxis and treatment of inflammation, pain, and other symptoms associated with ocular surgery or laser treatment of the eye. Bromfenac p. 1178 is used for the treatment of postoperative inflammation following cataract surgery.

- Diclofenac sodium and flurbiprofen are also used to prevent the prophylaxis of endophthalmitis after cataract surgery.

- Apraclonidine p. 1187, an alpha-2-adrenoreceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used to control
increases in intra-ocular pressure associated with ocular surgery and as short-term treatment to reduce intraocular pressure prior to surgery.

Acetylcholine chloride p. 1175, administered into the anterior chamber of the eye during surgery, rapidly produces miosis which lasts approximately 20 minutes. If prolonged miosis is required, it can be applied again.

Intra-ocular sodium hyaluronate p. 1169 and balanced salt solution are used during surgical procedures on the eye.

Povidone-iodine p. 1175 is used for peri-ocular and conjunctival antisepsis before ocular surgery to support postoperative infection control.

**Ocular local anaesthetics**

Oxybuprocaine hydrochloride below and tetracaine below are widely used topical local anaesthetics. Proxymetacaine hydrochloride below causes less initial stinging and is useful for children. Oxybuprocaine hydrochloride or a combined preparation of lidocaine hydrochloride and fluorescein sodium p. 1177 is used for tonometry. Tetracaine produces a more profound anaesthesia and is suitable for use before minor surgical procedures, such as the removal of corneal sutures. It has a temporary disruptive effect on the corneal epithelium. Lidocaine hydrochloride, with or without adrenaline/epinephrine p. 222, is injected into the eyelids for minor surgery. Local anaesthetics should never be used for the management of ocular symptoms.

**ANAESTHETICS, LOCAL**

**Fluorescein with lidocaine**

- **INDICATIONS AND DOSE**

  - Local anaesthetic
    - **TO THE EYE**
    - Adult: Apply as required

- **PRESCRIBING AND DISPENSING INFORMATION**

  Although multi-dose lidocaine and fluorescein eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye drops**
    - **Lidocaine and Fluorescein** (Bausch & Lomb UK Ltd)
      - Fluorescein sodium 2.5 mg per 1 ml
      - Lidocaine hydrochloride 40 mg per 1 ml
      - Minims lidocaine and fluorescein eye drops 0.5ml unit dose [POM] £11.69

**Oxybuprocaine hydrochloride**

(Benoxinate hydrochloride)

- **INDICATIONS AND DOSE**

  - Local anaesthetic
    - **TO THE EYE**
    - Adult: Apply as required

- **CONTRA-INDICATIONS**

  Avoid in preterm neonates

- **INTERACTIONS**

  → Appendix 1: anaesthetics, local

- **PRESCRIBING AND DISPENSING INFORMATION**

  Although multi-dose oxybuprocaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye drops**
    - **Oxybuprocaine hydrochloride** (Bausch & Lomb UK Ltd)
      - Oxybuprocaine hydrochloride 4 mg per 1 ml
      - Minims oxybuprocaine hydrochloride 0.4% eye drops 0.5ml unit dose [POM] £10.56

**Proxymetacaine hydrochloride**

- **INDICATIONS AND DOSE**

  - Local anaesthetic
    - **TO THE EYE**
    - Adult: Apply as required

- **CONTRA-INDICATIONS**

  Avoid in preterm neonates

- **INTERACTIONS**

  → Appendix 1: anaesthetics, local

- **PRESCRIBING AND DISPENSING INFORMATION**

  Although multi-dose proxymetacaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye drops**
    - **Proxymetacaine** (Bausch & Lomb UK Ltd)
      - Proxymetacaine hydrochloride 5 mg per 1 ml
      - Minims proxymetacaine hydrochloride 0.5% eye drops 0.5ml unit dose [POM] £12.12

**Tetracaine**

(Amethocaine)

- **INDICATIONS AND DOSE**

  - Local anaesthetic
    - **TO THE EYE**
    - Adult: Apply as required

- **INTERACTIONS**

  → Appendix 1: anaesthetics, local

- **SIDE-EFFECTS**

  Dermatitis · eye disorders · eye inflammation · paraesthesia

- **SIDE-EFFECTS, FURTHER INFORMATION**

  The systemic toxicity of local anaesthetics mainly involves the central nervous system; systemic side effects unlikely as minimal absorption following topical application.

- **PRESCRIBING AND DISPENSING INFORMATION**

  Although multi-dose tetracaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  - **Eye drops**
    - **Tetracaine** (Bausch & Lomb UK Ltd)
      - Tetracaine hydrochloride 5 mg per 1 ml
      - Minims tetracaine hydrochloride 0.5% eye drops 0.5ml unit dose [POM] £10.57 DT = £10.57
      - Tetracaine hydrochloride 10 mg per 1 ml
      - Minims tetracaine hydrochloride 1% eye drops 0.5ml unit dose [POM] £10.57 DT = £10.57

**Other drugs used for Post-operative pain and inflammation**

Diclofenac sodium, p. 1178

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Bromfenac**

- **INDICATIONS AND DOSE**

  Postoperative inflammation following cataract surgery

  - **TO THE EYE**
    - Adult: (consult product literature)

- **INTERACTIONS**

  → Appendix 1: NSAIDs
### Diclofenac sodium

**INDICATIONS AND DOSE**

Inhibition of intra-operative miosis during cataract surgery (but does not possess intrinsic mydriatic properties) Postoperative inflammation in cataract surgery, strabismus surgery or argon laser trabeculoplasty | Pain in corneal epithelial defects after photorefractive keratectomy, radial keratotomy or accidental trauma | Seasonal allergic conjunctivitis

**SIDE-EFFECTS**

- **Common or very common**: Eye discomfort, - dry eye, - accidental trauma, - photorefractive keratectomy, - seasonal allergic conjunctivitis, - keratic deposits, - rash, - injection site reactions, - pruritus.

**INTERACTIONS**

- **Appendix 1: NSAIDs**

**MEDICINAL FORMS**

- **Eye drops**: May contain Benzalkonium chloride, disodium edetate, propylene glycol.
  - **Voltarol Ophtha (Thea Pharmaceuticals Ltd)**: Diclofenac sodium 1 mg per 1 ml | 5 ml | 900 microgram per 1 ml | 0.4 ml dose
  - **Ocufer (Allergan Ltd)**: Ketorolac trometamol 5 mg per 1 ml | 5 ml | 37.5 micrograms/ml
  - **Acular (Allergan Ltd)**: Flurbiprofen sodium 300 microgram per 1 ml | 40 unit dose

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

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### Flurbiprofen

**INDICATIONS AND DOSE**

Inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties) Control of anterior segment inflammation following postoperative and post-laser trabeculoplasty when corticosteroids contra-indicated

**SIDE-EFFECTS**

- **Common or very common**: Dry eye, eye discomfort, - eye disorders, - headaches.

**INTERACTIONS**

- **Appendix 1: NSAIDs**

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
5 Glaucoma and ocular hypertension

Glaucoma and ocular hypertension

11-Apr-2018

Description of condition

Glaucoma is a group of eye disorders characterised by a loss of visual field associated with pathological cupping of the optic disc and optic nerve damage. While glaucoma is generally linked to raised intraocular pressure, which is the main treatable risk factor, it can also occur when the intraocular pressure is within the normal range. Other risk factors include age, family history, ethnicity, corticosteroid use, myopia, type 2 diabetes mellitus, cardiovascular disease, and hypertension.

The most common form of glaucoma is chronic open-angle glaucoma (also known as primary open-angle glaucoma) where drainage of the aqueous humour through the trabecular meshwork is restricted, and the angle between the iris and the cornea is normal. Initially, this condition tends to be asymptomatic, however, as glaucoma progresses, patients may present with irreversible sight loss or visual field defects. Patients with ocular hypertension (an intraocular pressure greater than 21 mmHg) are at high risk of developing chronic open-angle glaucoma. The diagnosis, monitoring, and management of patients with ocular hypertension, suspected chronic open-angle glaucoma, or chronic open-angle glaucoma should be carried out by a specialist.

Acute angle-closure glaucoma is less common and occurs when the outflow of aqueous humour from the eye is totally obstructed by bowing of the iris against the trabecular meshwork. It is characterised by its abrupt onset of symptoms, and it is a sight-threatening medical emergency that requires urgent reduction of intraocular pressure to prevent loss of vision.

Aims of treatment

The aim of treatment is to control intraocular pressure to prevent the development or progression of glaucoma and subsequent visual field damage, or sight loss.

Ocular hypertension

A topical prostaglandin analogue, such as latanoprost p. 1184, tafluprost p. 1185, travoprost p. 1186, or bimatoprost p. 1184 (a synthetic prostamide), is recommended as first-line treatment in patients with an intraocular pressure of 24 mmHg or greater and who are at risk of visual impairment within their lifetime. When assessing patient’s risk of future visual impairment, the level of intraocular pressure, central corneal thickness measurement, family history, and life expectancy should be taken into consideration. Patients who are not at risk of visual impairment in their lifetime do not require treatment but should be monitored regularly.

If initial treatment with a topical prostaglandin analogue is not tolerated, an alternative prostaglandin analogue should be tried before switching to a topical beta-blocker such as betaxolol p. 1180, levobunolol hydrochloride p. 1180, or timolol maleate p. 1180. If treatment is still not tolerated, alternative options include carbonic anhydrase inhibitors such as brinzolamide p. 1181 or dorzolamide p. 1182, a topical sympathomimetic such as apraclonidine p. 1187 [unlicensed use] or brimonidine tartrate p. 1187, or a topical miotic such as pilocarpine p. 1183 [unlicensed use], given either as monotherapy or as combination therapy.

Alternatives as either monotherapy or combination therapy with drugs from different therapeutic classes (topical beta-blockers, carbonic anhydrase inhibitors, or topical sympathomimetics), should also be offered to patients with an intraocular pressure of 24 mmHg or more whose current treatment is not reducing intraocular pressure sufficiently to prevent the risk of progression to sight loss. The patient’s adherence and drug instillation technique should also be checked. If drug treatment still does not sufficiently reduce intraocular pressure to a satisfactory level, patients should be referred to a consultant ophthalmologist to discuss other options.

Preservative free eye drops should be used in patients who are allergic to preservatives, or those who have clinically significant ocular surface disease and are at high risk of conversion to chronic open-angle glaucoma.

Note: based on cost-effective analysis, NICE guidelines 81 recommend treatment with generic prostaglandin analogues as first-line, and non-generic prostaglandin analogues as third-line if topical beta-blocker treatment is ineffective.

Suspected chronic open-angle glaucoma

In patients with suspected chronic open-angle glaucoma and an intraocular pressure of 24 mmHg or greater, the same treatment recommendations as for the management of ocular hypertension should be followed. Patients with an intraocular pressure below 24 mmHg do not require drug treatment, but should be regularly monitored for changes in intraocular pressure and visual impairment.

Chronic open-angle glaucoma

Topical prostaglandin analogues such as latanoprost p. 1184, tafluprost p. 1185, travoprost p. 1186, or bimatoprost p. 1184 (a synthetic prostamide), are used first-line in patients with confirmed chronic open-angle glaucoma. If first-line treatment does not sufficiently reduce intraocular pressure and the patient’s adherence to treatment and eye drop instillation technique are both satisfactory, treatment with either a topical beta-blocker such as betaxolol p. 1180, levobunolol hydrochloride p. 1180, and timolol maleate p. 1180, a carbonic anhydrase inhibitor such as brinzolamide p. 1181 or dorzolamide p. 1182, a topical sympathomimetic such as apraclonidine p. 1187 or brimonidine tartrate p. 1187, or a combination of these, should be offered. When a particular drug is not tolerated, another drug from a different therapeutic class can be tried. Preservative free eye drops should be used in patients who are allergic to preservatives, or those who have clinically significant ocular surface disease. Alternative treatment options are laser trabeculoplasty or surgery with pharmacological augmentation (with mitomycin p. 919 [unlicensed indication]).

Patients with advanced chronic open-angle glaucoma should be offered surgery with pharmacological augmentation (with mitomycin p. 919 [unlicensed indication]). Treatment with a topical prostaglandin analogue should be initiated and continued until surgery takes place.

If surgery fails to adequately reduce the intraocular pressure, alternative options include drug treatment (a combination of topical drugs from different therapeutic classes may be needed), further surgery, laser trabeculoplasty, or cyclodiode laser treatment.
Betaxolol

**INDICATIONS AND DOSE**

Primary open-angle glaucoma

- **TO THE EYE**
- Adult: Apply twice daily

**CONTRA-INDICATIONS** Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

**CAUTIONS** Patients with corneal disease

**CAUTIONS, FURTHER INFORMATION** Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

**INTERACTIONS** → Appendix 1: beta blockers, selective

**SIDE-EFFECTS**

- Common or very common Eye discomfort - eye disorders - vision disorders
- Uncommon Dry eye - eye inflammation - rhinitis
- Rare or very rare Cataract - rhinorrhea - skin reactions
- Frequency not known Angioedema - hypersensitivity

**SIDE-EFFECTS, FURTHER INFORMATION** Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose betaxolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate, sodium metabisulfite

- Betagan (Allergan Ltd)

Levobunolol hydrochloride 5 mg per 1 ml Betagan 0.5% eye drops 5 ml [POD] £1.85 DT = £1.85

Betagan Unit Dose 0.5% eye drops 0.4ml unit dose | 30 unit dose [POD] £9.98 DT = £9.98

**Levobunolol hydrochloride**

**INDICATIONS AND DOSE**

Primary open-angle glaucoma

- **TO THE EYE**
- Adult: Apply 1–2 times a day

**CONTRA-INDICATIONS** Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

**CAUTIONS** Patients with corneal disease

**CAUTIONS, FURTHER INFORMATION** Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

**INTERACTIONS** → Appendix 1: beta blockers, non-selective

**SIDE-EFFECTS**

- Common or very common Eye discomfort - eye disorders - eye inflammation
- Frequency not known Dry eye - eye disorders - vision blurred

**SIDE-EFFECTS, FURTHER INFORMATION** Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose levobunolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate, sodium metabisulfite

- Betagan (Allergan Ltd)

Levobunolol hydrochloride 5 mg per 1 ml Betagan 0.5% eye drops 5 ml [POD] £1.85 DT = £1.85

Betagan Unit Dose 0.5% eye drops 0.4ml unit dose | 30 unit dose [POD] £9.98 DT = £9.98

**Timolol maleate**

**INDICATIONS AND DOSE**

Reduction of intra-ocular pressure in primary open-angle glaucoma

- **TO THE EYE**
- Adult: Apply twice daily

**TIMOPTOL-LA ®**

Reduction of intra-ocular pressure in primary open-angle glaucoma

- **TO THE EYE**
- Adult: Apply once daily

**TIOPEX ®**

Reduction of intra-ocular pressure in primary open-angle glaucoma

- **TO THE EYE**
- Adult: Apply once daily, to be applied in the morning

**CONTRA-INDICATIONS** Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

**CAUTIONS** Consider also cautions listed for systemically administered beta blockers.

**INTERACTIONS** → Appendix 1: beta blockers, non-selective

**SIDE-EFFECTS**

- Common or very common Eye discomfort - eye disorders - eye inflammation - vision disorders
- Rare or very rare Angioedema

**SIDE-EFFECTS, FURTHER INFORMATION** Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose timolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate, sodium metabisulfite

- Betoptic (Novartis Pharmaceuticals UK Ltd)

Levobunolol hydrochloride 2.5 mg per 1 ml Betoptic 2.5% suspension eye drops 25% eye drops [POD] £0.25 DT = £0.25

Betoptic 2.5% eye drops suspension 0.25% unit dose | 50 unit dose [POD] £13.77 DT = £13.77

Betoptic (as Betaxolol hydrochloride) 5 mg per 1 ml Betoptic 0.5% eye drops 5 ml [POD] £1.90 DT = £1.90

**Scottish Medicines Consortium (SMC) decisions**

When used by eye the *Scottish Medicines Consortium* has advised (February 2014) that timolol gel eye drops (*Tiopex* ®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma who have proven sensitivity to preservatives.

**National Funding/Access Decisions Tiopex®**

- Scottish Medicines Consortium (SMC) decisions

- When used by eye the *Scottish Medicines Consortium* has advised (February 2014) that timolol gel eye drops (*Tiopex* ®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma who have proven sensitivity to preservatives.
CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

indications and dose
Reduction of intra-ocular pressure in open-angle glaucoma
Reduction of intra-ocular pressure in secondary glaucoma
Reduction of intra-ocular pressure peripheratively in angle-closure glaucoma

By mouth using immediate-release medicines, or by intravenous injection, or by intramuscular injection

Adult: 0.25–1 g daily in divided doses, intramuscular injection preferably avoided because of alkalinity

Glaucoma
By mouth using modified-release medicines
Adult: 250–500 mg daily

Epilepsy
By mouth using immediate-release medicines, or by intravenous injection, or by intramuscular injection
Adult: 0.25–1 g daily in divided doses, intramuscular injection preferably avoided because of alkalinity

contra-indications
Adrenocortical insufficiency
hypochloremic acidosis
hypokalaemia
hypotraumaemia
long-term administration in chronic angle-closure glaucoma

cautions
Avoid extravasation at injection site (risk of necrosis)
diabetes mellitus
elderly
impaired alveolar ventilation (risk of acidosis)
not generally recommended for long-term use
pulmonary obstruction (risk of acidosis)
renal calculi

interactions
Appendix 1: acetazolamide

side-effects

specific side-effects

frequency not known

specify possible side-effects

adverse effects, further information

Acetazolamide is a sulfonamide derivative; blood disorders, rashes, and other sulfonamide-related side-effects occur occasionally — patients should be told to report any unusual skin rash. If electrolyte disturbances and metabolic acidosis occur, these can be corrected by administering bicarbonate.

Allergy and cross-sensitivity
Contra-indicated if history of sulfonamide hypersensitivity.

pregnancy
Manufacturer advises avoid, especially in first trimester (toxicity in animal studies).

breast feeding
Amount too small to be harmful.

Hepatic impairment
Manufacturer advises avoid.

renal impairment
Avoid — risk of metabolic acidosis.

monitoring requirements
Monitor blood count and plasma electrolyte concentrations with prolonged use.

medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Eye gel

Excipients: May contain benzodiazepine bromide

Timolol (as Timolol maleate) 2.5 mg per 1 ml
Timolol-LA 0.25% ophthalmic gel-forming solution

Timolol (as Timolol maleate) 5 mg per 1 ml
Timolol-LA 0.5% ophthalmic gel-forming solution

Eye drops

Excipients: May contain benzalkonium chloride

Timolol maleate (Non-proprietary)

Timolol (as Timolol maleate) 2.5 mg per 1 ml
Timolol 0.25% eye drops
5 ml (PO) £0.98 DT = £0.98

Timolol (as Timolol maleate) 5 mg per 1 ml
Timolol 0.5% eye drops
5 ml (PO) £1.00 DT = £1.00

Eysano (Aspire Pharma Ltd)

Timolol (as Timolol maleate) 2.5 mg per 1 ml
Eysano 2.5 mg/ml eye drops
5 ml (PO) £8.45 DT = £8.45

Timolol (as Timolol maleate) 5 mg per 1 ml
Eysano 5 mg/ml eye drops
5 ml (PO) £9.65 DT = £9.65

Timolol (as Timolol maleate) 2.5 mg per 1 ml
Timolol 0.25% eye drops
5 ml (PO) £10.98 DT = £10.98

Timolol (as Timolol maleate) 5 mg per 1 ml
Timolol 0.5% eye drops
5 ml (PO) £13.12 DT = £13.12

Timolol (as Timolol maleate) 2.5 mg per 1 ml
Timolol 0.25% eye drops
5 ml (PO) £13.12 DT = £13.12

Timolol (as Timolol maleate) 5 mg per 1 ml
Timolol 0.5% eye drops
5 ml (PO) £13.12 DT = £13.12

Tiopex (Thea Pharmaceuticals Ltd)

Timolol (as Timolol maleate) 1 mg per 1 gram
Tiopex 1 mg/g eye gel 0.4 g unit dose
30 unit dose (PO) £7.49 DT = £7.49

Combinations available:
Bimatoprost with timolol, p. 1184
Brimonidine with timolol, p. 1188
Brinzolamide with timolol, p. 1182
Dorzolamide with timolol, p. 1183
Latanoprost with timolol, p. 1185
Travoprost with timolol, p. 1186

Glucone termal and ocular hypertension 1181

 disorders, leucopenia, nausea, renal colic, renal impairment, renal lesions, severe cutaneous adverse reactions (SCARs), skin reactions, thrombocytopenia, tinnitus, urinary tract discomfort, urine abnormalities, vomiting

frequency not known

Agranulocytosis, drowsiness, myopia, polyuria, taste altered, thirst

Specific side-effects

Médical forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 3

Acetazolamide (Non-proprietary)

Acetazolamide 250 mg Acetazolamide 250 mg tablets
112 tablet (PO) £75.36 DT = £12.81

Powder for solution for injection

Diamox (Advanz Pharma)

Acetazolamide 500 mg Diamox Sodium Parenteral 500 mg powder for solution for injection vials
1 vial (PO) £14.76

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 3, 25

Diamox SR (Advanz Pharma)

Acetazolamide 250 mg Diamox SR 250 mg capsules
30 capsule (PO) £16.66 DT = £16.66

Eyetox (Teva UK Ltd)

Acetazolamide 250 mg Eyetox 250 mg modified-release capsules
30 capsule (PO) £16.60 DT = £16.66

Brinzolamide

indications and dose
Reduction of intra-ocular pressure in oculc hypertension and open-angle glaucoma either as adjunct to beta-blockers or prostaglandin analogues or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated

to the eye

Adult: Apply twice daily, then increased if necessary up to 3 times a day

contra-indications
Hyperchloraemic acidosis

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**1182 Glaucoma and ocular hypertension**

- **CAUTIONS** Renal tubular immaturity or abnormality - systemic absorption follows topical application.
- **INTERACTIONS** → Appendix 1: brinzolamide
- **SIDE-EFFECTS**
  - **Common or very common** Eye discomfort - eye disorders - taste altered - vision disorders
  - **Rare or very rare** Alopecia - angina pectoris - drowsiness - irritability - optic nerve disorder - respiratory disorders - tinnitus
  - **Frequency not known** Appetite decreased - arthralgia - asthma - hypertension - malaise - peripheral oedema - tremor - urinary frequency increased - vertigo
- **SIDE-EFFECTS, FURTHER INFORMATION** Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.
- **PREGNANCY** Avoid—toxicity in animal studies.
- **BREAST FEEDING** Use only if benefit outweighs risk.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid—no information available.
- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - **Brinzolamide (Non-proprietary)**
        - Brinzolamide 10 mg per 1 ml Brinzolamide 10mg/ml eye drops | 5 ml | $6.92 DT = $2.18
        - Azopt (Novartis Pharmaceuticals UK Ltd)
          - Brinzolamide 10 mg per 1 ml Azopt 10mg/ml eye drops | 5 ml | $6.92 DT = $2.18
  - **Eye drops**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - **Timolol (as Timolol maleate)**
        - Timolol (as Timolol maleate) 5 mg per 1 ml, Brinzolamide 10 mg per 1 ml Azarga 10mg/ml mg/ml eye drops | 5 ml | $11.05 DT = $11.05

### Brinzolamide with timolol

The properties listed below are those particular to the combination only. For the properties of the components please consider, brinzolamide p. 1181, timolol maleate p. 1180.

- **INDICATIONS AND DOSE** Raised intra-ocular pressure in open-angle glaucoma or ocular hypertension when beta-blocker alone not adequate
  - **TO THE EYE**
  - **Adult:** Apply twice daily
- **INTERACTIONS** → Appendix 1: beta blockers, non-selective - brinzolamide
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
      - **Azarga** (Novartis Pharmaceuticals UK Ltd)
        - Timolol (as Timolol maleate) 5 mg per 1 ml, Brinzolamide 10 mg per 1 ml Azarga 10mg/ml mg/ml eye drops | 5 ml | $11.05 DT = $11.05

### Dorzolamide

10-Mar-2017

- **INDICATIONS AND DOSE** Raised intra-ocular pressure in ocular hypertension used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated | Open-angle glaucoma used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated | Pseudo-exfoliative glaucoma used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated
  - **TO THE EYE**
  - **Adult:** Apply 3 times a day
  - **Raised intra-ocular pressure in ocular hypertension as adjunct to beta-blocker** | Open-angle glaucoma as adjunct to beta-blocker | Pseudo-exfoliative glaucoma as adjunct to beta-blocker
    - **TO THE EYE**
    - **Adult:** Apply twice daily
- **CONTRA-INDICATIONS** Hyperchloraeamic acidosis
- **CAUTIONS** Chronic corneal defects - history of intra-ocular surgery - history of renal calculi - low endothelial cell count - systemic absorption follows topical application
- **INTERACTIONS** → Appendix 1: dorzolamide
- **SIDE-EFFECTS**
  - **Common or very common** Asthenia - eye discomfort - eye disorders - eye inflammation - headache - nauseae - paraesthesia - taste bitter - vision disorders
  - **Rare or very rare** Angioedema - bronchospasm - dizziness - dry mouth - dyspnoea - epistaxis - local reaction - pain - severe cutaneous adverse reactions (SCARs) - skin reactions - throat irritation - urolithiasis
- **SIDE-EFFECTS, FURTHER INFORMATION** Systemic absorption can cause sulfonamide-like side-effects and may require discontinuation if severe.
- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated if history of sulfonamide hypersensitivity.
- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available.
- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².
**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose dorzolamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS:** May contain Benzalkonium chloride
- **Dorzolamide** (Non-proprietary)
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Eydelto (Aspire Pharma Ltd)
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Eydelto 20mg/ml eye drops | 5 ml [POA] £5.69 DT = £2.38
  - Trusopt (Santen UK Ltd)
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Trusopt 20mg/ml eye drops 0.2ml unit dose preservative free | 60 unit dose [POA] £24.18 DT = £24.18
  - Trusopt 20mg/ml eye drops | 5 ml [POA] £6.33 DT = £2.38

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**Dorzolamide with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dorzolamide p. 1182, timolol maleate p. 1180.

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in ocular hypertension when beta-blockers alone not adequate. Raised intra-ocular pressure in open-angle glaucoma when beta-blockers alone not adequate. Raised intra-ocular pressure in pseudo-exfoliative glaucoma when beta-blockers alone not adequate.

**TO THE EYE**

Adult: Apply up to 4 times a day

**INTERACTIONS** → Appendix 1: beta blockers, non-selective.

- **dorzolamide**

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose dorzolamide with timolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **EXCIPIENTS:** May contain Benzalkonium chloride
- **Timolol with timolol** (Non-proprietary)
  - Timolol (as Timolol maleate) 5 mg per 1 ml, Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Dorzolamide 20mg/ml eye drops / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free | 60 unit dose [POA] £28.59 DT = £28.59
  - Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops | 5 ml [POA] £27.16 DT = £2.04
  - Cosopt (Santen UK Ltd)
  - Timolol (as Timolol maleate) 5 mg per 1 ml, Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free | 60 unit dose [POA] £28.59 DT = £28.59
  - Cosopt 20mg/ml / 5mg/ml eye drops | 5 ml [POA] £10.05 DT = £2.04
  - Cosopt iMulti (Santen UK Ltd)
  - Timolol (as Timolol maleate) 5 mg per 1 ml, Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free | 10 ml [POA] £28.00
  - Eylamdo (Aspire Pharma Ltd.)
  - Timolol (as Timolol maleate) 5 mg per 1 ml, Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Eylamdo 20mg/ml / 5mg/ml eye drops | 5 ml [POA] £14.29 DT = £14.29

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**PILOCARPINE**

**DRUG ACTION** Pilocarpine acts by opening the inefficient drainage channels in the trabecular meshwork.

**INDICATIONS AND DOSE**

Primary angle-closure glaucoma | Some secondary glaucomas

**TO THE EYE**

Adult: Apply up to 4 times a day

**CONTRA-INDICATIONS** Acute inflammatory disease of the anterior segment | acute iritis | anterior uveitis | conditions where pupillary constriction is undesirable | some forms of secondary glaucoma | (where pupillary constriction is undesirable)

**CAUTIONS** A darkly pigmented iris may require a higher concentration of the miotic or more frequent administration and care should be taken to avoid overdose | asthma | cardiac disease | care in conjunctival damage | care in corneal damage | epilepsy | gastrointestinal spasm | hypertension | hyperthyroidism | hypotension | marked vasomotor instability | Parkinson’s disease | peptic ulceration | retinal detachment has occurred in susceptible individuals and those with retinal disease | urinary-tract obstruction

**INTERACTIONS** → Appendix 1: pilocarpine

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea | headache | hyperhidrosis | hypersalivation | nausea | skin reactions | vision disorders | vomiting
- **Frequency not known** Bradycardia | bronchospasm | conjunctival vascular congestion | eye disorder (long term use) | eye disorders | hypotension | lens changes (long term use) | pain | paraesthesia | pulmonary oedema | sensitisation | vitreous haemorrhage

**PREGNANCY** Avoid unless the potential benefit outweighs risk—limited information available.

**BREAST FEEDING** Avoid unless the potential benefit outweighs risk—no information available.

**PRE-TREATMENT SCREENING** Fundus examination is advised before starting treatment with a miotic (retinal detachment has occurred).

**MONITORING REQUIREMENTS** Intra-ocular pressure and visual fields should be monitored in those with chronic simple glaucoma and those receiving long-term treatment with a miotic.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose pilocarpine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**PATIENT AND CARER ADVICE**

Driving and skilled tasks Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

- **EXCIPIENTS:** May contain Benzalkonium chloride
- **Pilocarpine** (Non-proprietary)
  - Pilocarpine hydrochloride 10 mg per 1 ml
  - Pilocarpine hydrochloride 1% eye drops | 10 ml [POA] £22.20 DT = £22.20
  - Pilocarpine hydrochloride 2% eye drops | 10 ml [POA] £22.77 DT = £22.77
  - Pilocarpine hydrochloride 4% eye drops | 10 ml [POA] £28.40 DT = £28.40

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1184 Glaucoma and ocular hypertension

Bimatoprost

**INDICATIONS AND DOSE**

*Raised intra-ocular pressure in open-angle glaucoma| Ocular hypertension*

- **Adult:** Apply once daily, to be administered preferably in the evening

**CAUTIONS**

- Angle-closure glaucoma (no experience of use)
- Aphakia - asthma - chronic obstructive pulmonary disease
- Compromised respiratory function - congenital glaucoma
- (no experience of use) - contact lens wearers - history of significant ocular viral infections - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - predisposition to bradycardia - predisposition to hypotension - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cystoid macular oedema - risk factors for iritis - risk factors for uveitis

**SIDE-EFFECTS**

- **Common or very common**  
  - Dry eye - eye discolouration - eye discomfort - eye disorders - eye inflammation - headache - hypertension - hyperviscosity - skin reactions - vision disorders
- **Uncommon**
  - Asthenia - dizziness - madarosis - nausea - retinal haemorrhage
- **Frequency not known**
  - Asthma - bradycardia - dyspnoea - hypotension - reactivation of infection

**PREGNANCY**

- Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

- Manufacturer advises avoid — present in milk in **animal** studies.

**HEPATIC IMPAIRMENT**

- Manufacturer advises use with caution in moderate-to-severe impairment — no information available.

**RENAL IMPAIRMENT**

- Use with caution — no information available.

**PRESCRIBING AND DISPENSING INFORMATION**

- Although multi-dose bimatoprost eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**PATIENT AND CARER ADVICE**

- Changes to eye colour  
  Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

**NATIONAL FUNDING/ACCESS DECISIONS**

*LUMIGAN®*

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (March 2013) that bimatoprost 300 micrograms/ml preservative-free eye drops (Lumigan® single-dose eye drops) are accepted for restricted use within NHS Scotland for the reduction of intra-ocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers) in adults who have proven sensitivity to benzalkonium chloride.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

**EXCIPIENTS:**  
- May contain Benzalkonium chloride

- **Bimatoprost (Non-proprietary)**
  - **Bimatoprost 300 microgram per 1 ml**
    - Bimatoprost 300 micrograms/ml eye drops | 3 ml | £10.30 DT = £10.30
  - **Eyreida (Aspire Pharma Ltd)**
    - **Bimatoprost 300 microgram per 1 ml**
      - Eyreida 0.3mg/ml eye drops | 3 ml | £11.71 DT = £11.71
  - **Lumigan (Allergan Ltd)**
    - **Bimatoprost 100 microgram per 1 ml**
      - Lumigan 100 micrograms/ml eye drops | 3 ml | £11.71 DT = £11.71 | 9 ml | £35.15
    - **Bimatoprost 300 microgram per 1 ml**
      - Lumigan 300 micrograms/ml eye drops 0.4ml unit dose | 30 unit dose | £13.75 DT = £13.75
  - **Sturilan (Actavis UK Ltd)**
    - **Bimatoprost 300 microgram per 1 ml**
      - Sturilan 0.3mg/ml eye drops | 3 ml | £9.27 DT = £10.30 | 9 ml | £27.81

**Bimatoprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bimatoprost above, timolol maleate p. 1180.

**INDICATIONS AND DOSE**

*Raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate*

- **TO THE EYE**
- **Adult:** Apply once daily

**INTERACTIONS**

- Appendix 1: beta-blockers, non-selective

**NATIONAL FUNDING/ACCESS DECISIONS**

*GANFORT® SINGLE USE*

**Scottish Medicines Consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (October 2013) that Ganfort® unit dose eye drops are accepted for restricted use within NHS Scotland for the reduction of intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension insufficiently responsive to topical beta-blockers or prostaglandin analogues who have proven sensitivity to preservatives.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

**EXCIPIENTS:**

- May contain Benzalkonium chloride

- **Ganfort (Allergan Ltd)**
  - Bimatoprost 300 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml
    - Ganfort 0.3mg/ml / 5mg/ml eye drops | 3 ml | £14.16 DT = £14.16 | 9 ml | £38.15
    - Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose | 30 unit dose | £17.94 DT = £17.94

**Latanoprost**

**INDICATIONS AND DOSE**

*Raised intra-ocular pressure in open-angle glaucoma| Ocular hypertension*

- **TO THE EYE**
- **Adult:** Apply once daily, to be administered preferably in the evening

**IMPORTANT SAFETY INFORMATION**

**MHRA/CiMH ADVICE:** LATANOPROST (XALATAN®): INCREASED REPORTING OF EYE IRRITATION SINCE REFORMULATION (JULY 2015)

Following reformulation of Xalatan® with timolol, to allow for long-term storage at room temperature, there has been an
increase in the number of reports of eye irritation from across the EU. Patients should be advised to tell their health professional promptly (within a week) if they experience eye irritation (e.g. excessive watering) severe enough to make them consider stopping treatment. Review treatment and prescribe a different formulation if necessary.

- **CONTRA-INDICATIONS** Active herpes simplex keratitis - history of recurrent herpetic keratitis associated with prostaglandin analogues
- **CAUTIONS** Angle-closure glaucoma (no experience of use) - aphakia - asthma - chronic obstructive pulmonary disease - compromised respiratory function - congenital glaucoma (no experience of use) - contact lens wearers - do not use within 5 minutes of thiomersal-containing preparations - history of significant ocular viral infections - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - peri-operative period of cataract surgery - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cystoid macular oedema - risk factors for iritis - risk factors for uveitis
- **SIDE-EFFECTS**
  - Common or very common Eye discolouration - eye discomfort - eye disorders - eye inflammation - vision disorders
  - Uncommon Dry eye - rash
  - Rare or very rare Asthma - chest pain - dyspnoea - unstable angina
- **FREQUENCY not known** Arthralgia - dizziness - headache - myalgia - ophthalmic herpes simplex - palpitations
- **PREGNANCY** Manufacturer advises avoid.
- **BREAST FEEDING** May be present in milk—manufacturer advises avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose latanoprost eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
- **PATIENT AND CARER ADVICE** Changes in eye colour Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.
- **NATIONAL FUNDING/ACCESS DECISIONS**
- **MONOPOST**
  - **Scottish Medicines Consortium (SMC) decisions** The Scottish Medicines Consortium has advised (June 2013) that Monopost is accepted for restricted use within NHS Scotland for the reduction of elevated intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension who have proven sensitivity to benzalkonium chloride.
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Eye drops**
    - **EXCIPIENTS:** May contain Benzalkonium chloride
    - Latanoprost (Non-proprietary)
      - Latanoprost 50 microgram per 1 ml Latanoprost 50micrograms/ml eye drops 0.2ml unit dose | 30 unit dose \( \text{POT} \) £8.49 DT + £8.49 | 90 unit dose \( \text{POT} \) £25.47 DT + £25.47
    - Xalatan (Pfizer Ltd)
      - Latanoprost 50 microgram per 1 ml Xalatan 50micrograms/ml eye drops | 2.5 ml \( \text{POT} \) £12.48 DT + £7.92

### Glaucoma and ocular hypertension

#### Latanoprost with timolol

The properties listed below are those particular to the combination only. For the properties of the components please consider, latanoprost p. 1184, timolol maleate p. 1180.

- **INDICATIONS AND DOSE** Raised intraocular pressure in patients with open-angle glaucoma and ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate
  - TO THE EYE
    - Adult: Apply once daily

- **INTERACTIONS** > Appendix 1: beta blockers, non-selective

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

#### Eye drops

**EXCIPIENTS:** May contain Benzalkonium chloride

- **Latanoprost with timolol (Non-proprietary)**
  - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops | 2.5 ml \( \text{POT} \) £14.32 DT + £6.57
  - Fixapost (Thea Pharmaceuticals Ltd)
    - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose | 30 unit dose \( \text{POT} \) £13.49
  - Medox (Medicon Healthcare Ltd)
    - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Medox 50micrograms/ml / 5mg/ml eye drops | 2.5 ml \( \text{POT} \) DT + £6.57
  - Xalacom (Pfizer Ltd)
    - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml xalacom eye drops | 2.5 ml \( \text{POT} \) £14.32 DT + £6.57

#### Tafluprost

- **INDICATIONS AND DOSE** Raised intra-ocular pressure in open-angle glaucoma | Ocular hypertension
  - TO THE EYE
    - Adult: Apply once daily, to be administered preferably in the evening

- **CAUTIONS** Angle-closure glaucoma (no experience of use) - aphakia - asthma - chronic obstructive pulmonary disease - compromised respiratory function - congenital glaucoma (no experience of use) - contact lens wearers - history of significant ocular viral infections - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cystoid macular oedema - risk factors for iritis - risk factors for uveitis

- **SIDE-EFFECTS**
  - **Common or very common** Dry eye - eye discolouration - eye discomfort - eye disorders - eye inflammation - headache - vision disorders
  - **Uncommon** Hypertrichosis
  - **Frequency not known** Asthma exacerbated - dyspnoea

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.
Glaucoma and ocular hypertension

**Travoprost**

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma

TO THE EYE

Adult: Apply once daily, to be administered preferably in the evening

**CAUTIONS**

History of significant ocular viral infections - angle-closure glaucoma (no experience of use) - aphakia

- asthma
- chronic obstructive pulmonary disease
- compromised respiratory function - congenital glaucoma (no experience of use) - contact lens wearers - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cystoid macular oedema - risk factors for iritis - risk factors for uveitis

**SIDE-EFFECTS**

- Common or very common
  - Dry eye
  - eye discoloration
  - eye discomfort
  - eye disorders

- Uncommon
  - Cataract
  - cough
  - eye inflammation
  - hair changes
  - headache
  - nasal complaints
  - palpitations - seasonal allergy
  - skin reactions
  - throat irritation
  - vision disorders

- Rare or very rare
  - Allergic rhinitis
  - arthralgia
  - asthenia
  - asthma
  - constipation
  - dizziness
  - dry mouth
  - dysphonia
  - dysphagia
  - gastrointestinal disorders - hypotension
  - hypertensive reactions - madarosis
  - musculoskeletal pain - myalgia
  - nausea
  - tinnitus
  - urinary disorders
  - vertigo
  - vomiting

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies.

**BREAST FEEDING**

Present in milk in animal studies; manufacturer advises avoid.

**PATIENT AND CARER ADVICE**

Changes to eye colour

Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with multicoloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Travoprost**

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma

Ocular hypertension

TO THE EYE

Adult: Apply once daily, to be administered preferably in the evening

**CAUTIONS**

History of significant ocular viral infections - angle-closure glaucoma (no experience of use) - aphakia

- asthma
- chronic obstructive pulmonary disease
- compromised respiratory function - congenital glaucoma (no experience of use) - contact lens wearers - inflammatory ocular conditions (no experience of use) - narrow-angle glaucoma (no experience of use) - neovascular glaucoma (no experience of use) - pseudophakia with torn posterior lens capsule or anterior chamber lenses - risk factors for cystoid macular oedema - risk factors for iritis - risk factors for uveitis

**SIDE-EFFECTS**

- Common or very common
  - Dry eye
  - eye discoloration
  - eye discomfort
  - eye disorders

- Uncommon
  - Cataract
  - cough
  - eye inflammation
  - hair changes
  - headache
  - nasal complaints
  - palpitations - seasonal allergy
  - skin reactions
  - throat irritation
  - vision disorders

- Rare or very rare
  - Allergic rhinitis
  - arthralgia
  - asthenia
  - asthma
  - constipation
  - dizziness
  - dry mouth
  - dysphonia
  - dysphagia
  - gastrointestinal disorders - hypotension
  - hypertensive reactions - madarosis
  - musculoskeletal pain - myalgia
  - nausea
  - tinnitus
  - urinary disorders
  - vertigo
  - vomiting

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk — toxicity in animal studies.

**BREAST FEEDING**

Present in milk in animal studies; manufacturer advises avoid.

**PATIENT AND CARER ADVICE**

Changes to eye colour

Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with multicoloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

**EXCIPIENTS:** May contain Propylene glycol

- Travoprost (Non-proprietary)
- Travoprost 40 microgram per 1 ml Travoprost 40 micrograms/ml eye drops | 2.5 ml [POD] £3.24 - £10.95 DT + £3.24

- Bonduc (Actavis UK Ltd)
- Travoprost 40 microgram per 1 ml Bonduc 40 micrograms/ml eye drops | 2.5 ml [POD] £10.94 DT + £3.24

- Travatan (Novartis Pharmaceuticals UK Ltd)
- Travoprost 40 microgram per 1 ml Travatan 40 micrograms/ml eye drops | 2.5 ml [POD] £10.95 DT + £3.24
Travoprost with timolol
The properties listed below are those particular to the combination only. For the properties of the components please consider, travoprost p. 1186, timolol maleate p. 1180.

I INDICATIONS AND DOSE
Raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate

TO THE EYE
Adult: Apply once daily

INTERACTIONS → Appendix 1: beta blockers, non-selective

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Eye drops
Travoprost with timolol (Non-proprietary)
Travoprost 40 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops | 2.5 ml  £13.95 DT + £13.95
DuoTrav (Novartis Pharmaceuticals UK Ltd) Travoprost 40 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml DuoTrav 40micrograms/ml / 5mg/ml eye drops | 2.5 ml  £13.95 DT + £13.95  7.5 ml  £39.68

SYMPATHOMIMETICS → Alpha-2-adrenoceptor agonists
Apraclonidine
DRUG ACTION Apraclonidine is an alpha-2-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. It is a derivative of clonidine.

INDICATIONS AND DOSE
Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery

TO THE EYE
Adult: Apply 1 drop, 1 hour before laser procedure, then 1 drop, immediately after completion of procedure, 1% eye drops to be administered

Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug

TO THE EYE
Adult: Apply 1 drop 3 times a day usually for maximum 1 month, 0.5% eye drops to be administered, may not provide additional benefit if patient already using two drugs that suppress the production of aqueous humour

CONTRA-INDICATIONS History of severe or unstable and uncontrolled cardiovascular disease

CAUTIONS Cerebrovascular disease · depression · heart failure · history of angina · hypertension · loss of effect may occur over time · Parkinson’s syndrome · Raynaud’s syndrome · recent myocardial infarction · reduction in vision in end-stage glaucoma (suspend treatment) · severe coronary insufficiency · thromboangiitis obliterans · vasovagal attack

INTERACTIONS → Appendix 1: apraclonidine

SIDE-EFFECTS
Common or very common Eye disorders
Uncommon Bradycardia · conjunctival haemorrhage · diarrhoea · dry eye · eye discomfort · eye inflammation · gastrointestinal discomfort · irritability · libido decreased · nasal dryness · palpitations · postural hypotension · sensation abnormal · sleep disorders · syncope · vision disorders · vomiting
Rare or very rare Chest pain · dry mouth · fatigue · headache · hyperhidrosis · pain in extremity · pruritus · taste altered · temperature sensation altered

SIDE-EFFECTS, FURTHER INFORMATION Since absorption may follow topical application, systemic effects may occur – see clonidine hydrochloride p. 145.

Ocular intolerance Manufacturer advises withdrawal if eye pruritus, ocular hyperaemia, increased lacrimation, or oedema of the eyelids and conjunctiva occur.

PREGNANCY Manufacturer advises avoid — no information available.

BREAST FEEDING Manufacturer advises avoid — no information available.

HEPATIC IMPAIRMENT Manufacturer advises use with caution and monitor, including close monitoring of cardiovascular parameters — no information available.

RENAL IMPAIRMENT Use with caution in chronic renal failure.

MONITORING REQUIREMENTS
Monitor intra-ocular pressure and visual fields.

PATIENT AND CARER ADVICE
Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Eye drops EXCIPIENTS: May contain Propylene glycol
Apraclonidine (as Apraclonidine hydrochloride) 10 mg per 1ml (Novartis Pharmaceuticals UK Ltd) Apraclonidine (as Apraclonidine hydrochloride) 5 mg per 1ml (Novartis Pharmaceuticals UK Ltd) Iopidine (as Iopidine hydrochloride) 5 mg per 1ml Iopidine (as Iopidine hydrochloride) 10 mg per 1ml

Use with caution in chronic renal failure.

Manufacturer advises withdrawal if eye pruritus, ocular hyperaemia, increased lacrimation, or oedema of the eyelids and conjunctiva occur.

Apraclonidine is an alpha-2-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. It is a derivative of clonidine.

Brimonidine tartrate
DRUG ACTION Brimonidine, an alpha-2-adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow.

INDICATIONS AND DOSE
Raised intra-ocular pressure in open-angle glaucoma in patients for whom beta-blockers are inappropriate.

TO THE EYE
Adult: Apply twice daily

CAUTIONS Cerebral insufficiency · coronary insufficiency · depression · postural hypotension · Raynaud’s syndrome · severe cardiovascular disease · thromboangiitis obliterans

INTERACTIONS → Appendix 1: brimonidine

SIDE-EFFECTS
Common or very common Asthenia · dizziness · drowsiness · dry eye · dry mouth · eye discomfort · eye disorders · eye inflammation · gastrointestinal disorder · headache · hyperaemia · hypersensitivity · pulmonary reaction · sensation of foreign body · skin reactions · taste altered · vision disorders
Uncommon Arrhythmias · nasal dryness · palpitations
Rare or very rare Dyspnoea · hypertension · hypotension · insomnia · syncope
Frequency not known Face oedema · vasodilatation
PREGNANCY Manufacturer advises use only if benefit outweighs risk — limited information available.

BREAST FEEDING Manufacturer advises avoid — no information available.

Since absorption may follow topical application, systemic effects may occur – see clonidine hydrochloride p. 145.

Recommended readings
JAMA 1999; 281: 2389–2396
Eye
BNF 78
www.getintopharma.com
Retinal disorders

6 Retinal disorders

6.1 Macular degeneration

Age-related macular degeneration

25-Apr-2018

Description of condition

Age-related macular degeneration is a progressive eye condition that affects the central area of the retina (macula). It occurs mainly in people aged 55 years and over and is a common cause of vision loss. The progressive loss of central vision affects the patient’s ability to see well enough to recognise faces, drive, and to read and write. Although the exact cause is unknown, known risk factors in addition to increasing age include smoking and a family history of age-related macular degeneration.

There are two types of age-related macular degeneration—dry and wet. Dry (non-neovascular) age-related macular degeneration progresses slowly as extensive wasting of macula cells occurs. Whereas, with wet (neovascular) age-related macular degeneration, new blood vessels develop beneath and within the retina, and can lead to a rapid deterioration of vision. Wet age-related macular degeneration is further classified as wet-active (neovascular lesions that may benefit from treatment) and wet-inactive (neovascular disease with irreversible structural change).

Aims of treatment

The aim of treatment is to slow down the progression of age-related macular degeneration and central vision loss; treatment is initiated under specialist care.

Treatment

Treatment is dependent on the stage and type of age-related macular degeneration, with drug treatment only recommended in patients with wet-active age-related macular degeneration. Counselling and support, advice on Smoking cessation p. 497, and use of visual aids is recommended in all patients with age related macular degeneration as appropriate.

Combigan An intravitreal anti-vascular endothelial growth factor (anti-VEGF), such as aflibercept p. 1008, ranibizumab p. 1190, or bevacizumab p. 862 (unlicensed use), is first-line treatment for patients with wet-active age-related macular degeneration. Counseling and support, advice on smoking cessation p. 497, and use of visual aids is recommended in all patients with age-related macular degeneration as appropriate.

Amsale An intravitreal anti-vascular endothelial growth factor (anti-VEGF), such as aflibercept p. 1008, ranibizumab p. 1190, or bevacizumab p. 862 (unlicensed use), is first-line treatment for patients with wet-active age-related macular degeneration. Counseling and support, advice on smoking cessation p. 497, and use of visual aids is recommended in all patients with age-related macular degeneration as appropriate.

Triamcinolone A corticosteroid designed for intraocular injection. It is approved for treating wet macular degeneration in the eye.

Photodynamic Therapy Photodynamic therapy alone should not be given to patients with wet-active age-related macular degeneration. It can be given as an adjunct to anti-VEGF treatment as a second-line option in the context of a randomised controlled trial. Intravitreal corticosteroids are not recommended in patients with wet-active age-related macular degeneration as there is limited evidence of benefit to a patient’s visual acuity.

Photodynamic therapy alone should not be given to patients with wet-active age-related macular degeneration. It can be given as an adjunct to anti-VEGF treatment as a second-line option in the context of a randomised controlled trial. Intravitreal corticosteroids are not recommended in patients with wet-active age-related macular degeneration as there is limited evidence of benefit to a patient’s visual acuity.

Patients should be advised to attend routine sight tests, self-monitor, and to report any changes in vision such as appearance of grey patches or blurred vision, straight lines appearing distorted, and objects appearing smaller than normal.

Useful Resources


www.nice.org.uk/guidance/ng82
Macular degeneration 1189

ANTINEOPLASTIC DISEASES > VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Aflibercept

DRUG ACTION Aflibercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Aflibercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels.

INDICATIONS AND DOSE

Neovascular (wet) age-related macular degeneration (specialist use only)
- BY INTRAVITREAL INJECTION
  - Adult: Initially 2 mg once a month for 3 months, then 2 mg every 2 months, review treatment frequency after 12 months

Macular oedema secondary to retinal vein occlusion (specialist use only)
- BY INTRAVITREAL INJECTION
  - Adult: Initially 2 mg once a month until maximum visual acuity is achieved or there are no signs of disease activity (discontinue treatment if no improvement in visual and anatomic outcomes)

Diabetic macular oedema (specialist use only)
- BY INTRAVITREAL INJECTION
  - Adult: Initially 2 mg once a month for 5 months, then maintenance 2 mg every 2 months, review treatment frequency after 12 months (discontinue treatment if no improvement in visual and anatomic outcomes)

Myopic choroidal neovascularisation (specialist use only)
- BY INTRAVITREAL INJECTION
  - Adult: 2 mg for 1 dose, if visual or anatomic outcomes indicate that disease persists, additional doses may be administered; the interval between 2 doses should be greater than 1 month

CONTRA-INDICATIONS Clinical signs of irreversible ischaemic visual function loss - ocular or periorcular infection - severe intra-ocular inflammation

CAUTIONS Active systemic infection - diabetic patients with uncontrolled hypertension - discontinue treatment if stage 3 or 4 macular holes develop - consult product literature for full details - discontinue treatment in the event of arterial retinal detachment - consult product literature for full details - discontinue treatment in the event of retinal detachment - consult product literature for full details - patients at risk of retinal pigment epithelial tear - poorly controlled glaucoma - recent history of myocardial infarction - recent history of stroke - recent history of transient ischaemic attack

CAUTIONS, FURTHER INFORMATION Aflibercept is given by intravitreal injection by specialists experienced in the management of this condition. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections — patients should be advised to report any signs of infection immediately.

INTERACTIONS Appendix 1: aflibercept

SIDE-EFFECTS
- Common or very common Cataract - eye discomfort - eye disorders - eye inflammation - haemorrhage - retinal pigment epithelial tear - vision disorders
- Uncommon Lens opacity

CONCEPTION AND CONTRACEPTION Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC FEEDING Manufacturer advises caution in severe impairment (no information available).

MONITORING REQUIREMENTS Monitor intra-ocular pressure following injection.

DIRECTIONS FOR ADMINISTRATION For further information on administration, consult product literature.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions
- Aflibercept solution for injection for treating wet age-related macular degeneration (July 2013) NICE TA294
  - Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:
    - it is used in accordance with the recommendations for ranibizumab in NICE TA 155 and
    - the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/TA294
- Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion (February 2014) NICE TA305
  - Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/TA305
- Aflibercept for treating diabetic macular oedema (July 2015) NICE TA346
  - Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if:
    - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
    - the manufacturer provides aflibercept with the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/TA346
- Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion (September 2016) NICE TA409
  - Aflibercept is recommended, within its marketing authorisation, as an option for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion, only if the manufacturer provides aflibercept with the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/TA409
- Aflibercept for treating choroidal neovascularisation (November 2017) NICE TA486
  - Aflibercept is recommended, within its marketing authorisation, as an option for treating visual impairment because of myopic choroidal neovascularisation in adults, only if the manufacturer provides aflibercept with the discount agreed in the patient access scheme.
  - If patients and their clinicians consider both aflibercept and ranibizumab to be suitable treatments, the least costly should be used, taking into account anticipated administration costs, dosage and price per dose.
  - www.nice.org.uk/guidance/TA486

Scottish Medicines Consortium (SMC) decisions
The Scottish Medicines Consortium has advised (October 2016) that aflibercept (Eylea®) is accepted for use within
**Retinal disorders**

Ranibizumab 24-Aug-2018

**Indications and Dose**

- **Neovascular (wet) age-related macular degeneration (specialist use only)**
- **Diabetic macular oedema (specialist use only)**
- **Macular oedema secondary to retinal vein occlusion (specialist use only)**
- **Choroidal neovascularisation (specialist use only)**
  - **By Intravitreal Injection**
    - Adult: Initially 500 micrograms once a month, to be administered into the affected eye, until maximum visual acuity is achieved or there are no signs of disease activity, for continued treatment and subsequent dose intervals—consult product literature, discontinue treatment if no improvement in visual and anatomic outcomes
  - **Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photoacoagulation (specialist use only)**
    - **By Intravitreal Injection**
      - Adult: 500 micrograms, to be administered at least 30 minutes after laser photoacoagulation

**Contraindications**

- Ocular or periocular infection—severe intraocular inflammation—signs of irreversible ischaemic visual function loss in patients with retinal vein occlusion

**Cautions**

- Active systemic infection—diabetic macular oedema due to type 1 diabetes (limited information available)—diabetic patients with HbA1c over 12%—history of stroke—history of transient ischemic attack—patients at risk of retinal pigment epithelial tear—previous intravitreal injections—proliferative diabetic retinopathy—retinal detachment or macular hole (discontinue treatment if rhegmatogenous retinal detachment or stage 5 or 4 macular holes develop)—uncontrolled hypertension

**Caution, Further Information**

Ranibizumab is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.

**Interactions**

- **Appendix 1: ranibizumab**

**Side-Effects**

- **Common or very common**
  - Anaemia
  - Anxiety
  - Arthralgia
  - Cataract
  - Cough
  - Dry eye
  - Eye discomfort
  - Eye disorders
  - Eye inflammation
  - Haemorrhage
  - Headache
  - Hypersensitivity
  - Increased risk of infection—lens opacity
  - Nausea
  - Retinal pigment epithelial tear
  - Vision disorders

- **Uncommon**
  - Corneal deposits

- **Frequency not known**
  - Arterial thromboembolism

**Conception and Contraception**

Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

**Pregnancy**

Manufacturer advises avoid unless potential benefit outweighs risk.

**Breast Feeding**

Manufacturer advises avoid—no information available.

**Monitoring Requirements**

- Manufacturer advises monitor intraocular pressure, perfusion of the optic nerve head, and for signs of ocular infection following injection.
- Manufacturer advises monitor visual acuity.

**Directions for Administration**

For further information on administration, consult product literature.

**National Funding/Access Decisions**

**NICE decisions**

- Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (November 2013) NICE TA298
- Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme.
  - www.nice.org.uk/guidance/ta298
- Ranibizumab for the treating visual impairment caused by macular oedema secondary to retinal vein occlusion (May 2013) NICE TA283
- Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:
  - following central retinal vein occlusion or
  - following branch retinal vein occlusion only if treatment with laser photoacoagulation is not beneficial, or when laser photoacoagulation is not suitable because of the extent of macular haemorrhage and
  - only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274. Patients currently receiving ranibizumab whose disease does not meet the criteria listed above should be able to continue treatment until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/guidance/ta283
- Ranibizumab for treating diabetic macular oedema (February 2013) NICE TA274
- Ranibizumab is recommended as an option for the treatment of visual impairment due to diabetic macular oedema only if:
  - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
  - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).
  - Patients currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.
  - www.nice.org.uk/guidance/ta274
- Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (updated May 2012) NICE TA155
- Ranibizumab is recommended for the treatment of wet age-related macular degeneration if all of the following apply:
  - the best corrected visual acuity is between 6/12 and 6/96;
  - there is no permanent structural damage to the central fovea;
  - the lesion size is less than or equal to 12 disc areas in greatest linear dimension;
  - there is evidence of recent presumed disease progression;
MACULAR ODEMA

1191

PHOTOSENSITISERS

Verteporfin

06-Feb-2019

- **DRUG ACTION** Following intravenous infusion, verteporfin is activated by local irradiation using non-thermal red light to produce cytotoxic derivatives.

- **INDICATIONS AND DOSE** Photodynamic treatment of age-related macular degeneration associated with predominantly classic subfoveal choroidal neovascularisation or with pathological myopia (specialist use only)
  - By intravenous infusion
  - Adult: 6 mg/m², dose to be given over 10 minutes

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058
- **CAUTIONS** Avoid extravasation - biliary obstruction - photosensitivity
- **INTERACTIONS** → Appendix 1: verteporfin
- **SIDE-EFFECTS**
  - Common or very common
    - Asthenia - dizziness - dyspnoea - headache - hypercholesterolaemia - hypersensitivity - infusion related chest pain - infusion related reaction - nausea - photosensitivity reaction - syncope - vision disorders
  - Uncommon
    - Eye inflammation - fever - haemorrhage - hyperaesthesia - hypertension - pain - retinal detachment - skin reactions
  - Rare or very rare
    - Malaise - retinal ischaemia
  - Frequency not known
    - Myocardial infarction - retinal pigment epithelial tear
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk (teratogenic in animal studies).
- **BREAST FEEDING** No information available—manufacturer advises avoid breast-feeding for 48 hours after administration.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment and avoid in severe impairment (no information available).
- **DIRECTIONS FOR ADMINISTRATION** For information on administration and light activation, consult product literature.
  - For intravenous infusion (Visudyne®), give intermittently in Glucose 5%; reconstitute each 15 mg with 7 ml water for injections to produce a 2 mg/mL solution then dilute requisite dose with infusion fluid to a final volume of 30 mL and give over 10 minutes; protect infusion from light and administer within 4 hours of reconstitution. Incompatible with sodium chloride infusion.
- **PATIENT AND CARER ADVICE** Photosensitivity—avoid exposure of unprotected skin and eyes to bright light during infusion and for 48 hours afterwards.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for infusion**
  - Exipients: May contain Butylated hydroxytoluene
  - Visudyne® (Novartis Pharmaceuticals UK Ltd)
    - Verteoporfin 15 mg Visudyne 15 mg powder for solution for infusion vials | 1 vial (PBN) £850.00 (Hospital only)

6.2 Macular oedema

Other drugs used for Macular oedema

- Afibercept, p. 1008
- Dexamethasone, p. 675
- Ranibizumab, p. 1190

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Fluocinolone acetonide

**INDICATIONS AND DOSE**

Treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: 190 micrograms, to be administered into the affected eye

**CONTRA-INDICATIONS**

- Active or suspected ocular infection
- Raised baseline intra-ocular pressure
- Concurrent vitreous haemorrhage or detachment within 2–7 days of the procedure
- Monitor intra-ocular pressure at least every 1–2 months following the procedure

**SIDE-EFFECTS**

- Common or very common: Cataract, eye discomfort, glaucoma, haemorrhage, vision blurred
- Uncommon: Eye disorders, headache
- Frequency not known: Thromboembolism

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**CAUTIONS**

- Raised baseline intra-ocular pressure
- Concurrent administration to both eyes not recommended.

**SIDE-EFFECTS, FURTHER INFORMATION**

The metabolites of idebenone may cause red-brown discolouration of the urine. This effect is harmless, but the manufacturer advises caution as it may mask colour changes due to other causes (e.g., renal or blood disorders).

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution (no information available).

**RENAL IMPAIRMENT**

Manufacturer advises use with caution—no information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**

- Fluocinolone acetone intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (November 2013) NICE TA301

- Fluocinolone acetone intravitreal implant (Iluvien) is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if:
  - the implant is to be used in an eye with an intra-ocular (pseudophakic lens), and
  - the manufacturer provides fluocinolone acetone intravitreal implant with the discount agreed in the patient access scheme.

Scottish Medicines Consortium (SMC) decisions

SMC No. 864/13

The Scottish Medicines Consortium has advised (February 2014) that fluocinolone acetone intravitreal implant (Iluvien) is recommended for restricted use within NHS Scotland for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies, only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery), and retreatment would take place only if the patient had previously responded to treatment with fluocinolone acetone and subsequently best corrected visual acuity had deteriorated to less than 20/32. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Implant**

- **Iluvien** (Alimera Sciences Ltd)
  - Fluocinolone acetone 190 microgram ILUVIEN 190 microgram intravitreal implant in applicator | 1 device | £5,500.00

### 6.3 Optic neuropathy

**DRUGS FOR METABOLIC DISORDERS**

**ANTIOXIDANTS**

**Idebenone**

**DRUG ACTION**

Idebenone is a nootropic and antioxidant that is thought to act by restoring cellular ATP generation, thereby reactivating retinal ganglion cells.

**INDICATIONS AND DOSE**

Leber’s Hereditary Optic Neuropathy (initiated by a specialist)

- **BY MOUTH**
  - Adult: 300 mg 3 times a day

**SIDE-EFFECTS**

- Common or very common: Cough, diarrheoa, increased risk of infection, pain
- Frequency not known: Agranulocytosis, anaemia, anxiety, appetite decreased, asthenia, delirium, dizziness, dyspepsia, hallucination, headache, hepatitis, leucopenia, malaise, movement disorders, nausea, neutropenia, poriomania, seizure, skin reactions, stupor, thrombocytopenia, urine discoloration, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

The metabolites of idebenone may cause red-brown discolouration of the urine. This effect is harmless, but the manufacturer advises caution as it may mask colour changes due to other causes (e.g., renal or blood disorders).

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution (no information available).

**RENAL IMPAIRMENT**

Manufacturer advises use with caution—no information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (May 2017) that idebenone (Raxone) is accepted for restricted use within NHS Scotland for the treatment of visual impairment in patients with Leber’s Hereditary Optic Neuropathy (LHON) who are not yet blind i.e., they do not meet the UK criteria to be registered as severely sight impaired. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Raxone** (Santhera (UK) Ltd)
  - **Idebenedone 150 mg** Raxone 150mg tablets | 180 tablet | £6,364.00
6.4 Vitreomacular traction

RECOMBINANT PROTEOLYTIC ENZYMES

Ocriplasmin

**INDICATIONS AND DOSE**
Treatment of vitreomacular traction, including when associated with a macular hole of diameter less than or equal to 400 microns (specialist use only)

- **BY INTRAVITREAL INJECTION**
- Adult: 125 micrograms for 1 dose, to be administered into the affected eye, concurrent administration to both eyes is not recommended

**CONTRA-INDICATIONS**
- Active or suspected ocular or periorbital infection
- Aphakia
- Exudative age-related macular degeneration
- High myopia
- History of rhegmatogenous retinal detachment
- Ischaemic retinopathies
- Large diameter macular hole (> 400 microns)
- Lens zonule instability
- Proliferative diabetic retinopathy
- Recent intra-ocular injection (including laser therapy)
- Recent ocular surgery
- Retinal vein occlusions
- Vitreous haemorrhage

**CAUTIONS**
- History of uveitis (including severe active inflammation)
- Non-proliferative diabetic retinopathy
- Significant eye trauma

**SIDE-EFFECTS**
- Common or very common: Dry eye, eye discomfort, eye disorders, eye inflammation, haemorrhage, retinal pigment epitheliopathy, vision disorders

**PREGNANCY**
- Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING**
- Manufacturer advises use only if potential benefit outweighs risk—no information available.

**MONITORING REQUIREMENTS**
- Monitor intra-ocular pressure, visual acuity, and for signs of intra-ocular inflammation or infection following injection.

**DIRECTIONS FOR ADMINISTRATION**
- For further information on administration, consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE decisions**
- Ocriplasmin for treating vitreomacular traction (October 2013) NICE TA297
  - Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if:
    - An epiretinal membrane is not present and
    - They have a stage II full-thickness macular hole with a diameter of 400 microns or less and/or
    - They have severe symptoms.
  - www.nice.org.uk/TA297

**Scottish Medicines Consortium (SMC) decisions**
- The Scottish Medicines Consortium has advised (July 2014) that ocriplasmin (Jetrea®) is accepted for restricted use within NHS Scotland for the treatment of patients with vitreomacular traction plus macular hole, regardless of whether they have epiretinal membrane formation, and in patients with vitreomacular traction alone (no epiretinal membrane and no macular hole).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Jetrea (Oxurion N.V.)
  - Ocriplasmin 1.25 mg per 1 ml
  - Jetrea 0.375mg/0.3ml solution for injection vials | 1 vial (£15.59) £2,500.00 (Hospital only)

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Chapter 12
Ear, nose and oropharynx

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Ear

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2 Removal of earwax 1200

Nose

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Oropharynx

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Ear

Otitis externa

Otitis externa is an inflammatory reaction of the meatal skin. It is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping. A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactorily to the relatively inaccessible affected skin. The most effective method is to introduce a ribbon gauze dressing or sponge wick soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution. When this is not practical, the ear should be gently cleansed with a probe covered in cotton wool and the patient encouraged to lie with the affected ear uppermost for ten minutes after the canal has been filled with a liberal quantity of the appropriate solution.

If infection is present, a topical anti-infective which is not used systemically (such as neomycin sulfate) may be used, but for only about a week as excessive use may result in fungal infections; these may be difficult to treat and require expert advice. Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use. Aluminium acetate ear drops are also effective against bacterial infection and inflammation of the ear. Chloramphenicol may be used but the ear drops contain propylene glycol and cause hypersensitivity reactions in about 10% of patients. Solutions containing an anti-infective and a corticosteroid are used for treating cases where infection is present with inflammation and eczema.

In view of reports of ototoxicity, manufacturers contraindicate treatment with topical aminoglycosides or polymyxins in patients with a perforated tympanic membrane or patent grommet. However, some specialists do use these drops cautiously in the presence of a perforation or patent grommet in patients with chronic supplicative otitis media and when other measures have failed for otitis externa; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;

- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances.

A solution of acetic acid 2% acts as an antifungal and antibacterial in the external ear canal. It may be used to treat mild otitis externa but in severe cases an anti-inflammatory preparation with or without an anti-infective drug is required. A proprietary preparation containing acetic acid 2% (EarCalm® spray) is on sale to the public.

For severe pain associated with otitis externa, a simple analgesic, such as paracetamol or ibuprofen, can be used. A systemic antibacterial can be used if there is spreading cellulitis or if the patient is systemically unwell. When a resistant staphylococcal infection (a boil) is present in the external auditory meatus, flucloxacillin is the drug of choice; ciprofloxacin may be needed in pseudomonal infections which may occur if the patient has diabetes or is immunocompromised.

The skin of the pinna adjacent to the ear canal is often affected by eczema. A topical corticosteroid cream or ointment is then required, but prolonged use should be avoided.

Otitis media

Acute otitis media

Acute otitis media is a self-limiting condition that mainly affects children. It is characterised by inflammation in the middle ear associated with effusion and accompanied by the rapid onset of signs and symptoms of an ear infection. The infection can be caused by viruses or bacteria; often both are present simultaneously.

Children with acute otitis media usually present with symptoms such as ear pain, rubbing of the ear, fever, irritability, crying, poor feeding, restlessness at night, cough, or rhinorrhea. Symptoms usually resolve within 3 to 7 days without antibacterial drugs. The use of antibacterials generally does not prevent common complications of acute otitis media such as short-term hearing loss, perforated eardrum, or recurrent infection. Acute complications such as mastoiditis, meningitis, intracranial abscess, sinus thrombosis, and facial nerve paralysis, are rare.

Children and their carers should be given advice about the usual duration of acute otitis media, self-care of...

See also: Acute otitis media

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symptoms such as pain and fever with paracetamol or ibuprofen p. 1141, and when to seek medical help. In children aged 3 years and over who do not have a perforated eardrum, pain can be relieved with anaesthetic ear drops in addition to oral analgesics [unlicensed use]. Children and their carers should be reassured that antibacterial drugs are usually not required.

An immediate antibacterial drug should be given if the child is systemically very unwell, has signs or symptoms of a more serious illness, or is at high risk of complications such as significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, or young children who were born prematurely. An immediate antibacterial drug can also be considered if otorrhoea is present, or in children under 2 years of age with bilateral otitis media. See Antibacterial therapy for otitis media in Ear infections, antibacterial therapy p. 511.

Children with acute otitis media associated with a severe systemic infection or acute complications should be referred to hospital. 

**Otitis media with effusion**

Otitis media with effusion (glue ear) occurs in about 10% of children and in 90% of children with cleft palates. Systemic antibacterials are not usually required. If glue ear persists for more than a month or two, the child should be referred for assessment and follow up because of the risk of long-term hearing impairment which can delay language development. Untreated or resistant glue ear may be responsible for some types of chronic otitis media.

**Chronic otitis media**

Opportunistic organisms are often present in the debris, keratin, and necrotic bone of the middle ear and mastoid in patients with chronic otitis media. The mainstay of treatment is thorough cleansing with aural microsuction which may completely resolve long-standing infection. Local cleansing of the meatal and middle ear may be followed by treatment with a sponge wick or ribbon gauze dressing soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution p. 1199; this is particularly beneficial for discharging ears or infections of the mastoid cavity. An antibacterial ear ointment may also be used. Acute exacerbations of chronic infection may also require systemic treatment with amoxicillin p. 548 (or erythromycin p. 539 if penicillin-allergic); treatment is adjusted according to the results of sensitivity testing.

In view of reports of ototoxicity, manufacturers contraindicate topical treatment with ototoxic antibacterials in the presence of a tympanic perforation or patent grommet. Ciprofloxacin p. 1196 or ofloxacin eye drops p. 1173 used in the ear [unlicensed use] or ear drops [both unlicensed; available from ‘special-order’ manufacturers or specialist importing companies] are an effective alternative to such ototoxic ear drops for chronic otitis media in patients with perforation of the tympanic membrane.

However, some specialists do use ear drops containing aminoglycosides or polymyxins [unlicensed indications] cautiously in patients with chronic suppurative otitis media and a perforation of the tympanic membrane, if the otitis media has failed to settle with systemic antibacterials; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;
- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiology should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances. It is considered that the pus in the middle ear associated with otitis media also carries a risk of ototoxicity.

**Removal of ear wax**

Ear wax (cerumen) is a normal bodily secretion which provides a protective film on the meatal skin and need only be removed if it causes hearing loss or interferes with a proper view of the ear drum.

Ear wax can be softened using simple remedies such as olive oil ear drops or almond oil ear drops; sodium bicarbonate ear drops p. 1200 are also effective, but may cause dryness of the ear canal. If the wax is hard and impacted, the drops can be used twice daily for several days and this may reduce the need for mechanical removal of the wax. The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Some proprietary preparations containing organic solvents can irritate the meatal skin, and in most cases the simple remedies indicated above are just as effective and less likely to cause irritation. Docusate sodium p. 1200 or urea hydrogen peroxide p. 1200 are ingredients in a number of proprietary preparations for softening ear wax.

If necessary, wax may be removed by irrigation with water (warmed to body temperature). Ear irrigation is generally best avoided in young children, in patients unable to cooperate with the procedure, in those with otitis media in the last six weeks, in otitis externa, in patients with cleft palate, a history of ear drum perforation, or previous ear surgery. A person who has hearing in one ear only should not have that ear irrigated because even a very slight risk of damage is unacceptable in this situation.

1 Otitis externa

**ANTIBACTERIALS → AMINOGLYCOSIDES**

**Framycetin sulfate**

- **INDICATIONS AND DOSE**
  - **Bacterial infection in otitis externa**
    - **TO THE EAR**
    - Adult: (consult product literature)

- **CONTRA-INDICATIONS**
  - Perforated tympanic membrane

- **CAUTIONS**
  - Avoid prolonged use

- **SIDE-EFFECTS**
  - Local reaction

- **MEDICINAL FORMS**
  - No licensed medicines listed.

Combinations available: Dexamethasone with framycetin sulfate and gramicidin, p. 1164

**Gentamicin**

- **INDICATIONS AND DOSE**
  - **Bacterial infection in otitis externa**
    - **TO THE EAR**
    - Child: Apply 2–3 drops 4–5 times a day, (including a dose at bedtime)
    - Adult: Apply 2–3 drops 4–5 times a day, (including a dose at bedtime)

- **CONTRA-INDICATIONS**
  - Patent grommet (although may be used by specialists, see Ear p. 1194) • perforated tympanic membrane (although may be used by specialists, see Ear p. 1194)

- **CAUTIONS**
  - Avoid prolonged use

- **INTERACTIONS → Appendix 1: aminoglycosides**
Otitis externa

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Ear/drops solution**

EXCIPIENTS: May contain Benzalkonium chloride

- **Gentamicin (Non-proprietary)**
- **Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml** Gentamicin 0.3% ear/drops | 10 ml | £2.63 DT + £2.47

**Gentamicin with hydrocortisone**

21-Dec-2017

**INDICATIONS AND DOSE**

Eczematous inflammation in otitis externa

- TO THE EAR
- Child: Apply 2–4 drops 4–5 times a day, (including a dose at bedtime)
- Adult: Apply 2–4 drops 4–5 times a day, (including a dose at bedtime)

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

See Corticosteroids, general use p. 670.

- **CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 1194) perforated tympanic membrane (although may be used by specialists, see Ear p. 1194)
- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS** Local reaction
- **PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Gentamicin and hydrocortisone ear drops for inflammatory ear infections


**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- **Gentamicin with hydrocortisone (Non-proprietary)**
- **Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml, Hydrocortisone acetate 10 mg per 1 ml** Gentamicin 0.3% / Hydrocortisone acetate 1% ear drops | 10 ml | £29.86 DT + £29.86

**Neomycin sulfate**

**INDICATIONS AND DOSE**

Bacterial infection in otitis externa

- TO THE EAR
- Child: (consult product literature)
- Adult: (consult product literature)

**CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 1194) perforated tympanic membrane (although may be used by specialists, see Ear p. 1194)

- **CAUTIONS** Avoid prolonged use
- **INTERACTIONS** → Appendix 1: neomycin
- **SIDE-EFFECTS** Local reaction

**MEDICINAL FORMS** No licensed medicines listed.

Combinations available: *Betamethasone with neomycin, p. 1164* - *Dexamethasone with glacial acetic acid and neomycin sulfate, p. 1199* - *Hydrocortisone with neomycin and polymyxin B sulfate, p. 1199*

**ANTIBACTERIALS**

**Ciprofloxacin (as Ciprofloxacin hydrochloride) 2 mg per 1 ml** Ciprofloxacin 0.25% unit dose | 15 unit dose (PFS) £6.01 DT + £1.01

Combinations available: *Ciprofloxacin with dexamethasone, p. 1198* - *Ciprofloxacin with fluocinolone acetonide, p. 1198*

**Chloramphenicol**

**DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

Bacterial infection in otitis externa

- TO THE EAR
- Child: Apply 2–3 drops 2–3 times a day
- Adult: Apply 2–3 drops 2–3 times a day

- **CAUTIONS** Avoid prolonged use
- **INTERACTIONS** → Appendix 1: chloramphenicol
- **SIDE-EFFECTS** Blood disorder - bone marrow depression
**Flumetasone pivalate with clioquinol**

**INDICATIONS AND DOSE**
- Eczematous inflammation in otitis externa | Mild bacterial or fungal infections in otitis externa
  - TO THE EAR
  - Child: 2–3 drops twice daily for 7–10 days, to be instilled into the ear
  - Adult: 2–3 drops twice daily for 7–10 days, to be instilled into the ear

**IMPORTANT SAFETY INFORMATION**
- MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)
  - See Corticosteroids, general use p. 670.

**CONTRA-INDICATIONS**
- Iodine sensitivity
- CAUTIONS: Avoid prolonged use, manufacturer advises avoid in perforated tympanic membrane (but used by specialists for short periods)
- SIDE-EFFECTS: Paraesthesia | skin reactions

**PATIENT AND CARER ADVICE**
- Clioquinol stains skin and clothing

**Prednisolone**

**DRUG ACTION**
- Prednisolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effects.

**INDICATIONS AND DOSE**
- Eczematous inflammation in otitis externa
  - TO THE EAR
  - Child: Apply 1–2 drops every 2–3 hours, frequency to be reduced when relief obtained
  - Adult: Apply 1–2 drops every 2–3 hours, frequency to be reduced when relief obtained

**CONTRA-INDICATIONS**
- Avoid alone in the presence of untreated infection (combine with suitable anti-infective)
- CAUTIONS: Avoid prolonged use
- INTERACTIONS → Appendix 1: corticosteroids
1198 Otitis externa

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ear drops

Ear/eye drops solution
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
Betnesol-N (RPH Pharmaceuticals AB)
Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml
Betamethasone ear/eye drops | 10 ml £2.39 DT + £2.39

CORTICOSTEROIDS  COMBINATIONS WITH ANTI-INFECTIVES

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1197, neomycin sulfate p. 1196.

INDICATIONS AND DOSE

ECZEMATOUS INFLAMMATION IN OTITIS EXTERNA

TO THE EAR USING EAR DROPS

Adult: Apply 2–3 drops 3–4 times a day
Child: Apply 2–3 drops 3–4 times a day

CONTRA-INDICATIONS  Patent grommet (although may be used by specialists, see Ear p. 1194) • perforated tympanic membrane (although may be used by specialists, see Ear p. 1194)

CAUTIONS  Avoid prolonged use

INTERACTIONS  → Appendix 1: corticosteroids • neomycin

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Ear/eye/nose drops solution
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

Betnesol-N (RPH Pharmaceuticals AB)
Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml
Betamethasone ear/eye/nose drops | 10 ml £2.39 DT + £2.39

Ciprofloxacin with dexamethasone

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 675, ciprofloxacin p. 1196.

INDICATIONS AND DOSE

ACUTE OTITIS MEDIA IN PATIENTS WITH TYPANOSTOMY TUBES

TO THE EAR

Adult: Apply 4 drops twice daily for 7 days
Child: Apply 4 drops twice daily for 7 days

CONTRA-INDICATIONS  Fungal ear infections • viral ear infections

CAUTIONS  Avoid prolonged use

INTERACTIONS  → Appendix 1: corticosteroids • quinolones

SIDE-EFFECTS

COMMON OR VERY COMMON  Ear discomfort

UNCOMMON  Ear infection fungal • flushing • irritability • malaise • otorrhoea • paraesthesia • skin reactions • taste altered • vomiting

RARE OR VERY RARE  Dizziness • headache • hearing loss • tinnitus

SIDE-EFFECTS, FURTHER INFORMATION  Manufacturer advises further evaluation of underlying conditions if otorrhoea persists after a full course, or if at least two episodes of otorrhoea occur within 6 months.

PREGNANCY  Manufacturer advises use only if potential benefit outweighs risk—no information available.

Breast Feeding  Manufacturer advises caution—no information available.

Patient and Carer Advice  Manufacturer advises counselling on administration.

Ciprofloxacin with fluocinolone acetonide

The properties listed below are those particular to the combination only. For the properties of the components please consider, ciprofloxacin p. 1196.

INDICATIONS AND DOSE

ACUTE OTITIS EXTERNA | ACUTE OTITIS MEDIA IN PATIENTS WITH TYPANOSTOMY TUBES

TO THE EAR

Adult: Apply 0.25 mL twice daily for 7 days

DOSE EQUIVALENCE AND CONVERSION

Each 0.25 mL dose contains 0.75 mg ciprofloxacin and 0.0625 mg of fluocinolone acetonide.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

See Corticosteroids, general use p. 670.
Dexamethasone with framycetin sulfate and gramicidin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 675, framycetin sulfate p. 1195.

- **INDICATIONS AND DOSE**
  - **Eczematous inflammation in otitis externa**
    - TO THE EAR
    - Child: 2–3 drops 3–4 times a day
    - Adult: 2–3 drops 3–4 times a day

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Ear drops**
  - EXCipients: May contain Polysorbates
    - Cetraxal Plus (Aspire Pharma Ltd)
      - Fluocinolone acetonide 0.05% per 1 ml, Dexamethasone 0.1% per 1 ml
    - Cetraxal plus 0.05mg/ml ear drops 0.25ml unit dose | 15 unit dose £6.01

Hydrocortisone with neomycin and polymyxin B sulfate

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 676, neomycin sulfate p. 1196.

- **INDICATIONS AND DOSE**
  - **Bacterial infection in otitis externa**
    - TO THE EAR
    - Child 3–17 years: Apply 3 drops 3–4 times a day for 7 days (review treatment if there is no clinical improvement)
    - Adult: Apply 3 drops 3–4 times a day for 7 days (review treatment if there is no clinical improvement)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Spray**
  - EXCipients: May contain Hydroxybenzoates (parabens)
    - Otomize (Teva UK Ltd)
      - Dexamethasone 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram, Acetic acid glacial 20 mg per 1 gram
        - Otomize spray | 5 ml £3.27

Dexamethasone with glacial acetic acid and neomycin sulfate

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 675, neomycin sulfate p. 1196.

- **INDICATIONS AND DOSE**
  - **Eczematous inflammation in otitis externa**
    - TO THE EAR
    - Child 2–17 years: Apply 1 spray 3 times a day
    - Adult: Apply 1 spray 3 times a day

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Ear/Eye drops**
  - EXCipients: May contain Polysorbates
    - Sofradex® (Sanofi)
      - Gramicidin 50 microgram per 1 ml, Framycetin sulfate 5 mg per 1 ml
        - Sofradex ear/eye drops | 8 ml £7.50

Aluminium acetate

- **INDICATIONS AND DOSE**
  - **Inflammation in otitis externa**
    - TO THE EAR
    - Adult: To be inserted into meatus or apply on a ribbon gauze dressing or sponge wick which should be kept saturated with the ear drops

- **DIRECTIONS FOR ADMINISTRATION**
  - For ear drops 8%—dilute 8 parts aluminium acetate ear drops (13%) with 5 parts purified water. Must be freshly prepared.

- **MEDICINAL FORMS**
  - Forms available from special-order manufacturers include: ear drops
2 Removal of earwax

BICARBONATE

Sodium bicarbonate

- **INDICATIONS AND DOSE**
  - Removal of earwax (with 5% ear drop solution)
    - TO THE EAR
    - Adult: (consult product literature)
    - Child: (consult product literature)
  - INTERACTIONS → Appendix 1: sodium bicarbonate
  - SIDE-EFFECTS
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
    - Ear drops
      - Sodium bicarbonate (non-proprietary)
        - Sodium bicarbonate 50 mg per 1 ml
        - Docusate sodium 5 mg per 1 ml
        - KliarVax Sodium Bicarbonate
        - Arjun
        - St George’s
      - Sodium bicarbonate 50 mg per 1 ml KliarVax Sodium Bicarbonate ear drops 10 ml £0.97
  - DIRECTIONS FOR ADMINISTRATION
    - The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear.
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
    - Liquid
      - Almond oil (non-proprietary)
        - Almond oil 1 ml per 1 ml
        - Urea-hydrogen peroxide 50 mg per 1 gram
        - Earol
        - Care
      - Almond oil 1 ml per 1 ml Almond oil liquid 50 ml £0.95 DT = £0.95
        - 70 ml £0.85
        - 200 ml £2.68
      - Urea hydrogen peroxide 50 mg per 1 gram
        - Exterol
        - Otex
        - Otex
        - Exterol
    - 20 ml £2.70
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
  - SIDE-EFFECTS
  - LESS SUITABLE FOR PRESCRIBING Ear drops less suitable for prescribing.
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
    - Ear drops
      - Molcer
      - Docusate sodium 50 mg per 1 ml Molcer ear drops 15 ml £5.60
    - Waxsol (Meda Pharmaceuticals Ltd)
      - Docusate sodium 5 mg per 1 ml Waxsol ear drops 10 ml £1.95 DT = £1.95

Olive oil

- **INDICATIONS AND DOSE**
  - Removal of earwax
    - TO THE EAR
    - Child: Apply twice daily for several days (if wax is hard and impacted)
    - Adult: Apply twice daily for several days (if wax is hard and impacted)
  - DIRECTIONS FOR ADMINISTRATION
    - The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Allow ear drops to warm to room temperature before use.
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
    - Spray
      - Earol
        - Earol olive oil ear spray 10 ml
      - Olive oil
        - Olive oil ear drops 10 ml £1.35–£1.42
    - Arjun
      - Arjun ear drops 10 ml £1.26
      - Cerumol (olive oil)
        - Cerumol olive oil ear drops 10 ml
      - KliarVax (Essential-Healthcare Ltd)
        - KliarVax Olive Oil Ear drops 10 ml £0.97
      - Oleax
        - Oleax ear drops 15 ml £1.40
    - Olive oil (Thornton & Ross Ltd)
      - Care olive oil ear drops 10 ml £1.42
    - St George’s
      - Olive oil ear drops 10 ml £1.40

Urea hydrogen peroxide

- **INDICATIONS AND DOSE**
  - Softening and removal of earwax
    - TO THE EAR
    - Adult: (consult product literature)
  - PATIENT AND CARER ADVICE
    - The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear.
  - LESS SUITABLE FOR PRESCRIBING
    - Urea-hydrogen peroxide ear drops are less suitable for prescribing.
  - MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
    - Ear drops
      - Exterol (Dermal Laboratories Ltd)
        - Urea hydrogen peroxide 50 mg per 1 gram Exterol 5% ear drops 8 ml £1.75 DT = £2.89
      - Otex (Dendron Ltd)
        - Urea hydrogen peroxide 50 mg per 1 gram Otex 5% ear drops 8 ml £2.89 DT = £2.89
Nose

Rhinitis

Rhinitis is often self-limiting. There are few indications for nasal sprays and drops except in allergic rhinitis and perennial rhinitis. Many nasal preparations contain sympathomimetic drugs which may damage the nasal cilia. Sodium chloride 0.9% solution p. 1040 may be used as a douche or ‘sniff’ following endonasal surgery.

Drugs used in nasal allergy

Mild allergic rhinitis is controlled by antihistamines (see under Antihistamines, allergen immunotherapy and allergic emergencies p. 277) or topical nasal corticosteroids; systemic nasal decongestants are of doubtful value. Topical nasal decongestants can be used for a short period to relieve congestion and allow penetration of a topical nasal corticosteroid.

More persistent symptoms and nasal congestion can be relieved by topical nasal corticosteroids; sodium cromoglicate p. 1208 is an alternative, but may be less effective. The topical antihistamine azelastine hydrochloride p. 1204 is useful for controlling breakthrough symptoms in allergic rhinitis. Topical antihistamines are considered less effective than topical corticosteroids but probably more effective than cromoglicate. In seasonal allergic rhinitis (e.g. hay fever), treatment should begin 2 to 3 weeks before the season commences and may have to be continued for several months; continuous treatment may be required for years in perennial rhinitis.

Montelukast p. 269 is less effective than topical nasal corticosteroids; montelukast can be used in patients with seasonal allergic rhinitis and concomitant asthma.

Sometimes allergic rhinitis is accompanied by vasomotor rhinitis. In this situation, the addition of topical nasal ipratropium bromide can reduce watery rhinorhoea.

Very disabling symptoms occasionally justify the use of systemic corticosteroids for short periods, for example, in students taking important examinations. They may also be used at the beginning of a course of treatment with a corticosteroid spray to relieve severe mucosal oedema and allow the spray to penetrate the nasal cavity.

Corticosteroids

Corticosteroid nasal preparations should be avoided in the presence of untreated nasal infections, after nasal surgery (until healing has occurred), and in pulmonary tuberculosis. Patients transferred from systemic corticosteroids may experience exacerbation of some symptoms. Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; for cautions and side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays. The height of children receiving prolonged treatment with nasal corticosteroids should be monitored; if growth is slowed, referral to a paediatrician should be considered.

Nasal polyps

Short-term use of corticosteroid nasal drops helps to shrink nasal polyps; to be effective, the drops must be administered with the patient in the ‘head down’ position. A short course of a systemic corticosteroid may be required initially to shrink large polyps. A corticosteroid nasal spray can be used to maintain the reduction in swelling and also for the initial treatment of small polyps.

Pregnancy

If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone dipropionate p. 1205, budesonide p. 1206, fluticasone p. 1206, or sodium cromoglicate may be considered.

Topical nasal decongestants

The nasal mucosa is sensitive to changes in atmospheric temperature and humidity and these alone may cause slight nasal congestion. The nose and nasal sinuses produce a litre of mucus in 24 hours and much of this finds its way silently into the stomach via the nasopharynx. Slight changes in the nasal airway, accompanied by an awareness of mucus passing along the nasopharynx causes some patients to be inaccurately diagnosed as suffering from chronic sinusitis. These symptoms are particularly noticeable in the later stages of the common cold. Sodium chloride 0.9% given as nasal drops or spray may relieve nasal congestion by helping to liquefy mucous secretions.

Inhalation of warm moist air may be useful in the treatment of symptoms of acute infective conditions. The addition of volatile substances such as menthol and eucalyptus may encourage the use of warm moist air (see under Aromatic inhalations, cough preparations and systemic nasal decongestants p. 286).

Symptoms of nasal congestion associated with vasomotor rhinitis and the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal mucosa. They are of limited value because they can give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events. Ephedrine hydrochloride p. 1205 nasal drops is the safest sympathomimetic preparation and can give relief for several hours. The more potent sympathomimetic drugs oxymetazoline and xylometazoline hydrochloride p. 1203 are more likely to cause a rebound effect.

Non-allergic watery rhinorhoea often responds well to treatment with the antimucuscarinic ipratropium bromide p. 1205.

Nasal preparations for infection

There is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis; see elimination of nasal staphylococci.

Nasal staphylococci

Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing chlorhexidine and neomycin (Nasent®), but re-colonisation frequently occurs. Coagulase-positive staphylococci are present in the noses of 40% of the population.

A nasal ointment containing mupirocin p. 1204 is also available; it should probably be held in reserve for resistant infections. In hospitals or in care establishments, mupirocin nasal ointment should be reserved for the eradication (in both patients and staff) of nasal carriage of meticillin-resistant Staphylococcus aureus (MRSA). A sample should be taken 2 days after treatment to confirm eradication. The course may be repeated if the sample is positive (and the throat is not colonised). To avoid the development of resistance, the treatment course should not exceed 7 days and the course should not be repeated on more than one occasion. If the MRSA strain is mupirocin-resistant or does not respond after 2 courses, consider alternative products such as chlorhexidine and neomycin cream.
1 Nasal congestion

SYMPATHOMIMETICS > VASOCONSTRICTOR

Ephedrine hydrochloride

- **INDICATIONS AND DOSE**
  - Nasal congestion | Sinusitis affecting the maxillary antrum
  - **BY INTRanasAL ADMINISTRATION**
    - Child 12-17 years: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril, administer ephedrine 0.5% nasal drops
    - Adult: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril

- **CAUTIONS**
  - Avoid excessive or prolonged use
  - Cardiovascular disease (in children) · diabetes mellitus · elderly · hypertension · hyperthyroidism · ischaemic heart disease (in adults) · prostatic hypertrophy (risk of acute urinary retention) (in adults)
- **INTERACTIONS**
  - Appendix 1: sympathomimetics, vasoconstrictor
- **SIDE-EFFECTS**
  - Common or very common
    - Anxiety · headache · insomnia · nausea
  - Frequency not known
    - Appetite decreased · arrhythmia · circulation impaired · dermatitis · dizziness · drug dependence · dry mouth · dyspnoea · hallucination · hyperglycaemia · hyperhidrosis · hypersalivation · hypertension · hypokalaemia · hypotension · irritability · muscle weakness · mydriasis · pain · palpitations · paranoia · piloerection · rebound congestion · syncope · thirst · tremor · urinary disorders · vasoconstriction · vasodilatation · vomiting
  - **PREGNANCY**
    - Manufacturer advises avoid.
  - **BREAST FEEDING**
    - May suppress lactation; avoid if lactation
  - **HEPATIC IMPAIRMENT**
    - Use with caution in mild to moderate renal impairment. Manufacturer advises avoid in severe renal impairment.
  - **RENAI IMPAIRMENT**
    - Use with caution in mild to moderate renal impairment. Manufacturer advises avoid in severe renal impairment.
  - **LESS SUITABLE FOR PRESCRIBING**
    - Pseudoephedrine hydrochloride is less suitable for prescribing.
  - **EXCEPTIONS TO LEGAL CATEGORY**
    - Galpseud® and Sudafed® can be sold to the public provided no more than 180 mg of pseudoephedrine base (or salts) are supplied, and ephedrine base (or salts) are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINE SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
    - Ephedrine nasal drops may be prescribed.
  - **EXCEPTIONS TO LEGAL CATEGORY**
    - Ephedrine nasal drops can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: nasal drops
    - **Nasal drops**
      - Ephedrine hydrochloride 10 mg per 1 ml
      - Ephedrine hydrochloride 5 mg per 1 ml
      - Ephedrine hydrochloride 0.5% nasal drops


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**Ephedrine hydrochloride 10 mg per 1 ml**

- 10 ml  £1.90–£1.94 DT = £1.94

**Ephedrine hydrochloride 5 mg per 1 ml**

- Ephedrine 1% nasal drops

**Pseudoephedrine hydrochloride**

- **INDICATIONS AND DOSE**
  - Congestion of mucous membranes of upper respiratory tract
  - **BY MOUTH**
    - Child 6-11 years: 30 mg 3–4 times a day
    - Child 12-17 years: 60 mg 3–4 times a day
    - Adult: 60 mg 3–4 times a day

- **IMPORTANT SAFETY INFORMATION**
    - Children under 6 years should not be given over-the-counter cough and cold medicines containing pseudoephedrine.

- **CAUTIONS**
  - Diabetes · heart disease · hypertension · hyperthyroidism · ischaemic heart disease (in adults) · prostatic hypertrophy (in adults) · raised intra-ocular pressure (in children) · susceptibility to angle-closure glaucoma (in adults)

- **INTERACTIONS**
  - Appendix 1: sympathomimetics, vasoconstrictor

- **SIDE-EFFECTS**
  - Angle closure glaucoma · anxiety · arrhythmias · circulation impaired · dry mouth · hallucination · headache · hypertension · irritability · nausea · palpitations · psychotonic disorder · skin reactions · sleep disorders · tremor · urinary retention · vomiting

- **PREGNANCY**
  - Defective closure of the abdominal wall (gastrochisis) reported very rarely in newborns after first trimester exposure.

- **BREAST FEEDING**
  - May suppress lactation; avoid if lactation not well established or if milk production insufficient.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment.

- **RENAI IMPAIRMENT**
  - Use with caution in mild to moderate renal impairment. Manufacturer advises avoid in severe renal impairment.

- **LESS SUITABLE FOR PRESCRIBING**
  - Pseudoephedrine hydrochloride is less suitable for prescribing.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Galpseud® and Sudafed® can be sold to the public provided no more than 720 mg of pseudoephedrine salts are supplied, and ephedrine base (or salts) are not supplied at the same time; for details see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINE SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
    - Ephedrine nasal drops may be prescribed.
  - **EXCEPTIONS TO LEGAL CATEGORY**
    - Ephedrine nasal drops can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**ORAL SOLUTION**

- **EXCIPIENTS:** May contain Alcohol
  - Galpseud® (Thornton & Ross Ltd)
    - Pseudoephedrine hydrochloride 6 mg per 1 ml
      - 30mg/5ml linctus sugar-free | 2000 ml  £14.00
    - Tablet
      - Galpseud® (Thornton & Ross Ltd)
        - Pseudoephedrine hydrochloride 60 mg
          - Galpseud 60mg tablets | 24 tablet  £2.25 | 100 tablet  £5.42 DT = £5.42

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www.getintopharma.com
2 Nasal infection

Sinusitis (acute)

Description of condition

Sinusitis is an inflammation of the mucosal lining of the paranasal sinuses. Acute sinusitis (rhinosinusitis) is a self-limiting condition usually triggered by a viral upper-respiratory tract infection such as the 'common cold'. Occasionally, acute sinusitis may become complicated by a bacterial infection (see Antibacterial therapy for acute sinusitis in Nose infections, antibacterial therapy p. 513).

Patients with acute sinusitis usually present with symptoms of nasal blockage or congestion, nasal discharge, dental or facial pain or pressure, and reduction or loss of the sense of smell. Symptoms usually improve within 2 to 3 weeks without requiring treatment. Rarely, acute sinusitis may lead to orbital, intracranial or skeletal complications (e.g. periorbital cellulitis, symptoms or signs of meningitis).

Aims of treatment

Treatment is aimed at managing symptoms including pain, fever, and nasal congestion as well as treatment of bacterial infection if present.

Treatment

Patients presenting with symptoms for around 10 days or less, should be given advice about the usual duration of acute sinusitis, self-care of pain or fever with paracetamol p. 444 or ibuprofen p. 1141, and when to seek medical help. Patients should be reassured that antibiotics are usually not required. Some patients may try nasal saline or nasal decongestants, however there is limited evidence to show they help to relieve nasal congestion.

Patients presenting with symptoms for around 10 days or more with no improvement could be considered for treatment with a high-dose nasal corticosteroid, such as mometasone furoate p. 1207 [unlicensed use] or fluticasone p. 1206 [unlicensed use] for 14 days. Supply of a back-up antibiotic prescription could be considered and used if symptoms do not improve within 7 days, or if they worsen rapidly or significantly.

If the patient is systematically very unwell, has signs and symptoms of a more serious illness or condition, or is at high-risk of complications, an immediate antibiotic should be given. (see Antibacterial therapy for acute sinusitis in Nose infections, antibacterial therapy p. 513).

Patients presenting with symptoms of acute sinusitis associated with a severe systemic infection or with orbital or intracranial complications should be referred to hospital.
**ANTIBACTERIALS > AMINOGLYCOSIDES**

**Chlorhexidine with neomycin**

**INDICATIONS AND DOSE**
- **Eradication of nasal carriage of staphylococci**
  - **BY INTRANASAL ADMINISTRATION**
  - Child: Apply 2–3 times a day for 5 days;
  - Adult: Apply 2–3 times a day after treatment to confirm eradication.
  - Course may be repeated once if sample positive (and throat not colonised), dose to be applied to the inner surface of each nostril
- **Preventing nasal carriage of staphylococci**
  - **BY INTRANASAL ADMINISTRATION**
  - Child: Apply twice daily
  - Adult: Apply twice daily

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **EXCIPIENTS:** May contain Arachis (peanut) oil, cetostearyl alcohol (including cetyl and stearyl alcohol).
    - **Naseptin** (Alliance Pharmaceuticals Ltd)
      - Chlorhexidine hydrochloride 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Naseptin nasal cream | 15 gram | £1.99 DT = £1.29

**Mupirocin**

**INDICATIONS AND DOSE**
- **BACTROBAN NASAL®**
  - **FOR ERADICATION OF NASAL CARRIAGE OF STAPHYLOCOCCUS AUREUS (MRSA)**
    - **BY INTRANASAL ADMINISTRATION**
    - Child: Apply 2–3 times a day for 10 days
    - Adult: Apply 4 times a day for 10 days

**SIDE-EFFECTS**
- Common or very common Skin reactions
- Uncommon Nasal mucosal disorder
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk — no information available.
- **BREAST FEEDING** No information available.
- **RENAL IMPAIRMENT** Manufacturer advises caution when mupirocin ointment used in moderate or severe impairment because it contains macrogols (polyethylene glycol).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Nasal ointment**
    - **Bactroban** (GlaxoSmithKline UK Ltd)
      - Mupirocin (as Mupirocin calcium) 20 mg per 1 gram Bactroban 2% nasal ointment | 3 gram | £4.24 DT = £4.24

**CORTICOSTEROIDS > CORTICOSTEROID COMBINATIONS WITH ANTI-INFECTIVES**

**Betamethasone with neomycin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 674, neomycin sulfate p. 520.

**INDICATIONS AND DOSE**
- **NASAL INFECTION**
  - **BY INTRANASAL ADMINISTRATION USING NASAL DROPS**
    - Child: Apply 2–3 drops 2–3 times a day, to be applied into each nostril
    - Adult: Apply 2–3 drops 2–3 times a day, to be applied into each nostril

**INTERACTIONS** → Appendix 1: corticosteroids - neomycin

**LESS SUITABLE FOR PRESCRIBING**
- Betamethasone with neomycin nasal-drops are less suitable for prescribing; there is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Nasal drops**
    - **EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate
    - **Betnesol-N** (RPH Pharmaceuticals AB)
      - Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml Betnesol-N nasal drops | 10 ml | £2.39 DT = £2.39

3 **Nasal inflammation, nasal polyps and rhinitis**

**Other drugs used for Nasal inflammation, nasal polyps and rhinitis**
- Deslurateadine, p. 280 - Fexofenadine hydrochloride, p. 280 - Ketotifen, p. 286 - Rupatadine, p. 282

**ANTIHISTAMINES > NON-SEDATING**

**Azelastine hydrochloride**

**INDICATIONS AND DOSE**
- **ALLERGIC RHINITIS**
  - **BY INTRANASAL ADMINISTRATION**
    - Child 6–17 years: 1 spray twice daily, to be administered into each nostril
    - Adult: 1 spray twice daily, to be administered into each nostril

**DOSE EQUIVALENCE AND CONVERSION**
- 1 spray equivalent to 140 micrograms.

**INTERACTIONS** → Appendix 1: antihistamines, non-sedating

**SIDE-EFFECTS**
- Common or very common Taste bitter (if applied incorrectly)
- Uncommon Epistaxis - nasal complaints

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Spray**
    - **Rhinolast** (Meda Pharmaceuticals Ltd)
      - Azelastine hydrochloride 140 microgram per 1 actuation Rhinolast 140micrograms/dose nasal spray | 22 ml | £10.50 DT = £10.50

Combinations available: **Fluticasone with azelastine**, p. 1207
ANTIMUSCARINICS

Ipratropium bromide

**INDICATIONS AND DOSE**

- Rhinorrhoea associated with allergic and non-allergic rhinitis
  - **BY INTRANASAL ADMINISTRATION**
    - Child 12-17 years: 2 sprays 2–3 times a day, dose to be sprayed into each nostril
    - Adult: 2 sprays 2–3 times a day, dose to be sprayed into each nostril

**DOSE EQUIVALENCE AND CONVERSION**

- 1 metered spray of nasal spray = 21 micrograms.

**SIDE-EFFECTS**

- **Common or very common**
  - Epistaxis
  - Gastrointestinal motility disorder
  - Headache
  - Nasal complaints
  - Throat complaints
- **Uncommon**
  - Corneal oedema
  - Eye disorders
  - Eye pain
  - Nausea
  - Respiratory disorders
  - Stomatitis
  - Vision disorders
- **Rare or very rare**
  - Palpitations

**ALLERGY AND CROSS-SENSITIVITY**

- Contra-indicated in patients with hypersensitivity to atropine or its derivatives.

**PREGNANCY**

- Manufacturer advises only use if potential benefit outweighs the risk.

**BREAST FEEDING**

- No information available—manufacturer advises only use if potential benefit outweighs the risk.

**PATIENT AND CARER ADVICE**

- Patients or carers should be counselled on appropriate administration technique and warned against accidental contact with the eye (due to risk of ocular complications).

**Driving and skilled tasks**

- Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and vision disorders.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **Excipients:** May contain Benzalkonium chloride, diisodium edetate
- **Rinotec** (Sanofi)
  - Ipratropium bromide 21 microgram per 1 dose
  - Rinotec 21 micrograms/dose nasal spray | 180 dose | £6.36 DT = £6.54

CORTICOSTEROIDS

**Corticosteroids (intransal)**

**IMPORTANT SAFETY INFORMATION**

- **MHRA/CHM ADVICE:** CORTICOSTEROIDS: RARE RISK OF CENTRAL SEROUS CHIARIOTREINOPIATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

- Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes. The MHRA recommends that patients should be advised to report any blurred vision or other visual disturbances with corticosteroid treatment given by any route; consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems.

**INDICATIONS AND DOSE**

- **BY INTRANASAL ADMINISTRATION**
  - Child 12–17 years: 200 micrograms per day
  - Adult: 400 micrograms per day

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Common or very common**
  - Altered smell sensation
  - Epistaxis
  - Headache
  - Nasal complaints
  - Taste altered
  - Throat irritation
- **Rare or very rare**
  - Glaucoma
  - Nasal septum perforation
  - Vision blurred

**INTERACTIONS**

- In children

**MONITORING REQUIREMENTS**

- Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged. Therefore also consider the side-effects of systemic corticosteroids.

**INTERACTIONS**

- **Important information**

**EXCEPTIONS TO LEGAL CATEGORY**

- In adults

**EXCEPTIONS TO LEGAL CATEGORY**

- Preparations of beclometasone dipropionate can be sold to the public for nasal administration as a nasal spray.

**INDICATIONS AND DOSE**

- **BY INTRANASAL ADMINISTRATION**
  - Child 6–17 years: 100 micrograms twice daily, dose to be administered into each nostril, reduced to 50 micrograms twice daily, dose to be administered into each nostril, dose to be reduced when symptoms controlled; maximum 400 micrograms per day
  - Adult: 100 micrograms twice daily, dose to be administered into each nostril, reduced to 50 micrograms twice daily, dose to be administered into each nostril, dose to be reduced when symptoms controlled; maximum 400 micrograms per day

**SIDE-EFFECTS**

- **Common or very common**
  - Altered smell sensation
  - Epistaxis
  - Headache
  - Nasal complaints
  - Taste altered
  - Throat irritation
- **Rare or very rare**
  - Glaucoma
  - Nasal septum perforation
  - Vision blurred

**INTERACTIONS**

- **Important information**

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **Excipients:** May contain Benzalkonium chloride, polysorbates
- **Beclometasone dipropionate (Non-proprietary)**
  - Beclometasone dipropionate 50 microgram per 1 dose
  - Beconase Aqueous 50 micrograms/dose nasal spray | 200 dose | £2.63 DT = £3.02
- **Beconase** (GlaxoSmithKline UK Ltd, Omega Pharma Ltd)
  - Beclometasone dipropionate 50 microgram per 1 dose
  - Beconase Aqueous 50 micrograms/dose nasal spray | 200 dose | £2.63 DT = £3.02

**Driving and skilled tasks**

- Manufacturer advises patients and carers should be counselled on appropriate administration technique and warned against accidental contact with the eye (due to risk of ocular complications).
Budesonide

**DRUG ACTION** Budesonide is a glucocorticoid, which exerts significant local anti-inflammatory effects.

**INDICATIONS AND DOSE**

**Allergic rhinitis** | **Nasal polyps**
--- | ---
**BY INTRANASAL ADMINISTRATION**
- Child 6-17 years: 128 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 64 micrograms twice daily, dose to be administered to each nostril, reduced dose when control achieved
- Adult: 128 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 64 micrograms twice daily, dose to be administered to each nostril, reduced dose when control achieved

Prophylaxis and treatment of allergic and vasomotor rhinitis

**BY INTRANASAL ADMINISTRATION**
- Child 12-17 years: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning, alternatively initially 100 micrograms twice daily, dose to be administered to each nostril, reduced to 100 micrograms once daily, dose to be administered into each nostril, dose can be reduced when control achieved
- Adult: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning, alternatively 100 micrograms twice daily, dose to be administered to each nostril, reduced to 100 micrograms once daily, dose to be administered into each nostril, dose can be reduced when control achieved

**CONTRAINDICATIONS**
- Known hypersensitivity to any component of the formulation
- Adrenal insufficiency
- Treated with systemic corticosteroids within 2 months

**SIDE-EFFECTS**
- Nasal irritation, burning, or dryness
- Itching of the nasal mucosa
- Nasal ulceration
- Rhinitis medicamentosa

**INTERACTIONS**
- Reduced effect of budesonide with corticosteroids

**MEDICINAL FORMS**
- Nasal polyps: 64 micrograms per 1 dose
- Allergic rhinitis: 32 micrograms per 1 dose
- Nasal spray: 64 micrograms per 1 dose

**PRECAUTIONS**
- Avoid use in patients with a history of nasal carcinoma
- Use with caution in patients with a history of peptic ulcer disease

**SAFETY INFORMATION**
- Do not use if the bottle or cap is damaged
- Keep out of reach of children

**PRESCRIBING INFORMATION**
- Store at 2–8°C
- Do not freeze

**EXCEPTIONS TO LEGAL CATEGORY**
- Rare or very rare
- Adrenal suppression

**JUBN**
- Budesonide (Non-proprietary)
- Budesonide 64 microgram per 1 dose
- Budesonide 32 microgram per 1 dose
- Budesonide 16 microgram per 1 dose
- Budesonide 8 microgram per 1 dose

**APPENDICES**
- Appendix 1: corticosteroids

**REFERENCE**
- Budesonide 16 microgram per 1 dose

Fluticasone

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of allergic rhinitis and perennial rhinitis**

**BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**
- Child 4-11 years: 50 micrograms once daily, to be administered into each nostril preferably in the morning
- Child 12-17 years: 100 micrograms once daily, to be administered into each nostril preferably in the morning

www.getintopharma.com
50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved

**Nasal polyps**

- **BY INTRANASAL ADMINISTRATION USING NASAL DROPS**
- **Child 6-17 years**: 27.5 micrograms once daily, to be sprayed into each nostril, reduced to 27.5 micrograms once daily, dose to be reduced once control achieved; use maximum effective dose
- **Child 12-17 years**: 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose
- **Adult**: 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose

**DOSE Equivalence and Conversion**

- With intransal use
- 1 spray equivalent to 27.5 micrograms.

**INTERACTIONS** → Appendix 1: corticosteroids

**SIDE-EFFECTS**

SIDE-EFFECTS, FURTHER INFORMATION: Nasal ulceration occurs commonly with nasal preparations containing fluticasone furoate.

**EXCEPTIONS TO LEGAL CATEGORY**

- With intranasal use in adults. Preparations of fluticasone propionate can be sold to the public for nasal administration (other than by pressurised nasal spray) if supplied for the prevention and treatment of allergic rhinitis in adults over 18 years, subject to max. single dose of 100 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. 3 months, and a pack size of 3 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **Excipients**: May contain Benzalkonium chloride, polysorbates
- **Fluticasone furoate 27.5 microgram per 1 dose** Avamys 27.5 micrograms/dose nasal spray
- **Flixonase** (GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline UK Ltd)
- **Fluticasone propionate 50 microgram per 1 dose** Flixonase 50 micrograms/dose nasal spray
- **Nasofan** (Teva UK Ltd)

**Fluticasone with azelastine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 1206, azelastine hydrochloride p. 1204.

**INDICATIONS AND DOSE**

Moderate to severe seasonal and perennial allergic rhinitis, if monotherapy with antihistamine or corticosteroid is inadequate

- **BY INTRANASAL ADMINISTRATION**
- **Child 12-17 years**: 1 spray twice daily, dose to be administered into each nostril
- **Adult**: 1 spray twice daily, dose to be administered into each nostril

**INTERACTIONS** → Appendix 1: antihistamines, non-sedating - corticosteroids

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **Excipients**: May contain Benzalkonium chloride, polysorbates
- **Dymista (Meda Pharmaceuticals Ltd)**
- **Fluticasone propionate 50 microgram per 1 actuation, Azelastine hydrochloride 137 microgram per 1 actuation** Dymista 137 micrograms/dose nasal spray

- **Mometasone furoate**

**INDICATIONS AND DOSE**

Prophylaxis and treatment of seasonal allergic or perennial rhinitis

- **BY INTRANASAL ADMINISTRATION**
- **Child 3-11 years**: 50 micrograms daily, dose to be sprayed into each nostril
- **Child 12-17 years**: 100 micrograms daily, increased if necessary up to 200 micrograms daily, dose to be sprayed into each nostril; reduced to 50 micrograms daily, dose to be reduced when control achieved, dose to be sprayed into each nostril
- **Adult**: 100 micrograms daily, increased if necessary up to 200 micrograms daily, dose to be sprayed into each nostril; reduced to 50 micrograms daily, dose to be reduced when control achieved, dose to be sprayed into each nostril

**INTERACTIONS** → Appendix 1: corticosteroids

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**: Nasal ulceration occurs commonly with preparations containing mometasone furoate.
**Medications**

**Mast-cell stabilisers**

Ear, nose and oropharynx (Sodium cromoglicate)

- **Sodium cromoglicate**
  - **Indications and dose**
    - Prophylaxis of allergic rhinitis
      - By intranasal administration
        - Child: 1 spray 2–4 times a day, to be administered into each nostril
        - Adult: 1 spray 2–4 times a day, to be administered into each nostril
  - **Unlicensed use**
    - In children. Licensed for use in children (age range not specified by manufacturers).
  - **Exclusions to legal category**
    - Bronchospasm (transient)
    - Frequency not known: Local reaction
  - **Side-effects**
    - Rare or very rare: Bronchospasm (transient)
    - Frequency not known: Local reaction
  - **Medicinal forms**
    - No licensed medicines listed.

**Triamcinolone acetonide**

- **Drug action**
  - Triamcinolone exerts predominantly glucocorticoid effects with minimal mineralocorticoid effect.
- **Indications and dose**
  - Prophylaxis and treatment of allergic rhinitis
    - By intranasal administration
      - Child: 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 55 micrograms once daily, dose to be sprayed into each nostril, reduced dose when control achieved; maximum duration of treatment 3 months
      - Adult: 110 micrograms once daily, dose to be sprayed into each nostril, reduced to 55 micrograms once daily, dose to be sprayed into each nostril, reduced dose when control achieved
  - **Side-effects**
    - Rare: Bronchospasm (transient)
    - Frequency not known: Local reaction
- **Exclusions to legal category**
  - Bronchospasm (transient)
  - Frequency not known: Local reaction
- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Spray**
    - **Excipients:** May contain benzalkonium chloride, polysorbates
    - **Mometasone furoate (Non-proprietary)**
      - Mometasone furoate 50 microgram per 1 dose — Nasacort
        - Nasacort (Sanofi) — 50 micrograms/dose nasal spray 140 dose [PND] £7.39 DT + £3.39
        - **Exciipients:** May contain benzalkonium chloride, disodium edetate, polysorbates
  - **Topical nasal spray**
    - **Excipients:** May contain benzalkonium chloride, disodium edetate, polysorbates
    - **Mometasone furoate (Non-proprietary)**
      - Mometasone furoate (Sanofi) — Nasonex
        - Nasonex (Merck Sharp & Dohme Ltd) — 50 micrograms/dose nasal spray 140 dose [PND] £7.68 DT + £1.71

**Treatment of dry mouth**

Overview

Dry mouth (xerostomia) may be caused by drugs with antimuscarinic (anticholinergic) side-effects (e.g., antispasmodics, tricyclic antidepressants, and some antipsychotics), by diuretics, by irradiation of the head and neck region or by damage to or disease of the salivary glands. Patients with a persistently dry mouth may develop a burning or scalded sensation and have poor oral hygiene; they may develop increased dental caries, periodontal disease, intolerance of dentures, and oral infections (particularly candidiasis). Dry mouth may be relieved in many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles. Sugar-free chewing gum stimulates salivation in patients with residual salivary function.

Artificial saliva can provide useful relief of dry mouth. A properly balanced artificial saliva should be of a neutral pH and contain electrolytes (including fluoride) to correspond approximately to the composition of saliva. The acidic pH of some artificial saliva products may be inappropriate. Of the proprietary preparations, Aquora®, Biotène Oralbalance®, gel or Xerolin® can be used for any condition giving rise to a dry mouth. BioXtra®, Glandosane®, Saliva Orthana® and Salivez®, have ACBS approval for dry mouth associated only with radiotherapy or sicca syndrome. Salivax® pastilles, which act locally as salivary stimulants, are also available for any condition leading to a dry mouth and SST tablets may be prescribed for dry mouth in patients with salivary gland impairment (and patent salivary ducts).

Pilocarpine tablets p. 1210 are licensed for the treatment of xerostomia following irradiation for head and neck cancer and for dry mouth and dry eyes (xerophthalmia) in Sjögren’s syndrome. They are effective only in patients who have some residual salivary gland function, and therefore should be withdrawn if there is no response.

**Artificial saliva products**

- **Artificial saliva products**
  - **As saliva orthana® lozenges**
    - Mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral
  - **Indications and dose**
    - Dry mouth as a result of having (or having undergone) radiotherapy (ACBS)
    - Dry mouth as a result of sicca syndrome (ACBS)
  - **Prescribing and dispensing information**
    - As saliva orthana® lozenges do not contain fluoride.
    - As saliva orthana® lozenges (A S Pharma Ltd) — 30 lozenges[ACBS] — NHS indicative price = £3.50 - Drug Tariff (Part VIII)
    - Category C price = £3.50

**Lubricants**

**Sodium cromoglicate**

(Sodium cromoglicate)

- **Indications and dose**
  - Prophylaxis of allergic rhinitis
    - By intranasal administration
      - Child: 1 spray 2–4 times a day, to be administered into each nostril
      - Adult: 1 spray 2–4 times a day, to be administered into each nostril
  - **Side-effects**
    - Rare or very rare: Bronchospasm (transient)
    - Frequency not known: Local reaction
  - **Exclusions to legal category**
    - Bronchospasm (transient)
    - Frequency not known: Local reaction
  - **Medicinal forms**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Spray**
      - **Excipients:** May contain benzalkonium chloride, disodium edetate, polysorbates
      - **Nasacort** (Sanofi)
        - Triamcinolone acetonide 55 microgram per 1 dose — Nasacort
          - Nasacort (Sanofi) — 50 micrograms/dose nasal spray 120 dose [PND] £7.39 DT + £3.39

**Ear, nose and oropharynx**

- **Bronchospasm (transient)**
  - **Frequency not known:** Local reaction
- **Side-effects**
  - Rare or very rare: Bronchospasm (transient)
  - Frequency not known: Local reaction
- **Interactions**
  - Appendix 1: Corticosteroids
- **Exclusions to legal category**
  - Bronchospasm (transient)
  - Frequency not known: Local reaction
- **Medicinal forms**
  - There can be variation in the licensing of different medicines containing the same drug.
AS SALIVA ORTHANA® SPRAY
Gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral.

- INDICATIONS AND DOSE
Symptomatic treatment of dry mouth
  - BY MOUTH
  - Adult: Apply 2–3 sprays as required, spray onto oral and pharyngeal mucosa

- PROFESION SPECIFIC INFORMATION
Dental practitioners’ formulary
AS Saliva Orthana® Oral Spray may be prescribed.

BIOXTRA® GEL
Lactoperoxidase, lactoferrin, lysozyme, whey colostrum, xylitol and other ingredients.

- INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy | Dry mouth as a result of sicca syndrome
  - BY MOUTH
  - Adult: As required, apply to oral mucosa

- PROFESION SPECIFIC INFORMATION
Dental practitioners’ formulary
BioXtra® Gel may be prescribed.

BioXtra Dry Mouth oral gel (R.I.S. Products Ltd)
40 ml - NHS indicative price = £3.94 • Drug Tariff (Part IXa)

BIOTENE ORALBALANCE®
Lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis

- INDICATIONS AND DOSE
Symptomatic treatment of dry mouth
  - BY MOUTH
  - Adult: Apply as required, apply to gums and tongue

- PATIENT AND CARER ADVICE
Avoid use with toothpastes containing detergents (including foaming agents).

- PROFESION SPECIFIC INFORMATION
Dental practitioners’ formulary
BioTene Oralbalance® Saliva Replacement Gel may be prescribed as Artificial Saliva Gel.

BioTene Oralbalance dry mouth saliva replacement gel (Glassmanns Consumer Healthcare) Glucose oxidase 12000 unit,
Lactoferrin 12 mg, Lactoperoxidase 12000 unit, Muramidase 12 mg 50 gram - NHS indicative price = £4.46 • Drug Tariff (Part IXa)

GLANDOSANE®
Carmellose sodium 500 mg, sorbitol 1.5 g, potassium chloride 60 mg, sodium chloride 42.2 mg, magnesium chloride 2.6 mg, calcium chloride 7.3 mg, and dipotassium hydrogen phosphate 17.1 mg/50 g, pH 5.75.

- INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy (ACBS) | Dry mouth as a result of sicca syndrome (ACBS)
  - BY MOUTH
  - Adult: As required, spray onto oral and pharyngeal mucosa

- PROFESION SPECIFIC INFORMATION
Dental practitioners’ formulary
Glandosane® Aerosol Spray may be prescribed.

Glandosane synthetic saliva spray lemon (Fresenius Kabi Ltd)
50 ml - NHS indicative price = £5.68 • Drug Tariff (Part IXa)

Glandosane synthetic saliva spray natural (Fresenius Kabi Ltd)
50 ml - NHS indicative price = £5.68 • Drug Tariff (Part IXa)

SALIVEZE®
Carmellose sodium (sodium carboxymethylcellulose), calcium chloride, magnesium chloride, potassium chloride, sodium chloride, and dibasic sodium phosphate, pH neutral

- INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy (ACBS) | Dry mouth as a result of sicca syndrome (ACBS)
  - BY MOUTH
  - Adult: Apply 1 spray as required, spray onto oral mucosa

- PROFESION SPECIFIC INFORMATION
Dental practitioners’ formulary
Saliveze® Oral Spray may be prescribed.

Saliveze mouth spray (Wyvern Medical Ltd)
50 ml - NHS indicative price = £3.50 • Drug Tariff (Part IXa)

SALIVIX®
Sugar-free, reddish-amber, acacia, malic acid and other ingredients.

- INDICATIONS AND DOSE
Symptomatic treatment of dry mouth
  - BY MOUTH USING PASTILLES
  - Adult: 1 unit as required, suck pastille
PARASYMPATHOMIMETICS

Pilocarpine

- INDICATIONS AND DOSE
  - Symptomatic treatment of dry mouth
  - BY MOUTH
  - Adult: 1 spray as required

- PROFESSION SPECIFIC INFORMATION
  - Dental practitioners’ formulary
    - Xerotic® Oral Spray may be prescribed as Artificial Saliva Oral Spray.
    - Xerotic® Pastilles (SpePharm UK Ltd)
      - 100 ml - NHS indicative price = £6.86 - Drug Tariff (Part Ixa)

- INDICATIONS AND CONTRA-INDICATIONS
  - Xerostomia following irradiation for head and neck cancer
    - BY MOUTH
    - Adult: 5 mg 3 times a day for 4 weeks; increased if tolerated to up to 30 mg daily in divided doses if required, to be taken with meals or immediately after eating (last dose always with evening meal); maximum therapeutic effect normally within 4–8 weeks; discontinue if no improvement after 2–3 months

  - Dry mouth and dry eyes in Sjögren's syndrome
    - BY MOUTH
    - Adult: 5 mg 4 times a day; increased if tolerated to up to 30 mg daily in divided doses if required, to be taken with meals and at bedtime, discontinue if no improvement after 2–3 months

- INTERACTIONS
  - Chloral hydrate:
  - Seizures

- SIDE-EFFECTS
  - Common or very common
    - Asthenia
    - Conjunctivitis
    - Constipation
    - Diarrhoea
    - Dizziness
    - Excessive tearing
    - Eye pain
    - Flushing
    - Gastrointestinal discomfort
    - Headache
    - Hyperhidrosis
    - Hypersalivation
    - Hypertension
    - Increased risk of infection
    - Nausea
    - Palpitations
    - Skin reactions
    - Urinary disorders
    - Vision disorders
    - Vomiting
  - Uncommon
    - Gastrointestinal disorders
  - Frequency not known
    - Afibrile: agitation
    - Arrhythmias
    - Atrialventricular block
    - Chills
    - Confusion
    - Hallucination
    - Hypotension
    - Memory loss
    - Psychiatric disorders
    - Respiratory distress
    - Shock
    - Tremor

- PREGNANCY
  - Avoid — smooth muscle stimulant; toxicity in animal studies.

- BREAST FEEDING
  - Manufacturer advises avoid — present in milk in animal studies.

- HEPATIC IMPAIRMENT
  - Manufacturer advises caution in moderate to severe cirrhosis.
  - Dose adjustments
    - Manufacturer advises initial dose reduction in moderate to severe cirrhosis.

- RENAL IMPAIRMENT
  - Manufacturer advises caution with tablets.

- PATIENT AND CARER ADVICE
  - Driving and skilled tasks
    - Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

  - Tablet

  - CAUTIONARY AND ADVISORY LABELS 21, 27

    - Salagen (Merus Labs Luxco S.a R.L.)
      - Pilocarpine hydrochloride 5 mg tablets, 84 tablet

- BNF 78

2 Oral hygiene

Mouthwashes and other preparations for oropharyngeal use

Lozenges and sprays

There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some of these preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

Mouthwashes, gargles, and dentifrices

Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. A warm saline mouthwash is ideal and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting compound sodium chloride mouthwash p. 1212 with an equal volume of warm water.

Mouthwashes containing an oxidising agent, such as hydrogen peroxide p. 1212, may be useful in the treatment of ulcerative gingivitis (Vincent’s infection) since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.

Chlorhexidine p. 1211 is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed.

Chlorhexidine mouthwash is used in the treatment of denture stomatitis. It is also used in the prevention of oral candidiasis in immunocompromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in patients undergoing dental procedures.
Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetic stomatitis) or if the patient has a haemorrhagic disorder, or is disabled.

Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing products.

There is no convincing evidence that gargles are effective in adults.

ANTISEPTICS AND DISINFECTANTS

Chlorhexidine

**INDICATIONS AND DOSE**

Oral hygiene and plaque inhibition | Oral candidiasis | Gingivitis | Management of apthous ulcers

- **BY MOUTH USING MOUTHWASH**
  - Child: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)
  - Adult: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)

Denture stomatitis

- **MOUTHWASH**
  - Adult: Cleanse and soak dentures in mouthwash solution for 15 minutes twice daily

Oral hygiene and plaque inhibition and gingivitis

- **BY MOUTH USING DENTAL GEL**
  - Child: Apply 1–2 times a day, to be brushed on the teeth
  - Adult: Apply 1–2 times a day, to be brushed on the teeth

Oral candidiasis | Management of apthous ulcers

- **BY MOUTH USING DENTAL GEL**
  - Child: Apply 1–2 times a day, to affected areas
  - Adult: Apply 1–2 times a day, to affected areas

Oral hygiene and plaque inhibition | Oral candidiasis | Gingivitis | Management of apthous ulcers

- **BY MOUTH USING OROMUCOSAL SPRAY**
  - Child: Apply up to 12 sprays twice daily as required, to be applied tooth, gingival, or ulcer surfaces
  - Adult: Apply up to 12 sprays twice daily as required, to be applied tooth, gingival, or ulcer surfaces

Bladder irrigation and catheter patency solutions

- **BY INTERVESICAL INSTILLATION**
  - Adult: (consult product literature)

**UNLICENSED USE**

*Corsodyl®* not licensed for use in children under 12 years (unless on the advice of a healthcare professional).

**SIDE-EFFECTS**

- Common or very common
  - With oromucosal use: Dry mouth, hypersensitivity, oral disorders, taste altered, tongue discolouration

**SIDE-EFFECTS, FURTHER INFORMATION**

If desquamation occurs with mucosal irritation, discontinue treatment.

**PATIENT AND CARER ADVICE**

- With oral (topical) use: Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing product.

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary**

*Corsodyl®* dental gel may be prescribed as Chlorhexidine Gluconate Gel; *Corsodyl®* mouthwash may be prescribed as Chlorhexidine Mouthwash; *Corsodyl®* oral spray may be prescribed as Chlorhexidine Oral Spray.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Dental gel**

- *Corsodyl* (GlaxoSmithKline Consumer Healthcare)
  - Chlorhexidine gluconate 10 mg per 1 gram
  - Chlorhexidine gluconate 0.2% catheter maintenance solution | 100 ml
- *Uro-Tainer* (chlorhexidine) (B.Braun Medical Ltd)
  - Chlorhexidine acetate 200 microgram per 1 ml

**Irrigation**

- Chlorhexidine (Non-proprietary)
  - Chlorhexidine acetate 200 microgram per 1 ml
  - Chlorhexidine acetate 0.2% irrigation solution | 100 ml

**Mouthwash**

- Chlorhexidine (Non-proprietary)
  - Chlorhexidine gluconate 2 mg per 1 ml
  - Chlorhexidine gluconate 0.2% mouthwash anised | 300 ml
  - Chlorhexidine gluconate 0.2% mouthwash natural | 300 ml
  - Chlorhexidine gluconate 0.2% mouthwash peppermint | 300 ml

**Hexetidine**

**INDICATIONS AND DOSE**

Oral hygiene

- **BY MOUTH USING MOUTHWASH**
  - Child 12-17 years: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted
  - Adult: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted

**SIDE-EFFECTS**

- Rare or very rare
  - Anaesthesia • taste altered
  - Frequency not known
  - Cough • dry mouth • dysphagia • dysphonia • nausea • salivary gland enlargement • vomiting

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Mouthwash**

- Oraldene (McNeil Products Ltd)
  - Hexetidine 1 mg per 1 ml
  - Oraldene 0.1% mouthwash peppermint sugar-free | 200 ml

**www.getintopharma.com**
Hydrogen peroxide

**DRUG ACTION** Hydrogen peroxide is an oxidising agent.

**INDICATIONS AND DOSE**

**Oral hygiene (with hydrogen peroxide 6%)**

- **BY MOUTH USING MOUTHWASH**
  - Child: Rinse or gargle 15 ml 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water
  - Adult: Rinse or gargle 15 ml 2–3 times a day for 2–3 minutes, to be diluted in half a tumblerful of warm water

**PEROXYL®**

**Oral hygiene**

- **BY MOUTH USING MOUTHWASH**
  - Child 6–17 years: Rinse or gargle 10 ml 3 times a day for about 1 minute, for maximum 7 days, to be used after meals and at bedtime
  - Adult: Rinse or gargle 10 ml up to 4 times a day for about 1 minute, to be used after meals and at bedtime

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Hydrogen Peroxide Mouthwash, BP consists of hydrogen peroxide 6% solution (= approx. 20 volume) BP.

**HANDLING AND STORAGE** Hydrogen peroxide bleaches fabric.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Hydrogen Peroxide Mouthwash may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Mouthwash**

- **Peroxyl** (Colgate-Palmolive (UK) Ltd)
  - Hydrogen peroxide 15 mg per 1 ml Peroxyl 1.5% mouthwash sugar-free £300 ml RET £2.94 OT £2.34

Sodium chloride

**INDICATIONS AND DOSE**

**Oral hygiene**

- **BY MOUTH USING MOUTHWASH**
  - Child: Rinse or gargle as required
  - Adult: Rinse or gargle as required

**DIRECTIONS FOR ADMINISTRATION** Extemporaneous mouthwash preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 ml, double-strength chloroform water 50 ml, water to 100 ml. To be diluted with an equal volume of warm water.

**PRESCRIBING AND DISPENSING INFORMATION** No mouthwash preparations available—when prepared extemporaneously, the BP states Sodium Chloride Mouthwash, Compound, BP consists of sodium bicarbonate 1%, sodium chloride 1.5% in a suitable vehicle with peppermint flavour.

In children The RCPCH and NPPG recommend that, when a liquid special of sodium chloride is required, the following strength is used: 5 mmol/mL.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Compound Sodium Chloride Mouthwash may be prescribed.

**MEDICINAL FORMS** No licensed medicines listed.

2.1 Dental caries

**Fluoride imbalance**

**Overview**

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect.

When the fluoride content of drinking water is less than 700 micrograms per litre (0.7 parts per million), daily administration of fluoride tablets or drops provides suitable supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply. Infants need not receive fluoride supplements until the age of 6 months.

Dentifrices which incorporate sodium fluoride or monofluorophosphate are also a convenient source of fluoride.

Individuals who are either particularly caries prone or medically compromised may be given additional protection by use of fluoride rinses or by application of fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied regularly under professional supervision; extreme caution is necessary to prevent children from swallowing any excess. Less concentrated gels are available for home use. Varnishes are also available and are particularly valuable for young or disabled children since they adhere to the teeth and set in the presence of moisture.
VITAMINS AND TRACE ELEMENTS

Sodium fluoride

- **INDICATIONS AND DOSE**
  - Prophylaxis of dental caries for water content less than 300 micrograms/litre (0.3 parts per million) of fluoride ion
    - **BY MOUTH USING TABLETS**
    - Child 6 months-2 years: 250 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 3-5 years: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 6-17 years: 1 mg daily, doses expressed as fluoride ion (F⁻)
    - Adult: 1 mg daily, doses expressed as fluoride ion (F⁻)
  - Prophylaxis of dental caries for water content between 300 and 700 micrograms/litre (0.3-0.7 parts per million) of fluoride ion
    - **BY MOUTH USING TABLETS**
    - Child 6-5 years: 250 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Child 6-17 years: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
    - Adult: 500 micrograms daily, doses expressed as fluoride ion (F⁻)
  - Prophylaxis of dental caries for water content above 700 micrograms/litre (0.7 parts per million) of fluoride ion
    - **BY MOUTH USING TABLETS**
    - Child 6-17 years: Supplements not advised
    - Adult: Supplements not advised
  - Prophylaxis of dental caries for individuals who are caries prone or medically compromised
    - **BY MOUTH USING MOUTHWASH**
    - Adult: Rinse or gargle 10 mL daily
  - **DOSE EQUIVALENCE AND CONVERSION**
    - Sodium fluoride 2.2 mg provides approx. 1 mg fluoride ion.
    - These doses reflect the recommendations of the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry *(Br Dent / 1997, 182: 6–7).*

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**

**Prophylaxis of dental caries**

- **BY MOUTH USING PASTE**
  - Child 10-17 years: Apply 1 centimetre twice daily, to be applied using a toothbrush
  - Adult: Apply 1 centimetre twice daily, to be applied using a toothbrush

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE**

**Prophylaxis of dental caries**

- **BY MOUTH USING PASTE**
  - Child 16-17 years: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush
  - Adult: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush

**EN-DE-KAY® FLUORRINSE**

**Prophylaxis of dental caries for individuals who are caries prone or medically compromised**

- **BY MOUTH USING MOUTHWASH**
  - Adult: 5 drops daily, dilute 5 drops to 10 mL of water, alternatively 20 drops once weekly, dilute 20 drops to 10 mL.

**CONTRA-INDICATIONS** Not for areas where drinking water is fluoridated

**SIDE-EFFECTS** Dental fluorosis

**DIRECTIONS FOR ADMINISTRATION**

- With oral use Tablets should be sucked or dissolved in the mouth and taken preferably in the evening.
- With oral (topical) use For mouthwash, rinse mouth for 1 minute and then spit out.

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE** Brush teeth for 3 minutes before spitting out.

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE** Brush teeth for 1 minute before spitting out.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral tablet formulations may include orange.

**PATIENT AND CARER ADVICE**

Mouthwash Avoid eating, drinking, or rinsing mouth for 15 minutes after use.

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE** Patients or carers should be given advice on how to administer Sodium fluoride toothpaste.

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE** Patients or carers should be given advice on how to administer sodium fluoride toothpaste.

Avoid drinking or rinsing mouth for 30 minutes after use.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary

Tablets may be prescribed as Sodium Fluoride Tablets. Oral drops may be prescribed as Sodium Fluoride Oral Drops.

Mouthwashes may be prescribed as Sodium Fluoride Mouthwash 0.05% or Sodium Fluoride Mouthwash 2%.

Dental information

Fluoride mouthwash, oral drops, tablets and toothpaste are prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).

There are also arrangements for health authorities to supply fluoride tablets in the course of pre-school dental schemes, and they may also be supplied in school dental schemes.

Fluoride gels are not prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE DENTAL PRACTITIONERS’ FORMULARY**

May be prescribed as Sodium Fluoride Toothpaste 1.1%.

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE DENTAL PRACTITIONERS’ FORMULARY**

May be prescribed as Sodium Fluoride Toothpaste 0.619%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Endekay** (Manx Healthcare Ltd)
  - Sodium fluoride 1.1 mg Endekay Fluotabs 3-6 Years 1.1mg tablets 200 tablet £2.38 DT = £2.38
  - Sodium fluoride 2.2 mg Endekay Fluotabs 6+ Years 2.2mg tablets 200 tablet £2.38 DT = £2.38

**Paste**

- **Colgate Duraphat** (Colgate-Palmolive (UK) Ltd)
  - Fluoride (as Sodium fluoride) 2.8 mg per 1 gram Colgate Duraphat 2800 ppm fluoride toothpaste sugar-free | 75 ml Pot £3.26 DT = £3.26
  - Fluoride (as Sodium fluoride) 5 mg per 1 gram Colgate Duraphat 5000 ppm fluoride toothpaste sugar-free | 51 gram Pot £6.50 DT = £6.50

**Chewable tablet**

- **Fluor-a-day** (DHP Healthcare Ltd)
  - Sodium fluoride 1.1 mg Fluor-a-day 1.1mg chewable tablets sugar-free | 200 tablet £3.38 DT = £3.38
  - Sodium fluoride 2.2 mg Fluor-a-day 2.2mg chewable tablets sugar-free | 200 tablet £3.38 DT = £3.38

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oral ulceration and inflammation

Ulceration and inflammation
Ulceration of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthae, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy (see also Chemotherapy induced mucositis and myelosuppression under Cytotoxic drugs p. 888). It is important to establish the diagnosis in each case as the majority of these lesions require specific management in addition to local treatment. Local treatment aims to protect the ulcerated area, to relieve pain, to reduce inflammation, or to control secondary infection. Patients with an unexplained mouth ulcer of more than 3 weeks’ duration require urgent referral to hospital to exclude oral cancer.

Simple mouthwashes
A saline mouthwash may relieve the pain of traumatic ulceration. The mouthwash is made up with warm water and used at frequent intervals until the discomfort and swelling subsides.

Antiseptic mouthwashes
Secondary bacterial infection may be a feature of any mucosal ulceration; it can increase discomfort and delay healing. Use of a chlorhexidine mouthwash p. 1211 is often beneficial and may accelerate healing of recurrent aphthae.

Corticosteroids
Topical corticosteroid therapy may be used for some forms of oral ulceration. In the case of aphthous ulcers it is most effective if applied in the ’prodromal’ phase. Thrush or other types of candidiasis are recognised complications of corticosteroid treatment.

Hydrocortisone oromucosal tablets p. 1216 are allowed to dissolve next to an ulcer and are useful in recurrent aphthae and erosive lichenoid lesions.

Beclometasone dipropionate inhaler p. 257 sprayed on the oral mucosa is used to manage oral ulceration [unlicensed indication]. Alternatively, betamethasone soluble tablets p. 1216 dissolved in water can be used as a mouthwash to treat oral ulceration [unlicensed indication].

Systemic corticosteroid therapy (see under Corticosteroids, inflammatory disorders p. 1153), is reserved for severe conditions such as pemphigus vulgaris.

Local analgesics
Local analgesics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration so that analgesia cannot be maintained continuously throughout the day. The main indication for a topical local analgesic is to relieve the pain of otherwise intractable oral ulceration particularly when it is due to major aphthae. For this purpose lidocaine hydrochloride 5% ointment p. 1214 or lozenges containing a local anaesthetic are applied to the ulcer. Lidocaine hydrochloride 10% solution as spray can be applied thinly to the ulcer [unlicensed indication] using a cotton bud. When local anaesthetics are used in the mouth care must be taken not to produce anaesthesia of the pharynx before meals as this might lead to choking.

Preparations on sale to the public: many mouth ulcer preparations, throat lozenges, and throat sprays on sale to the public contain a local anaesthetic. To identify the active ingredients in such preparations, consult the product literature of the manufacturer—the correct proprietary name should be ascertained as many products have very similar names but different active ingredients.

Benzydamine hydrochloride p. 1215 and flurbiprofen p. 1216 are non-steroidal anti-inflammatory drugs (NSAIDs). Benzydamine hydrochloride mouthwash or spray may be useful in reducing the discomfort associated with a variety of ulcerative conditions. It has also been found to be effective in reducing the discomfort of tonsillectomy and post-irradiation mucositis. Some patients find the full-strength mouthwash causes some stinging and, for them, it should be diluted with an equal volume of water. Flurbiprofen lozenges are licensed for the relief of sore throat.

Choline salicylate p. 1217 is a derivative of salicylic acid and has some analgesic action. The dental gel may provide relief for recurrent aphthae, but excessive application or confinement under a denture irritates the mucosa and can itself cause ulceration.

Other preparations
Doxycycline p. 564 rinsed in the mouth may be of value for recurrent aphthous ulceration.

Periodontitis
Low-dose doxycycline (Periostat®) is licensed as an adjunct to scaling and root planing for the treatment of periodontitis; a low dose of doxycycline reduces collagenase activity without inhibiting bacteria associated with periodontitis.

For anti-infectives used in the treatment of destructive (refractory) forms of periodontal disease, see under Oropharyngeal infections, antibacterial therapy p. 1217. See also Mouthwashes and other preparations for oropharyngeal use p. 1210 for mouthwashes used for oral hygiene and plaque inhibition.

Lidocaine hydrochloride
(Lignocaine hydrochloride)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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<tbody>
<tr>
<td>Dental practice</td>
</tr>
<tr>
<td>▶ BY BUCCAL ADMINISTRATION USING OINTMENT</td>
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<tr>
<td>▶ Adult: Rub gently into dry gum</td>
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Relief of pain in oral lesions
▶ TO THE LESION USING OINTMENT
▶ Adult: Apply as required, rub sparingly and gently on affected areas

LARYNOJECT®

Anaesthesia of mucus membranes of oropharynx, trachea, or respiratory tract
▶ TO MUCOUS MEMBRANES
▶ Adult: 40–200 mg, to be given as a single dose sprayed, instilled (if a cavity), or applied with a swab (reduce dose according to size, age and condition of patient); usual dose 160 mg

www.getintopharma.com
**Indications and Dose**

**Warning** Painful inflammatory conditions of the oral cavity and throat and/or following dental treatment or dental extraction

- **By mouth using mouthwash**
- Adult: Rinse or gargle 15 mL for 2–3 days a day for 7 days, treatment may be extended to 6 weeks in mucositis caused by radiotherapy.

**Interactions**

- **Appendix 1: NSAIDs**
- **Appendix 1: Angioedema**
- **Frequency not known**
- **Uncommon** Oral disorders
- **Rare or very rare** Photosensitivity reaction • respiratory disorders • skin reactions

**Special Information**

- **Dental practitioners’ formulary**

**Medicinal Forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **Benzydamine hydrochloride (non-proprietary)**
  - Benzydamine hydrochloride 1.5 mg per 1 mL | 30 mL | £1.24 DT + £3.46
  - Difflam (Meda Pharmaceuticals Ltd)
  - Benzydamine hydrochloride 1.5 mg per 1 mL | 30 mL | £1.24 DT + £3.46

**Mouthwash**

- **Benzydamine hydrochloride (non-proprietary)**
  - Benzydamine hydrochloride 1.5 mg per 1 mL | 300 mL | £7.25
  - Difflam (Meda Pharmaceuticals Ltd)
  - Benzydamine hydrochloride 1.5 mg per 1 mL | 200 mL | £4.64

**Diclofenac**

28-Aug-2018

**Indications and Dose**

- Painful inflammatory conditions of the oral cavity and throat and/or following dental treatment or dental extraction
  - **By mouth using mouthwash**
  - Adult: Rinse or gargle 15 mL for 2–3 days a day for 7 days, treatment may be extended to 6 weeks in mucositis caused by radiotherapy.

**Interactions**

- **Appendix 1: NSAIDs**
- **Pregnancy** Manufacturer advises avoid unless essential.
- **Breastfeeding** Manufacturer advises avoid unless essential.
- **Directions for administration** Manufacturer advises mouthwash may be diluted with a little water.
Flurbiprofen

**Indications and dose**

**Relief of sore throat**

- **By mouth using lozenges**
  - Child 12-17 years: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day
  - Adult: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day

**Contra-indications**

- **Apparent or known sensitivity to flurbiprofen** or any other NSAID
- **Corticosteroid-sensitive asthma, angioedema, urticaria or rhinitis** have been precipitated by aspirin or any other NSAID

**Side-effects**

- Oral ulceration (move lozenge around the mouth; maximum 1 lozenge every 3 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day)

**Pharmacological properties**

- High glucocorticoid activity
- Insignificant mineralocorticoid activity

**Unlicensed use**

- With oral (topical) use in children: Betamethasone soluble tablets not licensed for use as mouthwash or in oral ulceration.

**Contra-indications**

- Untreated local infection

**Interactions**

- Appendix 1: corticosteroids

**Patient and carer advice**

- Patient counselling is advised for betamethasone soluble tablets (administration).

**Profession specific information**

- Dental practitioners’ formulary: Betamethasone Soluble Tablets 500 micrograms may be prescribed.

**Corticosteroids**

**Beclometasone dipropionate (Beclometasone dipropionate)**

**Indications and dose**

**Management of oral ulceration**

- **To the lesion using buccal tablet**
  - Child 1 month: 2 micrograms twice daily
  - Child 12–17 years: 2 micrograms 4 times a day, to be dissolved in 20 mL water and rinsed around the mouth; not to be swallowed
  - Adult: 2 micrograms 4 times a day, to be dissolved in 20 mL water and rinsed around the mouth; not to be swallowed

**Unlicensed use**

- Use of soluble tablets and inhaler unlicensed in oral ulceration.

**Interactions**

- Appendix 1: corticosteroids

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Hydrocortisone**

**Drug action**

- Hydrocortisone has equal glucocorticoid and mineralocorticoid activity.

**Indications and dose**

- **Oral and perioral lesions**
  - **To the lesion using buccal tablet**
    - Child 1 month: 2 micrograms twice daily
    - Child 12–17 years: 2 micrograms 4 times a day
    - Adult: 2 micrograms 4 times a day

**Unlicensed use**

- With buccal use in children: Hydrocortisone mucoadhesive buccal tablets licensed for use in children (under 12 years—on medical advice only).

**Important safety information**

- MHRA/CHM Advice: Hydrocortisone muco-adhesive buccal tablets: Should not be used off-label for adrenal insufficiency in children due to serious risks (December 2018).

- The MHRA has received reports of off-label use of hydrocortisone muco-adhesive buccal tablets for adrenal insufficiency in children. Healthcare professionals are advised that:
  - Hydrocortisone muco-adhesive buccal tablets are indicated only for local use in the mouth for aphthous ulceration and should not be used to treat adrenal insufficiency;
  - Substitution of licensed oral hydrocortisone formulations with muco-adhesive buccal tablets can result in insufficient cortisol absorption and, in stress situations, life-threatening adrenal crisis;
  - Only hydrocortisone products licensed for adrenal replacement therapy should be used.

**Contra-indications**

- Untreated local infection

**Interactions**

- Appendix 1: corticosteroids

**Profession specific information**

- Dental practitioners’ formulary: Mucoadhesive buccal tablets may be prescribed as Hydrocortisone Oromucosal Tablets.
Salicylic acid and rhubarb extract

**INDICATIONS AND DOSE**
- Mild oral and perioral lesions
  - To the lesion
  - Child 16-17 years: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours
  - Adults: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours

**SIDE-EFFECTS**
- Common or very common Oral discolouration, tooth discolouration

**CONTRA-INDICATIONS**
- Children under 16 years

**PRESCRIBING AND DISPENSING INFORMATION**
- Choline Salicylate Dental Gel may be prescribed.
- Dental practitioners’ formulary

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- Oromucosal gel
  - Bonjela (Reckitt Benckiser Healthcare (UK) Ltd)
    - Choline salicylate 87 mg per 1 gram | 15 gram [G3] £3.55 DT + £2.91
    - Bonjela Original gel sugar-free | 15 gram [G3] £2.91 DT + £2.91

**EXCIPIENTS:**
- May contain Ethanol

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**Salicylic acid with rhubarb extract**

**INDICATIONS AND DOSE**
- To the lesion
- Child 16-17 years: Apply 3–4 times a day maximum duration 7 days
- Adults: Apply 3–4 times a day maximum duration 7 days

**SIDE-EFFECTS**
- Common or very common Oral discolouration, tooth discolouration

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**Oropharyngeal bacterial infections**

### Pericoronitis
Antibacterial required only in presence of systemic features of infection, or of trismus, or persistent swelling despite local treatment.
- Metronidazole p. 542, or alternatively, amoxicillin p. 548
- **Suggested duration of treatment** 3 days or until symptoms resolve.

### Gingivitis (acute necrotising ulcerative)
Antibacterial required only if systemic features of infection.
- Metronidazole, or alternatively, amoxicillin
- **Suggested duration of treatment** 3 days or until symptoms resolve.

### Abscess (periapical or periodontal)
Antibacterial required only in severe disease with cellulitis or if systemic features of infection.
- Amoxicillin, or alternatively, metronidazole
- **Suggested duration of treatment** 5 days.

### Periodontitis
Antibacterial used as an adjunct to debridement in severe disease or disease unresponsive to local treatment alone.
- Metronidazole, or alternatively in adults and children over 12 years, doxycycline p. 564

### Sore throat (acute)
Acute sore throat is usually triggered by a viral infection and is self-limiting. Symptoms can last for around 1 week, and most people will improve within this time without treatment with antibiotics, regardless of the cause.
- **Antibacterial therapy** is required only in patients with severe systemic symptoms, signs and symptoms of a more serious illness or condition, or those at high risk of complications. Patients with severe systemic infection or severe suppurative complications such as peri-tonsillar abscess (quinsy), acute otitis media, acute sinusitis or cellulitis should be referred to hospital.
- Phenoxymethylpenicillin p. 548
- **Suggested duration of treatment** 5 to 10 days.
- If penicillin-allergic, clarithromycin p. 538 (or erythromycin p. 539)
- **Suggested duration of treatment** 5 days.
5 Oropharyngeal fungal infections

Oropharyngeal fungal infections

Overview

Fungal infections of the mouth are usually caused by Candida spp. (candidiasis or candidosis). Different types of oropharyngeal candidiasis are managed as follows:

Thrush

Acute pseudomembranous candidiasis (thrush), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics or broad-spectrum antibacterials. Thrush also occurs in patients with serious systemic disease associated with reduced immunity such as leukaemia, other malignancies, and HIV infection. Any predisposing condition should be managed appropriately. When thrush is associated with corticosteroid inhalers, rinsing the mouth with water (or cleaning a child’s teeth) immediately after using the inhaler may avoid the problem. Treatment with nystatin p. 1219 or miconazole p. 1219 may be needed. Fluconazole p. 595 is effective for unresponsive infections or if a topical antifungal drug cannot be used or if the patient has dry mouth. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

Acute erythematous candidiasis

Acute erythematous (atrophic) candidiasis is a relatively uncommon condition associated with corticosteroid and broad-spectrum antibacterial use and with HIV disease. It is usually treated with fluconazole.

Denture stomatitis

Patients with denture stomatitis (chronic atrophic candidiasis), should cleanse their dentures thoroughly and leave them out as often as possible during the treatment period. To prevent recurrence of the problem, dentures should not normally be worn at night. New dentures may be required if these measures fail despite good compliance.

Miconazole oral gel can be applied to the fitting surface of the denture before insertion (for short periods only). Denture stomatitis is not always associated with candidiasis and other factors such as mechanical or chemical irritation, bacterial infection, or rarely allergy to the dental base material, may be the cause.

Chronic hyperplastic candidiasis

Chronic hyperplastic candidiasis (candidial leucoplakia) carries an increased risk of malignancy; biopsy is essential—this type of candidiasis may be associated with varying degrees of dysplasia, with oral cancer present in a high proportion of cases. Chronic hyperplastic candidiasis is treated with a systemic antifungal such as fluconazole to eliminate candidal overgrowth. Patients should avoid the use of tobacco.

Angular cheilitis

Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It is commonly associated with denture stomatitis but may represent a nutritional deficiency or it may be related to orofacial granulomatosis or HIV infection. Both yeasts (Candida spp.) and bacteria (Staphylococcus aureus and beta-haemolytic streptococci) are commonly involved as interacting, infective factors. A reduction in facial height related to ageing and tooth loss with maceration in the deep occlusive folds that may subsequently arise, predisposes to such infection. While the underlying cause is being identified and treated, it is often helpful to apply miconazole cream or fusidic acid ointment p. 571; if the angular cheilitis is unresponsive to treatment, hydrocortisone with miconazole cream or ointment p. 1252 can be used.

Immunocompromised patients

See advice on prevention of fungal infections in Immunocompromised patients under Antifungals, systemic use p. 591.

Drugs used in oropharyngeal candidiasis

Nystatin is not absorbed from the gastro-intestinal tract and is applied locally (as a suspension) to the mouth for treating local fungal infections. Miconazole is applied locally (as an oral gel) in the mouth but it is absorbed to the extent that potential interactions need to be considered. Miconazole also has some activity against Gram-positive bacteria including streptococci and staphylococci. Fluconazole is given by mouth for infections that do not respond to topical therapy or when topical therapy cannot be used. It is reliably absorbed and effective. Itraconazole p. 597 can be used for fluconazole-resistant infections.
If candidal infection fails to respond to 1 to 2 weeks of treatment with antifungal drugs the patient should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by reinfection from the genito-urinary or gastro-intestinal tract. Infection can be eliminated from these sources by appropriate antifungal therapy; the patient’s partner may also require treatment to prevent reinfection.

Antiseptic mouthwashes are used in the prevention of oral candidiasis in immunocompromised patients and in the treatment of denture stomatitis.

**ANTIFUNGALS**  
**IMIDAZOLE ANTIFUNGALS**

### Miconazole

**INDICATIONS AND DOSE**

**Oral candidiasis**

- **BY MOUTH USING ORAL GEL**
  - Child 2–17 years: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)
  - Adult: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)

**Intestinal candidiasis**

- Child 4 months-17 years: 5 mg/kg 4 times a day (max. per dose 250 mg) treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared
- Adult: 5 mg/kg 4 times a day (max. per dose 250 mg) treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared

**CONTRA-INDICATIONS** Infants with impaired swallowing reflex

**CAUTIONS** Avoid in Acute porphyrias p. 1058

**INTERACTIONS** → Appendix 1: antifungals, azoles

**SIDE-EFFECTS**

- Common or very common Skin reactions (in adults)
- Frequency not known Angioedema

**PREGNANCY** Manufacturer advises avoid if possible—toxicity at high doses in animal studies.

**BREAST FEEDING** Manufacturer advises caution—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid.

**DIRECTIONS FOR ADMINISTRATION** Oral gel should be held in mouth, after food.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral gel may include orange.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer miconazole oromucosal gel.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulation
Miconazole Oromucosal Gel may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY** 15-g tube of oral gel can be sold to the public.

### Nystatin

**INDICATIONS AND DOSE**

**Oral candidiasis**

- Child: 100,000 units 4 times a day usually for 7 days, and continued for 48 hours after lesions have resolved
- Adult: 100,000 units 4 times a day usually for 7 days, and continued for 48 hours after lesions have resolved

**CONTRA-INDICATIONS** Infants with impaired swallowing reflex

**CAUTIONS** Avoid in Acute porphyrias p. 1058

**SIDE-EFFECTS**

- Common or very common Skin reactions (in adults)
- Frequency not known Angioedema

**PREGNANCY** Manufacturer advises avoid if possible— to toxic at high doses in animal studies.

**BREAST FEEDING** Manufacturer advises caution—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid.

**DIRECTIONS FOR ADMINISTRATION** Oral gel should be held in mouth, after food.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral gel may include orange.

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**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulation
Miconazole Oromucosal Gel may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY** 15-g tube of oral gel can be sold to the public.

### Oropharyngeal viral infections

**Management**

Viral infections are the most common cause of a sore throat. They do not benefit from anti-infective treatment.

The management of primary herpetic gingivostomatitis is a soft diet, adequate fluid intake, and analgesics as required, including local use of benzylamine hydrochloride p. 1215. The use of chlorhexidine mouthwash p. 1211 will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In the case of severe herpetic stomatitis, a systemic antiviral such as aciclovir p. 633 is required. Valaciclovir p. 636 and famciclovir p. 635 are suitable alternatives for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used for the prevention of frequently recurring herpes simplex lesions of the mouth, particularly when implicated in the initiation of erythema multiforme.
Skin conditions, management

Vehicles

The British Association of Dermatologists list of preferred unlicensed dermatological preparations (specials) is available at www.bad.org.uk/specials.

Both vehicle and active ingredients are important in the treatment of skin conditions; the vehicle alone may have more than a mere placebo effect. The vehicle affects the degree of hydration of the skin, has a mild anti-inflammatory effect, and aids the penetration of active drug.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin (including the scalp) or nails.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsions of oil and water and are generally well absorbed into the skin. They may contain an antimicrobial preservative unless the active ingredient or basis is intrinsically bactericidal and fungicidal. Generally, creams are cosmetically more acceptable than ointments because they are less greasy and easier to apply.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; they generally have a high water content. Gels are particularly suitable for application to the face and scalp.

Lotions have a cooling effect and may be preferred to ointments or creams for application over a hairy area. Lotions in alcoholic basis can sting if used on broken skin. Shake lotions (such as calamine lotion) contain insoluble powders which leave a deposit on the skin surface.

Ointments are greasy preparations which are normally anhydrous and insoluble in water, and are more occlusive than creams. They are particularly suitable for chronic, dry lesions. The most commonly used ointment bases consist of soft paraffin or a combination of soft, liquid, and hard paraffin. Some ointment bases have both hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, encourage hydration, and also be miscible with water; they often have a mild anti-inflammatory effect. Water-soluble ointments contain macrogols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in an ointment. They are used for circumscribed lesions such as those which occur in lichen simplex, chronic eczema, or psoriasis. They are less occlusive than ointments and can be used to protect inflamed, lichenified, or excoriated skin.

Dusting powders are used only rarely. They reduce friction between opposing skin surfaces. Dusting powders should not be applied to moist areas because they can cake and abrade the skin. Talc is a lubricant but it does not absorb moisture; it can cause respiratory irritation. Starch is less lubricant but absorbs water.

Dilution

The BP directs that creams and ointments should not normally be diluted but that should dilution be necessary care should be taken, in particular, to prevent microbial contamination. The appropriate diluent should be used and heating should be avoided during mixing; excessive dilution may affect the stability of some creams. Diluted creams should normally be used within 2 weeks of preparation.

Suitable quantities for prescribing

<table>
<thead>
<tr>
<th>Suitable quantities of dermatological preparations to be prescribed for specific areas of the body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of body</td>
</tr>
<tr>
<td>Face</td>
</tr>
<tr>
<td>Both hands</td>
</tr>
<tr>
<td>Scalp</td>
</tr>
<tr>
<td>Both arms or both legs</td>
</tr>
<tr>
<td>Trunk</td>
</tr>
<tr>
<td>Groins and genitalia</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for twice daily application for 1 week. The recommendations do not apply to corticosteroid preparations. For suitable quantities of corticosteroid preparations, see relevant table.
Excipients and sensitisation

Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, products containing the substance should be avoided. The following excipients in topical preparations are associated, rarely, with sensitisation; the presence of these excipients is indicated in the entries for topical products.

- Beeswax
- Benzyl alcohol
- Butylated hydroxyanisole
- Butylated hydroxytoluene
- Cetostearyl alcohol (including cetyl and stearyl alcohol)
- Chlororeresol
- Edetic acid (EDTA)
- Ethylendiamine
- Fragrances
- Hydroxybenzoates (parabens)
- Imidurea
- Isopropyl palmitate
- N-(3-Chloroallyl)lhexaminium chloride (quaternium 15)
- Polysorbates
- Propylene glycol
- Sodium metabisulphite
- Sorbic acid
- Wool fat and related substances including lanolin (purified versions of wool fat have reduced the problem)

1 Dry and scaling skin disorders

Emollient and barrier preparations

Borderline substances

The preparations marked ‘ACBS’ are regarded as drugs when prescribed in accordance with the advice of the Advisory Committee on Borderline Substances for the clinical conditions listed. Prescriptions issued in accordance with this advice and endorsed ‘ACBS’ will normally not be investigated.

Emollients

Emollients soothe, smooth and hydrate the skin and are indicated for all dry or scaling disorders. Their effects are short lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis. The choice of an appropriate emollient will depend on the severity of the condition, patient preference, and the site of application. Some ingredients rarely cause sensitisation and this should be suspected if an eczematous reaction occurs. The use of aqueous cream as a leave-on emollient may increase the risk of skin reactions, particularly in eczema.

Preparations such as aqueous cream and emulsifying ointment can be used as soap substitutes for hand washing and in the bath; the preparation is rubbed on the skin before rinsing off completely. The addition of a bath oil may also be helpful.

Urea is occasionally used with other topical agents such as corticosteroids to enhance penetration of the skin.

Emollient bath and shower preparations

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. In dry skin conditions soap should be avoided.

The quantities of bath additives recommended for adults are suitable for an adult-size bath. Proportionately less should be used for a child-size bath or a washbasin;

recommended bath additive quantities for children reflect this.

MHRA/CHM advice (updated December 2018): Emollients: new information about risk of severe and fatal burns with paraffin-containing and paraffin-free emollients

Emollients are an important and effective treatment for chronic dry skin disorders and people should continue to use these products. However, healthcare professionals must ensure that patients and their carers understand the fire risk associated with the build-up of residue on clothing and bedding and can take action to minimise the risk. There is a fire risk with all paraffin-containing emollients, regardless of paraffin concentration, and it cannot be excluded with paraffin-free emollients. A similar risk may apply to products that are applied to the skin over large body areas, or in large volumes for repeated use for more than a few days.

Healthcare professionals should advise patients not to smoke or go near naked flames because clothing, bedding, dressings, and other fabrics that have been in contact with an emollient or emollient-treated skin can rapidly ignite. Washing these materials at high temperature may reduce emollient build-up but not totally remove it.

Barrier preparations

Barrier preparations often contain water-repellent substances such as dimeticone p. 1236 or other silicones. They are used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. Barrier preparations are not a substitute for adequate nursing care.

Nappy rash

The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting water-proof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation, applied with each nappy change, can be helpful. A mild corticosteroid such as hydrocortisone 0.5% or 1% p. 1247 can be used if inflammation is causing discomfort, but it should be avoided in neonates. The barrier preparation should be applied after the corticosteroid preparation to prevent further damage. Preparations containing hydrocortisone should be applied for no more than a week; the hydrocortisone should be discontinued as soon as the inflammation subsides. The occlusive effect of nappies and waterproof pants may increase absorption of corticosteroids. If the rash is associated with candidal infection, a topical antifungal such as clotrimazole cream p. 1232 can be used. Topical antibacterial preparations can be used if bacterial infection is present; treatment with an oral antibacterial may occasionally be required in severe or recurrent infection. Hydrocortisone may be used in combination with antimicrobial preparations if there is considerable inflammation, erosion, and infection.

Dermatological Drugs > Barrier Preparations

Barrier creams and ointments

- **Indications and Dose**
  - For use as a barrier preparation
    - To the skin
    - Child: (consult product literature)
    - Adult: (consult product literature)

- **Medicinal Forms**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Ointment
    - Excipients: May contain Woolfat and related substances (including lanolin)
### Skin

**DERMATOLOGICAL DRUGS > EMOLLIENTS**

<table>
<thead>
<tr>
<th><strong>Indications and Use</strong></th>
<th><strong>Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DERMOL</strong> 200 SHOWER EMOLLIENT</td>
<td><strong>Dry and pruritic skin conditions including eczema and dermatitis</strong></td>
</tr>
<tr>
<td><strong>TO THE SKIN</strong></td>
<td><strong>Child:</strong> To be applied to the skin or used as a soap substitute. <strong>Adult:</strong> To be applied to the skin or used as a soap substitute.</td>
</tr>
<tr>
<td><strong>DERMOL</strong> 600 BATH EMOLLIENT</td>
<td><strong>Dry and pruritic skin conditions including eczema and dermatitis</strong></td>
</tr>
<tr>
<td><strong>TO THE SKIN</strong></td>
<td><strong>Child 1-23 months:</strong> 5–15 mL/bath, not to be used undiluted. <strong>Child 2-17 years:</strong> 15–30 mL/bath, not to be used undiluted. <strong>Adult:</strong> Up to 30 mL/bath, not to be used undiluted.</td>
</tr>
</tbody>
</table>

**IMMEDIATE SAFETY INFORMATION**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**PRESCRIBING AND DISPENSING INFORMATION**

Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

**CAUTIONARY AND ADVISORY LABELS**

**EMULSIDERM**

**Dry skin conditions including eczema and ichthyosis**

**TO THE SKIN**

- **Child 1-23 months:** 5–10 mL/bath, alternatively, to be rubbed into dry skin until absorbed.
- **Child 2-17 years:** 7–30 mL/bath, alternatively, to be rubbed into dry skin until absorbed.
- **Adult:** 7–30 mL/bath, alternatively, to be rubbed into dry skin until absorbed.

**OILATUM PLUS**

**Topical treatment of eczema, including eczema at risk from infection**

**TO THE SKIN**

- **Child 6-11 months:** 1 mL/bath, not to be used undiluted.
- **Child 1-7 years:** 1–2 capfuls/bath, not to be used undiluted.
- **Adult:** 1–2 capfuls/bath, not to be used undiluted.

**Barrier creams and ointments (Non-proprietary)**

- Cetostearyl alcohol 20 mg per 1 gram, Zinc oxide 75 mg per 1 gram, Beeswax white 100 mg per 1 gram, Arachis oil 305 mg per 1 gram, Castor oil 500 mg per 1 gram. **Zinc and Castor oil ointment:** 500 gram **GSL** £5.19.
- Metanium (Thornon & Ross Ltd)
  - Titanium salicylate 30 mg per 1 gram, Titanium peroxide 50 mg per 1 gram, Titanium dioxide 200 mg per 1 gram.
  - Metanium Nappy Rash ointment: 30 gram **GSL** £2.24 DT = £2.24

**Spray**

**CAUTIONARY AND ADVISORY LABELS**

- **Adult:** To the skin.
- **Child 2**
- **Child 1**
- **Child:** To be applied to the skin or used as a soap substitute.
- **Adult:** To be applied to the skin or used as a soap substitute.

**DIRECTIONS FOR ADMINISTRATION**

- **Emollients** may contain Beeswax, butylated hydroxyanisole, butylated hydroxytoluene, cetostearyl alcohol (including cetetyl and stearyl alcohol), chlorocresol, fragrances, hydroxybenzoates (parabens), propylene glycol, woolfat and related substances (including lanolin).
- **Sprion** (M Loveridge Ltd)
  - Dimeticon 10.4 mg per 1 gram, Zinc oxide 125 mg per 1 gram.
- **Sprion aerosol spray:** 115 gram **GSL** £8.90 DT = £8.90

**Cream**

**EXCIPIENTS:** May contain Beeswax, butylated hydroxyanisole, butylated hydroxytoluene, cetostearyl alcohol (including cetetyl and stearyl alcohol), chlorocresol, fragrances, hydroxybenzoates (parabens), propylene glycol, woolfat and related substances (including lanolin).

- **Contrane** (LED Pharma)
  - Benzalkonium chloride 1 mg per 1 gram, Dimeticone 220 mg per 1 gram. **Contrace cream:** 100 gram **GSL** £0.88 DT = £0.88. 500 gram **GSL** £3.51.
- **Drapoline** (Supra Enterprises Ltd)
  - Benzalkonium chloride 100 microgram per 1 gram, Cetrimide 2 mg per 1 gram. **Drapoline cream:** 100 gram **GSL** £1.76. 200 gram **GSL** £2.86. 350 gram **GSL** £4.28.
- **Siopel** (Derma UK Ltd)
  - Cetrimide 3 mg per 1 gram, Dimeticone 1000 100 mg per 1 gram **Siopel cream:** 50 gram **GSL** £4.65.
- **Sudocrem** (Teva UK Ltd)
  - Benzyl cinnamate 1.5 mg per 1 gram, Benzyl alcohol 3.9 mg per 1 gram, Benzylo alcohol 1.0 mg per 1 gram, Wool fat hydrous 40 mg per 1 gram, Zinc oxide 152.5 mg per 1 gram. **Sudocrem antiseptic healing cream:** 30 gram **GSL** £1.45. 60 gram **GSL** £1.45. 125 gram **GSL** £2.15. 250 gram **GSL** £3.67. 400 gram **GSL** £5.25.

**NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS**

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS:

These preparations make skin and surfaces slippery—particular care is needed when bathing.

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS:

**NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS**

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**PRESCRIBING AND DISPENSING INFORMATION**

Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

**CAUTIONARY AND ADVISORY LABELS**

**DERMOL** 200 SHOW EMOLLIENT | **Dry and pruritic skin conditions including eczema and dermatitis** |
| **TO THE SKIN** | **Child:** To be applied to the skin or used as a soap substitute. **Adult:** To be applied to the skin or used as a soap substitute. |

**DERMOL** 600 BATH EMOLLIENT | **Dry and pruritic skin conditions including eczema and dermatitis** |
| **TO THE SKIN** | **Child 1-23 months:** 5–15 mL/bath, not to be used undiluted. **Child 2-17 years:** 15–30 mL/bath, not to be used undiluted. **Adult:** Up to 30 mL/bath, not to be used undiluted. |

**DERMOL WASH EMOLLISION** | **Dry and pruritic skin conditions including eczema and dermatitis** |
| **TO THE SKIN** | **Child:** To be applied to the skin or used as a soap substitute. **Adult:** To be applied to the skin or used as a soap substitute. |
Pruritus of the elderly associated with dry skin

TO THE SKIN
- Elderly: To be used as a soap substitute

HYDROMOL® BATH AND SHOWER EMOLLIENT

Dry skin conditions | Eczema | Ichthyosis

TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively apply to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively apply to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

Pruritus of the elderly

TO THE SKIN
- Elderly: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

LPL 63.4®

Dry skin conditions

TO THE SKIN
- Child 1 month-11 years: Apply 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

OILATUM® EMOLLIENT BATH ADDITIVE

Dry skin conditions including dermatitis and ichthyosis

TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

Pruritus of the elderly

TO THE SKIN
- Elderly: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

OILATUM® JUNIOR BATH ADDITIVE

Dry skin conditions including dermatitis and ichthyosis

TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively, apply to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

Pruritus of the elderly

TO THE SKIN
- Elderly: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus

TO THE SKIN
- Child 1-11 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
- Child 1-17 years: 10 mL/bath, alternatively, to be applied to wet skin and rinse
- Adult: 10 mL/bath, alternatively, to be applied to wet skin and rinse

OQ® GENTLE WASH

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus

TO THE SKIN
- Child: To be used as a soap substitute
- Adult: To be used as a soap substitute

continued
Dry and scaling skin disorders

**ZEROLATUM®**

**Dry skin conditions | Dermatitis | Ichthyosis**

▶ **TO THE SKIN**
- Child 1 month–11 years: 5–10 mL/bath
- Child 12–17 years: 15–20 mL/bath
- Adult: 15–20 mL/bath

**Pruritus of the elderly**

▶ **TO THE SKIN**
- Elderly: 15–20 mL/bath

**IMPORTANT SAFETY INFORMATION**

These preparations make the skin and surfaces slippery—particular care is needed when bathing.

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, isopropyl palmitate

- **Cetaben** (Genus Pharmaceuticals Ltd)
  - Liquid paraffin light 828 mg per 1 gram Cetaben emollient 82.8% bath additive | 500 ml G$5 £5.75 DT + £5.75
- **Dermalo** (Dermal Laboratories Ltd)
  - Acetylated wool alcohols 50 mg per 1 gram, Liquid paraffin 650 mg per 1 gram Dermalo bath emollient | 500 ml G$3 £3.44
- **Doublebase** (Dermal Laboratories Ltd)
  - Liquid paraffin 650 mg per 1 gram Doublebase emollient bath additive | 500 ml G$5 £5.45 DT + £5.45
- **E45 emollient bath** (Fork Health Products Ltd)
  - E45 emollient bath oil | 250 mL(ACBS) £3.30 | 500 mL(ACBS) £5.29
- **Hydromol** (Alliance Pharmaceuticals Ltd)
  - Isopropyl myristate 130 mg per 1 mL, Liquid paraffin light 378 mg per 1 mL Hydromol bath & Shower emollient | 350 mL £3.91 | 500 ml £4.46 | 2500 ml £8.87
- **LPL** (Unley Europe Ltd)
  - Liquid paraffin light 634 mg per 1 mL LPL 63.4 bath additive and emollient | 500 ml £3.10 DT = £5.27
- **Olatum (GosoSmithKline Consumer Healthcare)**
  - Liquid paraffin light 634 mg per 1 mL Olatum Bath Formula | 150 ml G$2.95 DT + £2.95 | 300 ml G$5.02 DT + £5.02
- **Olatum Junior (GosoSmithKline Consumer Healthcare)**
  - Soya-bean oil-containing
  - Liquid paraffin light 634 mg per 1 mL Olatum Junior bath additive | 150 ml G$2.95 DT + £2.95 | 250 ml G$4.44 DT + £2.75 | 300 ml G$5.02 DT + £5.02 | 600 mL G$6.67 DT + £6.67
- **QV (Crawford Healthcare Ltd)**
  - Liquid paraffin light 850.9 mg per 1 gram QV 85.09% bath oil | 250 mL £2.93 | 500 ml £4.79
- **Zerolatun** (Thorton & Ross Ltd)
  - Acetylated wool alcohols 50 mg per 1 gram, Liquid paraffin 650 mg per 1 gram Zerolatun Emollient bath additive | 500 ml £4.79

**Gel**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)

- **Doublebase** (Dermal Laboratories Ltd)
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Doublebase emollient shower gel | 200 gram G8 £5.21

**Emollient bath and shower products, soya-bean oil-containing**

**INDICATIONS AND DOSE**

**BALNEUM® BATH OIL**

Dry skin conditions including those associated with dermatitis and eczema

▶ **TO THE SKIN**
- Child 1–23 months: 5–15 mL/bath, not to be used undiluted
- Child 2–17 years: 20–60 mL/bath, not to be used undiluted
- Adult: 20–60 mL/bath, not to be used undiluted

**BALNEUM® PLUS BATH OIL**

Dry skin conditions including those associated with dermatitis and eczema where pruritus also experienced

▶ **TO THE SKIN**
- Child 1–23 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
- Child 2–17 years: 10–20 mL/bath, alternatively, to be applied to wet skin and rinse
- Adult: 20 mL/bath, alternatively, to be applied to wet skin and rinse

**ZERONEUM®**

Dry skin conditions, including eczema

▶ **TO THE SKIN**
- Child 1 month–11 years: 5 mL/bath
- Child 12–17 years: 20 mL/bath
- Adult: 20 mL/bath

**IMPORTANT SAFETY INFORMATION**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Acetylated lanolin alcohols, cetostearyl alcohol, isopropyl palmitate, fragrances, isopropyl myristate, lauroyl macrogol ethers, parabens, propylene glycol

- **Balneum** (Almirall Ltd)
  - Soya oil 847.5 mg per 1 gram, Lauromacrogols 150 mg per 1 gram Balneum bath emollient | 250 ml G$5 £6.66 DT + £6.66
- **Dermal Laboratories Ltd**
  - Soya oil 829.5 mg per 1 gram, Lyophilized lanolin 250 mg per 1 gram Dermalo bath emollient | 500 ml G$5 £5.38 DT + £5.38 | 1000 ml G$15 £10.39
- **Intrapharm Laboratories Ltd**
  - Soya oil 847.5 mg per 1 gram, Lauramin 150 mg per 1 gram Intrapharm bath emollient | 500 ml G$5 £5.38 DT + £5.38
- **Crawford Healthcare Ltd**
  - Soya oil 847.5 mg per 1 gram, Lauramin 150 mg per 1 gram Crawford bath emollient | 500 ml G$5 £5.38 DT + £5.38
- **Intrapharm Laboratories Ltd**
  - Soya oil 847.5 mg per 1 gram, Lauramin 150 mg per 1 gram Intrapharm bath emollient | 500 ml G$5 £5.38 DT + £5.38
- **Crawford Healthcare Ltd**
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  - Soya oil 847.5 mg per 1 gram, Lauramin 150 mg per 1 gram Crawford bath emollient | 500 ml G$5 £5.38 DT + £5.38
- **Crawford Healthcare Ltd**
  - Soya oil 847.5 mg per 1 gram, Lauramin 150 mg per 1 gram Crawford bath emollient | 500 ml G$5 £5.38 DT + £5.38
Emollient bath and shower products, tar-containing

**INDICATIONS AND DOSE**

**POLYTAR EMOLLIENT**

- **Psoriasis, eczema, atopic and pruritic dermatoses**
  - **TO THE SKIN**
  - **Adult:** 2–4 capfuls/bath, add 15–30 mL to an adult-size bath; soak for 20 minutes
  - **Child:** To be applied to the skin or used as a soap substitute

**PSORIDERM EMULSION**

- **Psoriasis**
  - **TO THE SKIN**
  - **Adult:** Up to 30 mL/bath, use 30mL in adult-size bath, soak for 5 minutes

**IMPORTANT SAFETY INFORMATION**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

**MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS**

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

**CAUTIONARY AND ADVISORY LABELS 15**

**EXCIPIENTS:** May contain Isopropyl palmitate, polysorbates

- **Psoriderm** (Dermal Laboratories Ltd)
  - Coal tar distilled 400 mg per 1 mL
  - Psoriderm Emulsion 40% bath additive 200 mL (£2.74 DT = £2.74)

**Emollient creams and ointments, colloidal oatmeal-containing**

**INDICATIONS AND DOSE**

**Endogenous and exogenous eczema | Xeroderma | Ichthyosis**

- **TO THE SKIN**
- **Child:** (consult product literature)
- **Adult:** (consult product literature)

**Senile pruritus (pruritus of the elderly) associated with dry skin**

- **TO THE SKIN**
- **Elderly:** (consult product literature)

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS**

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Lotion/Cream**

**CAUTIONARY AND ADVISORY LABELS 15**

**EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), isopropyl palmitate

- **Aveeno** (Johnson & Johnson Ltd)
  - Aveeno cream 500 mL(ACBS) £6.66
  - Aveeno cream 100 mL(ACBS) £3.97
  - Aveeno cream 300 mL(ACBS) £6.80
  - Aveeno cream 500 mL(ACBS) £6.47

**Emollient creams and ointments, antimicrobial-containing**

**INDICATIONS AND DOSE**

**Dry and pruritic skin conditions including eczema and dermatitis**

- **TO THE SKIN**
- **Child:** To be applied to the skin or used as a soap substitute
- **Adult:** To be applied to the skin or used as a soap substitute

**IMPORTANT SAFETY INFORMATION**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

**MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS**

See Emollient and barrier preparations p. 1221.

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Emollient and barrier preparations**
Emollient creams and ointments, paraffin-containing

**INDICATIONS AND DOSE**

- **Dry skin conditions**: Eczema | Psoriasis | Ichthyosis
- **Pruritus**
- **Child**: (consult product literature)
- **Adult**: (consult product literature)

**TO THE SKIN**

<table>
<thead>
<tr>
<th>Exciipients:</th>
<th>May contain Benzyl alcohol, cetostearyl alcohol (including paraffin-containing and paraffin-free emollients)</th>
</tr>
</thead>
</table>

**IMPORTANT SAFETY INFORMATION**

- **MHRA/CHM ADVICE (UPDAPTED DECEMBER 2018): EMMOILENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMMOILENTS**
- **See Emollient and barrier preparations p. 1221.**

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

- **CAUTIONARY AND ADVISORY LABELS**: 15
- **Dermamist (Alliance Pharmaceuticals Ltd)**
  - White soft paraffin 100 mg per 1 gram Dermamist 10% spray |
  - 250 ml | £5.97 DT = £5.97
- **Emollin (C D Medical Ltd)**
  - Emollin aerosol spray | 150 ml £4.00 | 240 ml £6.39

**Gel**

- **CAUTIONARY AND ADVISORY LABELS**: 15
- **AproDerm (Isopropyl myristate / liquid paraffin)** (Fontus Health Ltd)
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram AproDerm gel | 100 gram £1.99 DT = £2.65 | 500 gram £3.99 DT = £5.83
- **Doublebase (Dermal Laboratories Ltd)**
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Doublebase Day/Even gel | 100 gram | £2.65 DT = £2.65 | 500 gram | £6.29 DT = £5.83
  - Doublebase gel | 100 gram | £2.65 DT = £2.65 | 500 gram | £5.83 DT = £5.83 | 1000 gram | £10.86
  - Doublebase emollient wash gel | 200 gram | £5.21
  - Doublebase emollient shower gel | 200 gram | £5.21
- **Exbasea (Ascot Laboratories Ltd)**
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Exbasea gel | 500 gram £2.85 DT = £5.83
- **HypoBase (Aspire Pharma Ltd)**
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram HypoBase gel | 500 gram £3.63 DT = £5.83
- **MyrBase (Galen Ltd)**
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram MyrBase gel | 100 gram £2.12 DT = £2.65 | 500 ml £4.66
- **Zerodouble (Thornton & Ross Ltd)**
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Zerodouble gel | 100 gram £2.25 DT = £2.65 | 500 gram £4.90 DT = £5.83
  - Isomol (Dermato Logical Ltd)
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Isomol gel | 100 gram £1.99 DT = £2.65 | 500 gram £2.92 DT = £5.83
  - Isomol (Dermato Logical Ltd)
  - Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram Isomol gel | 100 gram £1.99 DT = £2.65 | 500 gram £2.92 DT = £5.83

**Cream**

- **CAUTIONARY AND ADVISORY LABELS**: 15
- **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, disodium edetate, fragrances, hydroxybenzoates (parabens), polysorbates, propylene glycol, sorbic acid, lanolin
- **Aquamol (Thornton & Ross Ltd)**
  - Aquamol cream | 50 gram £1.22 | 500 gram £6.40
  - **Cetabrafen (Thornton & Ross Ltd)**
  - Liquid paraffin light 105 mg per 1 gram, White soft paraffin 132 mg per 1 gram Cetabrafen cream | 50 gram £1.40 | 150 gram £3.95 | 500 gram £5.99 | 1050 gram £11.62
- **Diprobase (Bayer Plc)**
  - Diprobase cream | 50 gram £1.28 | 500 gram £6.32
- **E45 (Forum Health Products Ltd)**
  - Wool fat 10 mg per 1 gram, Liquid paraffin light 126 mg per 1 gram, White soft paraffin 145 mg per 1 gram E45 cream | 50 gram | £1.93 | 125 gram | £3.22 | 350 gram | £5.81 | 500 gram | £5.99
- **Enopen (Enogen Healthcare Ltd)**
  - Liquid paraffin light 105 mg per 1 gram, White soft paraffin 132 mg per 1 gram Enopen cream | 50 gram £1.40 | 150 gram £3.98 | 500 gram £5.99 | 1050 gram £11.62
- **Epaderm (Molnlycke Health Care Ltd)**
  - Epaderm cream | 50 gram £3.71 | 150 gram £5.38 | 500 gram £7.01
- **Epimax (Dermato Logical Ltd)**
  - Epimax cream | 100 gram £0.75 | 500 gram £2.49
- **ExCetra (Dermato Logical Ltd)**
  - Liquid paraffin light 105 mg per 1 gram, White soft paraffin 132 mg per 1 gram ExCetra cream | 100 gram £1.75 | 500 gram £2.95
- **Exm obsessed (Ascot Laboratories Ltd)**
  - Liquid paraffin light 60 mg per 1 gram, White soft paraffin 150 mg per 1 gram Exm obsessed cream | 500 gram £4.25
- **Exmalatum (Ascot Laboratories Ltd)**
  - Liquid paraffin light 60 mg per 1 gram, White soft paraffin 150 mg per 1 gram Exmalatum cream | 500 mg £4.45
- **Lipobase (LEO Pharma)**
  - Lipobase cream | 500 gram | £1.46
- **Oliatum (GlaxoSmithKline Consumer Healthcare)**
  - Liquid paraffin light 60 mg per 1 gram, White soft paraffin 150 mg per 1 gram Oliatum cream | 150 gram | £3.06 DT = £3.06 | 500 ml | £5.28 DT = £5.28
- **Oliatum junior (GlaxoSmithKline Consumer Healthcare)**
  - Liquid paraffin light 60 mg per 1 gram, White soft paraffin 150 mg per 1 gram Oliatum Junior cream | 150 gram | £3.06 DT = £3.06 | 350 ml | £4.65 DT = £4.65 | 500 ml | £5.28 DT = £5.28
- **Soffen (Vitame Ltd)**
  - Liquid paraffin light 105 mg per 1 gram, White soft paraffin 132 mg per 1 gram Soffen cream | 500 gram £4.79
- **Unguentum M (Almirall Ltd)**
  - Unguentum M cream | 100 gram | £2.78 | 500 gram | £8.48
  - Zerodous (Thornton & Ross Ltd)
  - ZeroDOS emollient cream | 500 gram £3.29
  - Zerobase (Thornton & Ross Ltd)
  - Liquid paraffin 110 mg per 1 gram Zerobase 11% cream | 50 gram £1.04 | 500 gram £5.26
  - Zerocream (Thornton & Ross Ltd)
  - Liquid paraffin 126 mg per 1 gram, White soft paraffin 145 mg per 1 gram Zerocream | 50 gram £1.17 | 500 gram £4.08
  - Zeroguent (Thornton & Ross Ltd)
  - White soft paraffin 40 mg per 1 gram, Soya oil 50 mg per 1 gram, Liquid paraffin light 80 mg per 1 gram Zeroguent cream | 100 gram £2.33 | 500 gram £6.99

**Ointment**

- **CAUTIONARY AND ADVISORY LABELS**: 15
- **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
- **Emollient creams and ointments, paraffin-containing (Non proprietary)**
  - Liquid paraffin 200 mg per 1 gram, Emulsifying wax 300 mg per 1 gram, White soft paraffin 500 mg per 1 gram Emulsifying ointment | 100 gram (GSL) £4.57
  - Liquid paraffin 500 mg per 1 gram, White soft paraffin 500 mg per 1 gram White soft paraffin 50% / Liquid paraffin 50% ointment | 250 gram £1.92 | £1.99 | 500 gram | £3.42 DT = £4.57 | 500 gram | £4.57 DT = £4.57
  - Magnesium sulfate dried 5 mg per 1 gram, Phenoxethanol 10 mg per 1 gram, Wool alcohols ointment 500 mg per 1 gram Hydros ointment | 500 gram | £22.50
  - White soft paraffin 1 mg per 1 mg, White soft paraffin solid | 500 gram | £0.08 DT = £0.04 | 4500 gram | £22.50-£36.00
**DRUG ACTION**

**AQUADRATE**  
Includes ichthyosis and may be useful in elderly patients.

**INDICATIONS AND DOSE**

**DRY, SCALING, AND ITCHING SKIN**

**AQUADRATE**

- **Adult**: Apply twice daily, to be applied thinly
- **Child**: Apply twice daily, to be applied thinly

**DRY, SCALING, AND DRY SKIN CONDITIONS**

- **Adult**: Apply twice daily, to be applied thinly and rubbed into area
- **Child**: Apply twice daily, to be applied thinly and rubbed into area

**NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS**

- **Adult**: Apply twice daily, to be applied sparingly and rubbed into area
- **Child**: Apply twice daily, to be applied sparingly and rubbed into area

**E45® ITCH RELIEF CREAM**

- **To the skin**: Apply twice daily
- **Adult**: Apply twice daily

**EUCERIN® INTENSIVE CREAM**

- **To the skin**: Apply twice daily
- **Adult**: Apply twice daily

**EUCERIN® INTENSIVE LOTION**

- **To the skin**: Apply twice daily
- **Adult**: Apply twice daily

**FLEXITOL® INTENSIVE**

- **To the skin**: Apply twice daily
- **Adult**: Apply twice daily

**IMPORTANCE OF SAFETY INFORMATION**

**MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOILMENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOILMENTS**

See Emollient and barrier preparations p. 1221.
Skin infections

Antibacterial preparations for the skin

**Cellulitis**, a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment. Lower leg infections or infections spreading around wounds are almost always cellulitis. *Erysipelas*, a superficial infection with clearly defined edges (and often affecting the face), is also treated with a systemic antibiotic.

In the community, acute *impetigo* on small areas of the skin may be treated by short-term topical application of fusidic acid p. 571; mupirocin p. 1232 should be used only to treat meticillin-resistant *Staphylococcus aureus*. If the impetigo is extensive or longstanding, an oral antibacterial such as fluclaxacin p. 554 (or clarithromycin p. 538 in penicillin allergy) should be used. Mild antisepsics can be used to soften crusts.

Although many antibacterial drugs are available in topical preparations, some are potentially hazardous and frequently their use is not necessary if adequate hygienic measures can be taken. Moreover, not all skin conditions that are oozing, crusted, or characterised by pustules are actually infected.

**Bacterial colonisation is generally inappropriate.** To minimise the development of resistant organisms it is advisable to limit the choice of antibacterials applied topically to those not used systemically. Unfortunately some of these, for example neomycin sulphate p. 1230, may cause sensitisation, and there is cross-sensitivity with other aminoglycoside antibiotics, such as gentamicin p. 519. If large areas of skin are being treated, ototoxicity may also be a hazard with aminoglycoside antibiotics (and also with polymyxins p. 1231, particularly in children, in the elderly, and in those with renal impairment. Resistant organisms are more common in hospitals, and whenever possible swabs should be taken for bacteriological examination before beginning treatment.

Mupirocin is not related to any other antibacterial in use; it is effective for skin infections, particularly those due to Gram-positive bacteria but it is not indicated for pseudomonal infection. Although *Staphylococcus aureus* strains with low-level resistance to mupirocin are emerging, it is generally useful in infections resistant to other antibacterials. To avoid the development of resistance, mupirocin or fusidic acid should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital. In the presence of mupirocin-resistant MRSA infection, a topical antiseptic such as povidone–iodine p. 1276, chlorhexidine p. 1277, or alcohol can be used; their use should be discussed with the local microbiologist.

Tetrazol is p. 573 is licensed for the treatment of acute bacterial skin and skin structure infections. Silver sulfadiazine p. 1231 is used in the treatment of infected burns.

**Antibacterial preparations also used systemically**

Fusidic acid is a narrow-spectrum antibacterial used for staphylococcal infections. Fusidic acid has a role in the treatment of impetigo.

An ointment containing fusidic acid is used in the fissures of angular cheilitis when associated with staphylococcal infection. See Oropharyngeal fungal infections p. 1218 for further information on angular cheilitis.

Metronidazole p. 1230 is used topically for rosacea and to reduce the odor associated with anaerobic infections; oral metronidazole is used to treat wounds infected with anaerobic bacteria.

**Antifungal preparations for the skin**

Most localised fungal infections are treated with topical preparations. To prevent relapse, local antifungal treatment should be continued for 1–2 weeks after the disappearance of all signs of infection. Systemic therapy is necessary for scalp infection or if the skin infection is widespread, disseminated, or intractable; although topical therapy may be used to treat some nail infections, systemic therapy is more effective. Skin scrapings should be examined if systemic therapy is being considered or where there is doubt about the diagnosis.

**Dermatophytose**

Ringworm infection can affect the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum),
foot (tinea pedis, athlete’s foot), or nail (tinea unguium). Scalp infection requires systemic treatment; additional application of a topical antifungal, during the early stages of treatment, may reduce the risk of transmission. A topical antifungal can also be used to treat asymptomatic carriers of scalp ringworm. Most other local ringworm infections can be treated adequately with topical antifungal preparations (including shampoos). The imidazole antifungals clotrimazole p. 1232, econazole nitrate p. 1232, ketoconazole p. 1233, and miconazole p. 1233 are all effective. Terbinafine p. 1234 cream is also effective but it is more expensive. Other topical antifungals include griseofulvin p. 1234 and the undecenoates. Compound benzoic acid ointment (Whitfield’s ointment) has been used for ringworm infections but it is cosmetically less acceptable than proprietary preparations. Topical preparations for athlete’s foot containing tolnaftate are on sale to the public.

Antifungal dusting powders are of little therapeutic value in the treatment of fungal skin infections and may cause skin irritation; they may have some role in preventing re-infection.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. However, topical application of amorolfine p. 1234 or toconazole p. 1233 may be useful for treating early onychomycosis when involvement is limited to mild distal disease, or for superficial white onychomycosis, or where there are contra-indications to systemic therapy.

Pityriasis versicolor

Pityriasis (tinea) versicolor can be treated with ketoconazole shampoo. Alternatively, selenium sulfide shampoo [unlicensed indication] can be used as a lotion (diluting with a small amount of water can reduce irritation) and left on the affected area for 10 minutes before rinsing off; it should be applied once daily for 7 days, and the course repeated if necessary.

Topical imidazole antifungals such as clotrimazole, econazole nitrate, ketoconazole, and miconazole, or topical terbinafine are alternatives, but large quantities may be required.

If topical therapy fails, or if the infection is widespread, pityriasis versicolor is treated systemically with a triazole antifungal. Relapse is common, especially in the immunocompromised.

Candidiasis

Candidal skin infections can be treated with a topical imidazole antifungal, such as clotrimazole, econazole nitrate, ketoconazole, or miconazole; topical terbinafine is an alternative. Topical application of nystatin p. 1219 is also effective for candidiasis but it is ineffective against dermatophytoysis. Refractory candidiasis requires systemic treatment generally with a triazole such as fluconazole p. 595; systemic treatment with terbinafine is not appropriate for refractory candidiasis.

Angular cheilitis

Miconazole cream is used in the fissures of angular cheilitis when associated with Candida.

Compound topical preparations

Combination of an imidazole and a mild corticosteroid (such as hydrocortisone 1% p. 1247) may be of value in the treatment of eczematous intertrigo and, in the first few days only, of a severely inflamed patch of ringworm.

Combination of a mild corticosteroid with either an imidazole or nystatin p. 1219 may be of use in the treatment of intertrigo associated with candida.

Scabies

Permethrin p. 1237 is used for the treatment of scabies (Sarcoptes scabiei); malathion p. 1237 can be used if permethrin is inappropriate.

Benzy1 benzoate p. 1236 is an irritant and should be avoided in children; it is less effective than malathion and permethrin.

Ivermectin p. 604 (available on a named patient basis from ‘special-order’ manufacturers or specialist importing companies) by mouth has been used, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone; further doses may be required.

Application

Although acaricides have traditionally been applied after a hot bath, this is not necessary and there is even evidence that a hot bath may increase absorption into the blood, removing them from their site of action on the skin.

All members of the affected household should be treated simultaneously. Treatment should be applied to the whole body including the scalp, neck, face, and ears. Particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails. It is now recommended that malathion and permethrin should be applied twice, one week apart; in the case of benzyl benzoate in adults, up to 3 applications on consecutive days may be needed. It is important to warn users to reapply treatment to the hands if they are washed. Patients with hyperkeratotic scabies may require 2 or 3 applications of acaricide on consecutive days to ensure that enough penetrates the skin crusts to kill all the mites.

Herpes labialis

Aciclovir cream can be used for the treatment of initial and recurrent oral herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.

Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream.

Systemic treatment is necessary if cold sores recur frequently or for infections in the mouth.

Antiviral preparations for the skin

Aciclovir cream p. 1238 is licensed for the treatment of initial and recurrent labial and genital herpes simplex infections; treatment should begin as early as possible. Systemic treatment is necessary for buccal or vaginal infections and for herpes zoster (shingles).

Herpes labialis

Aciclovir cream can be used for the treatment of initial and recurrent labial herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.

Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream.

Systemic treatment is necessary if cold sores recur frequently or for infections in the mouth.

Parasiticidal preparations for the skin

Suitable quantities of parasiticidal preparations

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Skin creams</th>
<th>Lotions</th>
<th>Cream rinses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp (head lice)</td>
<td>50–100 mL</td>
<td>50–100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (scabies)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (crab lice)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for single application.
not successful. Oral administration of a sedating antihistamine at night may also be useful.

Head lice

Dimeticon p. 1236 is effective against head lice (Pediculus humanus capitis). It coats head lice and interferes with water balance in lice by preventing the excretion of water; it is less active against eggs and treatment should be repeated after 7 days. Malathion, an organophosphorus insecticide, is an alternative, but resistance has been reported. Benzyl benzoate is licensed for the treatment of head lice but it is less effective than other drugs and not recommended for use in children. Permethrin is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice.

Head lice infestation (pediculosis) should be treated using lotion or liquid formulations only if live lice are present. Shampoos are diluted too much in use to be effective. A contact time of 8–12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs.

In general, a course of treatment for head lice should be 2 applications of product 7 days apart to kill lice emerging from any eggs that survive the first application. All affected household members should be treated simultaneously.

MHRA/CHM advice: Head lice eradication products: risk of serious burns if treated hair is exposed to open flames or other sources of ignition (March 2018)

Some products for the eradication of head lice infestations are combustible/flammable when on the hair and can ignite and cause serious harm in the presence of an open flame or other source of ignition such as when lighting cigarettes.

Patients and carers should be advised on the safe and correct use of head lice eradication treatments and if necessary, should be advised that they should not smoke around treated hair and that it should be kept away from open flames or other sources of ignition, including in the morning after overnight application until hair is washed.

Wet combing methods

Head lice can be mechanically removed by combing wet hair meticulously with a plastic detection comb (probably for at least 30 minutes each time) over the whole scalp at intervals for a minimum of 3 consecutive sessions; hair conditioner or vegetable oil can be used to facilitate the process.

Several devices for the removal of head lice such as combs and topical solutions, are available and some are prescribable on the NHS.

The Drug Tariffs can be accessed online at:

- National Health Service Drug Tariff for England and Wales: [www.ppa.org.uk/ppa/edt_intro.htm](http://www.ppa.org.uk/ppa/edt_intro.htm)
- Health and Personal Social Services for Northern Ireland Drug Tariff: [www.hscbusiness.hscni.net/services/2034.htm](http://www.hscbusiness.hscni.net/services/2034.htm)

Crab lice

Permethrin and malathion are used to eliminate crab lice (Phthirus pubis). An aqueous preparation should be applied, allowed to dry naturally and washed off after 12 hours; a second treatment is needed after 7 days to kill lice emerging from surviving eggs. All surfaces of the body should be treated, including the scalp, neck, and face (paying particular attention to the eyebrows and other facial hair). A different insecticide should be used if a course of treatment fails.
ROSCIDEC®
Inflammatory papules and pustules of rosacea
▶ TO THE SKIN
▶ Adult: Apply twice daily for 6 weeks (longer if necessary)

ROZEX® CREAM
Inflammatory papules, pustules and erythema of rosacea
▶ TO THE SKIN
▶ Adult: Apply twice daily for 3–4 months

ROZEX® GEL
Inflammatory papules, pustules and erythema of rosacea
▶ TO THE SKIN
▶ Adult: Apply twice daily for 3–4 months

ZYOMET®
Acute inflammatory exacerbation of rosacea
▶ TO THE SKIN
▶ Adult: Apply twice daily for 8–9 weeks, to be applied thinly

• CAUTIONS Avoid exposure to strong sunlight or UV light
• INTERACTIONS ▶ Appendix 1: metronidazole
• SIDE-EFFECTS
  ▶ Common or very common Skin reactions
  ▶ Rare or very rare
• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Gel
  EXCIPIENTS: May contain Benzyl alcohol, disodium edetate, hydroxybenzoates (parabens), propylene glycol
  ▶ Acea (Ferdnade Pharmaceuticals Ltd)
  Metronidazole 7.5 mg per 1 gram
  Acea 0.75% gel | 40 gram [PDA] £9.95 DT = £22.63
  ▶ Anabact (Cambridge Healthcare Supplies Ltd)
  Metronidazole 7.5 mg per 1 gram
  Anabact 0.75% gel | 15 gram [PDA] £4.47 DT = £4.47 | 30 gram [PDA] £7.89 | 40 gram [PDA] £15.89 DT = £22.63
  ▶ Metrogel (Galderma (UK) Ltd)
  Metronidazole 7.5 mg per 1 gram
  Metrogel 0.75% gel | 15 gram [PDA] £12.00 | 40 gram [PDA] £19.90 DT = £22.63
  ▶ Metrosa (M & A Pharmachem Ltd)
  Metronidazole 7.5 mg per 1 gram
  Metrosa 0.75% gel | 30 gram [PDA] £6.60 | 40 gram [PDA] £9.88 DT = £22.63
  ▶ Rozex (Galderma (UK) Ltd)
  Metronidazole 7.5 mg per 1 gram
  Rozex 0.75% gel | 30 gram [PDA] £6.60 | 40 gram [PDA] £9.88 DT = £22.63
  ▶ Zymet® (Advanz Pharma)
  Metronidazole 7.5 mg per 1 gram
  Zymet 0.75% gel | 30 gram [PDA] £12.00
  Cream
  EXCIPIENTS: May contain Benzyl alcohol, isopropyl palmitate, propylene glycol
  ▶ Rosced (Pierre Fabre Dermo-Cosmetique)
  Metronidazole 7.5 mg per 1 gram
  Rosced 0.75% cream | 30 gram [PDA] £6.60 DT = £6.60
  ▶ Rozex (Galderma (UK) Ltd)
  Metronidazole 7.5 mg per 1 gram
  Rozex 0.75% cream | 30 gram [PDA] £6.60 DT = £6.60 | 40 gram [PDA] £9.88 DT = £9.88

ANTIBACTERIALS ▶ POLYMIXINS

Polymyxins

• INDICATIONS AND DOSE
  Bacterial skin infections
  ▶ TO THE SKIN
  ▶ Adult: Apply twice daily, may be applied more frequently if required

• CAUTIONS If large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children, in the elderly, and in those with renal impairment.
• INTERACTIONS ▶ Appendix 1: polymyxins

SILVER SULFONAMIDES

Silver sulfadiazine

• INDICATIONS AND DOSE
  Prophylaxis and treatment of infection in burn wounds
  ▶ TO THE SKIN
  ▶ Child: Apply daily, may be applied more frequently if very exudative
  ▶ Adult: Apply daily, may be applied more frequently if very exudative

For conservative management of finger-tip injuries
▶ TO THE SKIN
▶ Child: Apply every 2–3 days, consult product literature for details
▶ Adult: Apply every 2–3 days, consult product literature for details

Adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions
▶ TO THE SKIN
▶ Adult: (consult product literature)

Adjunct to short-term treatment of infection in pressure sores
▶ TO THE SKIN
▶ Adult: Apply once daily or on alternate days

As an adjunct to short-term treatment of infection in leg ulcers
▶ TO THE SKIN
▶ Adult: Apply once daily or on alternate days, not recommended if ulcer is very exudative

• UNLICENSED USE
  ▶ In children No age range specified by manufacturer.

• CONTRA-INDICATIONS
  Not recommended for neonates

• CAUTIONS
  G6PD deficiency

CAUTIONS, FURTHER INFORMATION Plasma-sulfadiazine concentrations may approach therapeutic levels with side-effects and interactions as for sulfonamides if large areas of skin are treated.

• INTERACTIONS ▶ Appendix 1: silver sulfadiazine

• SIDE-EFFECTS
  ▶ Common or very common Leucopenia - skin reactions
  ▶ Rare or very rare Argyria (following treatment of large areas of skin or long term use) - renal failure

SIDE-EFFECTS, FURTHER INFORMATION Leucopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not usually be discontinued provided blood counts are monitored carefully to ensure return to normality within a few days.

• ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with sensitivity to sulfonamides.

• PREGNANCY
  Risk of neonatal haemolysis and methaemoglobinemia in third trimester.

• BREAST FEEDING
  Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants.

• HEPATIC IMPAIRMENT
  Manufacturer advises caution in significant hepatic impairment.

• RENAL IMPAIRMENT
  Manufacturer advises caution if significant impairment.

• MONITORING REQUIREMENTS
  Monitor for leucopenia.

• DIRECTIONS FOR ADMINISTRATION Apply with sterile applicator.
2.2 Fungal skin infections

Other drugs used for Fungal skin infections
Hydrocortisone with clotrimazole, p. 1251

ANTIFUNGALS > IMIDAZOLE ANTIFUNGALS

Clotrimazole

- **INDICATIONS AND DOSE**

  **Fungal skin infections**
  - **TO THE SKIN**
  - Child: Apply 2–3 times a day
  - Adult: Apply 2–3 times a day

- **CAUTIONS**
  - Avoid contact with eyes and mucous membranes

- **INTERACTIONS**
  - Contact with eyes and mucous membranes should be avoided
  - Other antifungals should be avoided

- **SIDE-EFFECTS**
  - Oedema, pain, paraesthesia, skin reactions, syncope

- **PREGNANCY**
  - Minimal absorption from skin; not known to be harmful

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Spray may be useful for application of clotrimazole to large or hairy areas of the skin

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Clotrimazole for fungal infections www.medicinesforchildren.org.uk/clotrimazole-fungal-infections

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  - **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol
  - Flamazine (Smith & Nephew Healthcare Ltd)
  - Sulfadiazine silver 10 mg per 1 gram Flamazine 1% cream |
    - 20 gram (P) £2.91 | 50 gram (P) £3.85 |
    - 250 gram (P) £10.32 DT = £10.32 | 500 gram (P) £18.27 DT = £18.27

ANTIBACTERIALS > OTHER

Mupirocin

- **INDICATIONS AND DOSE**

  **Bacterial skin infections, particularly those caused by Gram-positive organisms (except pseudomonal infection)**
  - **TO THE SKIN**
  - Child: Apply up to 3 times a day for up to 10 days
  - Adult: Apply up to 3 times a day for up to 10 days

- **UNLICENSED USE**


- **SIDE-EFFECTS**

  - Common or very common  Skin reactions

- **PREGNANCY**

  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING**

  - No information available.

- **RENAL IMPAIRMENT**

  - Manufacturer advises caution when mupirocin ointment used in moderate or severe impairment because it contains macrogols (polyethylene glycol).

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  **Ointment**
  - **Mupirocin (Non-proprietary)**
    - Mupirocin 20 mg per 1 gram Mupirocin 2% ointment |
      - 15 gram (P) £12.50 DT = £5.26
    - Bactroban® (GlaxoSmithKline UK Ltd)
      - Mupirocin 20 mg per 1 gram Bactroban 2% ointment |
        - 15 gram (P) £5.26 DT = £5.26
  - **Cream**
    - **EXCIPIENTS**: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol)
      - Bactroban® (GlaxoSmithKline UK Ltd)
      - Mupirocin (as Mupirocin calcium) 20 mg per 1 gram Bactroban 2% cream |
        - 15 gram (P) £5.26 DT = £5.26

- **SIDE-EFFECTS**

  - Oedema, pain, paraesthesia, skin reactions, syncope

  - **PREGNANCY**

  - Minimal absorption from skin; not known to be harmful

  - **PRESCRIBING AND DISPENSING INFORMATION**

  - Spray may be useful for application of clotrimazole to large or hairy areas of the skin

  - **PATIENT AND CARER ADVICE**

  - Medicines for Children leaflet: Clotrimazole for fungal infections www.medicinesforchildren.org.uk/clotrimazole-fungal-infections

  - **MEDICINAL FORMS**

    - There can be variation in the licensing of different medicines containing the same drug.

    **Cream**
    - **EXCIPIENTS**: May contain Butylated hydroxyanisole, fragrances
      - Flamazine 1% cream |
        - 20 gram (P) £1.80 DT = £0.95 | 50 gram (P) £5.45 DT = £2.38
      - Canesten (clotrimazole) (Bayer Plc)
        - Clotrimazole 10 mg per 1 gram Canesten 1% cream |
          - 20 gram (P) £2.20 DT = £0.95 | 50 gram (P) £3.64 DT = £2.38
        - Canesten Antifungal 1% cream |
          - 20 gram (P) £1.85 DT = £0.95
        - Clotrimazole 20 mg per 1 gram Canesten 2% thrush cream |
          - 20 gram (£4.76 DT = £4.76

    - **Liquid**
      - Canesten (clotrimazole) (Bayer Plc)
      - Clotrimazole 10 mg per 1 ml Canesten 1% solution |
        - 20 ml (£2.53 DT = £2.53

    - Combinations available: Hydrocortisone with clotrimazole, p. 1251

**Econazole nitrate**

- **INDICATIONS AND DOSE**

  **Fungal skin infections**
  - **TO THE SKIN**
  - Child: Apply twice daily
  - Adult: Apply twice daily

  **Fungal nail infections**
  - **BY TRANSSUNGULAR APPLICATION**
  - Child: Apply once daily, applied under occlusive dressing
  - Adult: Apply once daily, applied under occlusive dressing

- **CAUTIONS**

  - Avoid contact with eyes and mucous membranes

- **SIDE-EFFECTS**

  - Common or very common  Pain  skin reactions

  - Uncommon  Swelling

  - Frequency not known  Angioedema

  - **SIDE-EFFECTS, FURTHER INFORMATION**

    - Treatment should be discontinued if side-effects are severe

  - **PREGNANCY**

    - Minimal absorption from skin; not known to be harmful

  - **MEDICINAL FORMS**

    - There can be variation in the licensing of different medicines containing the same drug.

    **Cream**
    - **EXCIPIENTS**: May contain Butylated hydroxyanisole, fragrances
      - Pevaryl (Janssen-Cilag Ltd)
      - Econazole nitrate 10 mg per 1 gram Pevaryl 1% cream |
        - 30 gram (P) £3.71

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Fungal skin infections 1233

Ketoconazole 02-Apr-2019

- **INDICATIONS AND DOSE**
  - **Tinea pedis**
    - To the skin using cream
    - Adult: Apply twice daily
  - **Fungal skin infection (not Tinea pedis)**
    - To the skin using cream
    - Adult: Apply 1–2 times a day
  - **Treatment of seborrhoeic dermatitis and dandruff**
    - To the skin using shampoo
    - Child 12-17 years: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing
    - Adult: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing
  - **Prophylaxis of seborrhoeic dermatitis and dandruff**
    - To the skin using shampoo
    - Child 12-17 years: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing
    - Adult: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing
  - **Treatment of pityriasis versicolor**
    - To the skin using shampoo
    - Child 12-17 years: Apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing
    - Adult: Apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing
  - **Prophylaxis of pityriasis versicolor**
    - To the skin using shampoo
    - Child 12-17 years: Apply once daily for up to 3 days before sun exposure, leave preparation on for 3–5 minutes before rinsing
    - Adult: Apply once daily for up to 3 days before sun exposure, leave preparation on for 3–5 minutes before rinsing

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058

- **CAUTIONS** Avoid contact with eyes; avoid contact with mucous membranes

- **INTERACTIONS** Appendix 1: antifungals, azoles

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common Skin reactions
    - Uncommon Alopecia; angioedema; excessive tearing; folliculitis; hair changes
    - Rare or very rare Eye irritation; taste altered

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NHS restrictions Nizoral® cream is not prescribable in NHS primary care except for the treatment of seborrhoeic dermatitis and pityriasis versicolor; endorse prescription 'SLS'.

- **EXCEPTIONS TO LEGAL CATEGORY** A 15-g tube is available for sale to the public for the treatment of tinea pedis, tinea cruris, and candidal intertrigo.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Cream**
    - EXCIPIENTS: May contain imidurea
    - Ketoconazole (Non-proprietary)
      - Ketoconazole 20 mg per 1 gram
      - Daktarin® (Transdermal Ltd)
    - Dandrazol Anti-dandruff 2% shampoo 120 ml (POM) £3.39 DT + £3.36
    - Daktarin® (Janssen-Cilag Ltd; Thornton & Ross Ltd)
    - Ketoconazole 20 mg per 1 gram
      - Nizoral® 2% shampoo 120 ml (POM) £3.59 DT + £3.36

  - **Shampoo**
    - EXCIPIENTS: May contain imidurea
      - Ketoconazole (Non-proprietary)
      - Ketoconazole 2% shampoo 120 ml (POM) £3.36 DT + £3.36
      - Dandrazol Anti-dandruff 2% shampoo 120 ml (POM) £3.39 DT + £3.36
      - Nizoral® (Janssen-Cilag Ltd; Thornton & Ross Ltd)
      - Ketoconazole 20 mg per 1 gram
        - Nizoral® 2% shampoo 120 ml (POM) £3.59 DT + £3.36

Miconazole 02-Apr-2019

- **INDICATIONS AND DOSE**
  - **Fungal skin infections**
    - To the skin
    - Child: Apply twice daily continuing for 10 days after lesions have healed
    - Adult: Apply twice daily continuing for 10 days after lesions have healed
  - **Fungal nail infections**
    - To the skin
    - Child: Apply 1–2 times a day
    - Adult: Apply 1–2 times a day

- **UNLICENSED USE**
  - In children. Licensed for use in children (age range not specified by manufacturer).

- **CAUTIONS** Avoid in acute porphyrias p. 1058; contact with eyes and mucous membranes should be avoided

- **INTERACTIONS** Appendix 1: antifungals, azoles

- **SIDE-EFFECTS**
  - Common or very common Skin reactions
  - Frequency not known Angioedema

- **PREGNANCY** Absorbed from the skin in small amounts; manufacturer advises caution.

- **BREAST FEEDING** Manufacturer advises caution—no information available.

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Miconazole cream may be prescribed.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NHS restrictions Daktarin® powder and Daktarin® cream 15g is not prescribable in NHS primary care.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  - **Cream**
    - EXCIPIENTS: May contain Butylated hydroxyanisole
      - Daktarin® (McNeil Products Ltd, Janssen-Cilag Ltd, Johnson & Johnson Ltd)
    - Miconazole nitrate 20 mg per 1 gram
      - Daktarin 2% cream 15 g (P) £2.51 | 30 g (P) £1.82 DT + £1.82
      - Powder
        - Daktarin® (McNeil Products Ltd)
        - Miconazole nitrate 20 mg per 1 gram
          - Daktarin 2% powder 20 g (P) £2.95 DT + £2.95

Tioconazole

- **INDICATIONS AND DOSE**
  - **Fungal nail infection**
    - By transungual application
    - Child: Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin
    - Adult: Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin

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### Amorolfine

#### INDICATIONS AND DOSE

**Fungal nail infections**

- **BY TRANSGUNGAL APPLICATION**
  - Child 12-17 years: Apply 1–2 times a week for 6 months to treat fingernails and for toenails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allow to dry for approximately 3 minutes
  - Adult: Apply 1–2 times a week for 6 months to treat fingernails and for toenails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allow to dry for approximately 3 minutes

#### CAUTIONS

Avoid contact with ears - avoid contact with eyes and mucous membranes - use with caution in child likely to suck affected digits

#### SIDE-EFFECTS

- Rare or very rare Nail discolouration - skin reactions

#### PATIENT AND CARER ADVICE

Avoid nail varnish or artificial nails during treatment.

#### EXCEPTIONS TO LEGAL CATEGORY

In adults Amorolfine nail lacquer can be sold to the public if supplied for the treatment of mild cases of distal and lateral subungual onychomycoses caused by dermatophytes, yeasts and moulds; subject to treatment of max. 2 nails, max. strength of nail lacquer amorolfine 5% and a pack size of 3 mL.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Medicated nail lacquer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAUTIONARY AND ADVISORY LABELS</strong> 10</td>
</tr>
<tr>
<td>Amorolfine (Non-proprietary)</td>
</tr>
<tr>
<td>Amorolfine (as Amorolfine hydrochloride) 50 mg per 1 ml</td>
</tr>
<tr>
<td>Amorolfine 5% medicated nail lacquer</td>
</tr>
<tr>
<td>Loceryl (Galderma (UK) Ltd)</td>
</tr>
<tr>
<td>Amorolfine (as Amorolfine hydrochloride) 50 mg per 1 ml</td>
</tr>
<tr>
<td>Loceryl 5% medicated nail lacquer</td>
</tr>
<tr>
<td>Omicur (Morningside Healthcare Ltd)</td>
</tr>
<tr>
<td>Amorolfine (as Amorolfine hydrochloride) 50 mg per 1 ml</td>
</tr>
<tr>
<td>Omicur 5% medicated nail lacquer</td>
</tr>
</tbody>
</table>
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SPECIFIC SIDE-EFFECTS
- Common or very common
- With oral use Appetite decreased· arthralgia· diarrhoea· gastrointestinal discomfort· gastrointestinal disorder· headache· myalgia· nausea
- Uncommon
- With oral use Taste altered· weight decreased
- With topical use Pain
- Rare or very rare
- With oral use Agranulocytosis· alopecia· cutaneous lupus erythematosus· dizziness· hepatic disorders· malaise· neutropenia· photosensitivity reaction· sensation abnormal· severe cutaneous adverse reactions (SCARs)· systemic lupus erythematosus (SLE)· thrombocytopenia· vertigo
- Frequency not known
- With oral use Anaemia· anxiety· depressive symptom· fatigue· fever· hearing impairment· influenza like illness· pancreatitis· pancytopenia· rhombodylosis· serum sickness-like reaction· smell altered· tinnitus· vasculitis· vision disorders
- With topical use Hypersensitivity

SIDE-EFFECTS, FURTHER INFORMATION
Liver toxicity With oral use; discontinue treatment if liver toxicity develops (including jaundice, cholestasis and hepatitis).

Serious skin reactions With oral use; discontinue treatment in progressive skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

PREGNANCY
- With topical use Manufacturer advises use only if potential benefit outweighs risk—animal studies suggest no adverse effects.
- With oral use Manufacturer advises use only if potential benefit outweighs risk—no information available.

BREAST FEEDING
- With topical use Manufacturer advises avoid—present in milk. Less than 5% of the dose is absorbed after topical application of terbinafine; avoid application to mother’s chest.
- With oral use Avoid—present in milk.

HEPATIC IMPAIRMENT
- With oral use Manufacturer advises avoid (risk of increased exposure).

RENAL IMPAIRMENT
Dose adjustments
- With oral use Use half normal dose if eGFR less than 50 mL/minute/1.73 m² and no suitable alternative available.

MONITORING REQUIREMENTS
- With oral use Monitor hepatic function before treatment and then periodically after 4–6 weeks of treatment—discontinue if abnormalities in liver function tests.

PATIENT AND CARER ADVICE
- With oral use Manufacturer advises that patients should immediately report any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, decreased appetite, anorexia, jaundice, vomiting, fatigue, right upper abdominal pain, dark urine, or pale stools. Patients with these symptoms should discontinue taking terbinafine and the patient’s liver function should be immediately evaluated.

EXCEPTIONS TO LEGAL CATEGORY
- With topical use Preparations of terbinafine hydrochloride (maximum 1%) can be sold to the public for use in those over 16 years for external use for the treatment of tinea pedis as a cream in a pack containing maximum 15 g, or for the treatment of tinea pedis and cruris as a cream in a pack containing maximum 15 g, or for the treatment of tinea pedis, cruris, and corporis as a spray in a pack containing maximum 30 mL spray or as a gel in a pack containing maximum 30 g gel.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS
- Terbinafine (Non-proprietary)
  Terbinafine (as Terbinafine hydrochloride) 250 mg Terbinafine 250mg tablets | 14 tablet (£34.39)
  Terbinafine (as Terbinafine hydrochloride) 250 mg Terbinafine 250mg tablet | 28 tablet (£2.04–£54.93)
- Lamisil (Novartis Pharmaceuticals UK Ltd)
  Lamisil 250mg tablets | 14 tablet (£1.27) | 28 tablet (£1.20)
  Lamisil 250mg tablet | 14 tablet (£1.27) | 28 tablet (£1.20)

Cream
EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohols), poloxamers
- Terbinafine (Non-proprietary)
  Terbinafine hydrochloride 10 mg per 1 gram Terbinafine 1% cream | 15 gram (£3.76) | 30 gram (£3.76)
  Terbinafine hydrochloride 10 mg per 1 gram Lamisil 1% cream | 15 gram (£1.37) | 30 gram (£3.37)
  Lamisil GSK (Smithkline Consumer Healthcare)
  Terbinafine hydrochloride 10 mg per 1 gram Lamisil 1% cream | 15 gram (£3.76) | 30 gram (£3.76)

ANTISEPTICS AND DISINFECTANTS
- Undecenoic acid with zinc undecenoate

Undecenoic acid with zinc undecenoate

INDICATIONS AND DOSE
Treatment of athletes foot
- TO THE SKIN
- Child: Apply twice daily, continue use for 7 days after lesions have healed
- Adult: Apply twice daily, continue use for 7 days after lesions have healed

Prevention of athletes foot
- TO THE SKIN
- Child: Apply once daily
- Adult: Apply once daily

UNLICENSED USE
- In children Mycota® licensed for use in children (age range not specified by manufacturer).

CAUTIONS
Avoid broken skin· contact with eyes should be avoided· contact with mucous membranes should be avoided

SIDE-EFFECTS
- Rare or very rare Skin irritation

SIDE-EFFECTS, FURTHER INFORMATION
- Treatment should be discontinued if irritation is severe.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Cream
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohols), fragrances
- Mycota (zinc undecenoate / undecenoic acid) (Thornon & Ross Ltd)
  Undecenoic acid 50 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram Mycota cream | 25 gram (£3.01)
- Mycota (zinc undecenoate / undecenoic acid) (Thornon & Ross Ltd)
  Undecenoic acid 20 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram Mycota powder | 70 gram (£3.04)

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohols), fragrances
- Mycota (zinc undecenoate / undecenoic acid) (Thornon & Ross Ltd)
  Undecenoic acid 20 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram Mycota powder | 70 gram (£3.04)

FIXED COMBINATIONS
- Lamisil (Novartis Pharmaceuticals UK Ltd)
  Lamisil 250mg tablets | 14 tablet (£1.27) | 28 tablet (£1.20)
  Lamisil 250mg tablet | 14 tablet (£1.27) | 28 tablet (£1.20)

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ANTISEPTICS AND DISINFECTANTS  >  OTHER

Chlorhexidine with nystatin

- **INDICATIONS AND DOSE**
  - Skin infections due to Candida spp.
    - TO THE SKIN
      - Child: Apply 2–3 times a day, continuing for 7 days after lesions have healed
      - Adult: Apply 2–3 times a day, continuing for 7 days after lesions have healed

- **LICENSED USE**
  - In children: Licensed for use in children (age range not specified by manufacturer).

- **CAUTIONS**
  - Avoid contact with eyes and mucous membranes

- **SIDE-EFFECTS**
  - Hypersensitivity · skin reactions

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Cream**
      - **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
      - Chlorhexidine hydrochloride 10 mg per 1 gram, Nystatin 100000 unit per 1 gram
      - Nystatin 100,000 units/g · Chlorhexidine hydrochloride 1% cream · 30 gram
      - £4.99 DT = £4.99

BENZOATES

Benzoic acid with salicylic acid

- **INDICATIONS AND DOSE**
  - Ringworm (tinea)
    - TO THE SKIN
      - Child: Apply twice daily
      - Adult: Apply twice daily

- **LICENSED USE**
  - In children: Licensed for use in children (age range not specified by manufacturer).

- **CAUTIONS**
  - Avoid broken or inflamed skin · avoid contact with eyes · avoid contact with mucous membranes

- **SIDE-EFFECTS**
  - Hypersensitivity · skin burning sensation (mild) · skin reactions

- **MEDICINAL FORMS**
  - Forms available from special-order manufacturers include: cream, ointment

2.3 Parasitic skin infections

Other drugs used for Parasitic skin infections Ivermectin, p. 604

PARASITICIDES

Benzyl benzoate

- **INDICATIONS AND DOSE**
  - Scabies
    - TO THE SKIN
      - Adult: Apply over the whole body; repeat without bathing on the following day and wash off 24 hours later; a third application may be required in some cases

- **CAUTIONS**
  - Avoid contact with eyes and mucous membranes · children (not recommended) · do not use on broken or secondarily infected skin

- **SIDE-EFFECTS**
  - Skin burning sensation · skin reactions

- **LICENSED USE**
  - In children: Licensed for use in children (age range not specified by manufacturer).

- **SIDE-EFFECTS**
  - Avoid contact with eyes and mucous membranes · genitalia and excoriations

- **MEDICINAL FORMS**
  - Forms available from special-order manufacturers include: liquid

Dimeticone

- **INDICATIONS AND DOSE**
  - Head lice
    - TO THE SKIN
      - Child: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)
      - Adult: Apply once weekly for 2 doses, rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)

- **LICENSED USE**
  - In children: Not licensed for use in children under 6 months except under medical supervision

- **SIDE-EFFECTS**
  - Alopecia · dyspnoea · eye irritation · hypersensitivity · scalp changes · skin reactions

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  | Liquid | Dimeticone 40 mg per 1 gram | Hedrin 4% lotion | 50 ml | £3.28 DT = £3.28 |
  | | Dimeticone 40 mg per 1 gram | Hedrin 4% spray | 120 ml | £ 7.85 |

See Skin infections p. 1228.
Parasitic skin infections 1237

Malathion 06-Apr-2018

- INDICATIONS AND DOSE
  - Head lice
    - Child: Apply once weekly for 2 doses, rub preparation into dry hair and scalp, allow to dry naturally, remove by washing after 12 hours.
    - Adult: Apply once weekly for 2 doses, rub preparation into dry hair and scalp, allow to dry naturally, remove by washing after 12 hours.
  - Crab lice
    - Child: Apply once weekly for 2 doses, apply preparation over whole body,允许 to dry naturally, wash off after 12 hours or overnight.
    - Adult: Apply once weekly for 2 doses, apply preparation over whole body, allow to dry naturally, wash off after 12 hours or overnight.

- SIDE-EFFECTS
  - Scabies
    - Child: Apply once weekly for 2 doses, apply preparation over whole body, and wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated.
    - Adult: Apply once weekly for 2 doses, apply preparation over whole body, and wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated.

- CAUTIONS
  - In children Not licensed for use in children under 6 months except under medical supervision.

- IMPORTANT SAFETY INFORMATION
  - MHRA/CHM ADVICE: HEAD LICE ERADICATION PRODUCTS: RISK OF SERIOUS BURNS IF TREATED HAIR IS EXPOSED TO OPEN FLAMES OR OTHER SOURCES OF IGNITION (MARCH 2018)
  - See Skin infections p. 1228.

- UNLICENSED USE
  - In children Not licensed for use in children under 6 months except under medical supervision.

- CAUTIONS
  - Alcoholic lotions not recommended for use in children with severe eczema or asthma, or for scabies or crab lice.

- SIDE-EFFECTS
  - Scalp irritation - skin reactions

- PRESCRIBING AND DISPENSING INFORMATION
  - For scabies, manufacturer recommends application to the body but not necessarily to the head and neck. However, application should be extended to the scalp, neck, face, and ears.

- MEDICINAL FORMS
  - "Mervit" (proprietary) Permethrin 50 mg per 1 gram
  - "Creme Rinse" (proprietary) Permethrin 50 mg per 1 gram

Permethrin 12-Apr-2018

- INDICATIONS AND DOSE
  - Scabies
    - Child: Apply once weekly for 2 doses, apply 5% preparation over whole body including face, neck, scalp and ears then wash off after 8–12 hours. If hands are washed with soap within 8 hours of application, they should be treated again with cream.
  - Crab lice
    - Child: Apply once weekly for 2 doses, apply 5% cream over whole body, allow to dry naturally and wash off after 12 hours or after leaving on overnight.

- UNLICENSED USE
  - In children "Dermal Cream" (scabies), not licensed for use in children under 2 months; not licensed for treatment of crab lice in children under 18 years. "Creme Rinse" (head lice) not licensed for use in children under 6 months except under medical supervision.

- IMPORTANT SAFETY INFORMATION
  - MHRA/CHM ADVICE: HEAD LICE ERADICATION PRODUCTS: RISK OF SERIOUS BURNS IF TREATED HAIR IS EXPOSED TO OPEN FLAMES OR OTHER SOURCES OF IGNITION (MARCH 2018)
  - See Skin infections p. 1228.

- CAUTIONS
  - Avoid contact with eyes - children aged 2 months–2 years, medical supervision required for dermal cream (scabies) - children under 6 months, medical supervision required for cream rinse (head lice) - do not use on broken or secondarily infected skin.

- SIDE-EFFECTS
  - Scalp irritation - skin reactions

- PRESCRIBING AND DISPENSING INFORMATION
  - Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears.

- MEDICINAL SUITABLE FOR PRESCRIBING
  - "Lyceal" Creme Rinse is less suitable for prescribing.
2.4 Viral skin infections

**ANTIVIRALS > NUCLEOSIDE ANALOGUES**

Aciclovir

(Acyclovir)

- **INDICATIONS AND DOSE**
  - Herpes simplex infection (local treatment)
  - TO THE SKIN
  - Child: Apply 5 times a day for 5–10 days, to be applied to lesions approximately every 4 hours, starting at first sign of attack
  - Adult: Apply 5 times a day for 5–10 days, to be applied to lesions approximately every 4 hours, starting at first sign of attack

- **UNLICENSED USE**
  - In children Cream licensed for use in children (age range not specified by manufacturer).

- **CAUTIONS**
  - Avoid cream coming in to contact with eyes and mucous membranes

- **INTERACTIONS**
  - Appendix 1: aciclovir

- **SIDE-EFFECTS**
  - Uncommon Skin reactions

- **PREGNANCY**
  - Limited absorption from topical aciclovir preparations.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Aciclovir cream for herpes
  - www.medicinesforchildren.org.uk/aciclovir-cream-herpes-0

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Aciclovir Cream may be prescribed.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - A 2-g tube and a pump pack are on sale to the public for the treatment of cold sores.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  - Excipients: May contain Ceteosteryl alcohol (including cetyl and stearyl alcohol), propylene glycol
  - Aciclovir (Non-proprietary)
  - Aciclovir 50 mg per 1 gram  Aciclovir 5% cream  |  2 gram [POST]  £1.09 DT + £1.09 |  10 gram [POST]  £3.45 DT + £5.45
  - Zovirax (GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline UK Ltd)
  - Aciclovir 50 mg per 1 gram  Zovirax 5% cream  |  2 gram [POST]  £4.63 DT + £1.09 |  10 gram [POST]  £13.96 DT + £5.45

3 Inflammatory skin conditions

3.1 Eczema and psoriasis

Eczema

Types and management

Eczema (dermatitis) has several causes, which may influence treatment. The main types of eczema are irritant, allergic contact, atopic, venous and discoid; different types may co-exist. Lichenification, due to scratching and rubbing, may complicate any chronic eczema. Atopic eczema is the most common type and it usually involves dry skin as well as infection and lichenification.
eczema for its antiseptic and astringent effects; treatment should be stopped when exudation stops.

**Severe refractory eczema**

Severe refractory eczema is best managed under specialist supervision; it may require phototherapy or drugs that act on the immune system. Alitretinoin p. 1262 is licensed for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids; patients with hyperkeratotic features are more likely to respond to alitretinoin than those with pompholyx.

**Seborrhoeic dermatitis**

Seborrhoeic dermatitis (seborrhoeic eczema) is associated with species of the yeast Malassezia and affects the scalp, paranasal areas, and eyebrows. Shampoos active against the yeast (including those containing ketoconazole p. 1233 or coal tar p. 1253) and combinations of mild corticosteroids with suitable antimicrobials are used.

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**Psoriasis**

**Management**

Psoriasis is characterised by epidermal thickening and scaling. It commonly affects extensor surfaces and the scalp.

Occasionally, psoriasis is provoked or exacerbated by drugs such as lithium, chloroquine and hydroxychloroquine, beta-blockers, non-steroidal anti-inflammatory drugs, and ACE inhibitors. Psoriasis may not be seen until the drug has been taken for weeks or months.

**Emollients**, in addition to their effects on dryness, scaling and cracking, may have an anti-proliferative effect in psoriasis, and may be the only treatment necessary for mild psoriasis. They are particularly useful in inflammatory psoriasis and in plaque psoriasis of palms and soles, in which irritant factors can perpetuate the condition. Emollients are useful adjuncts to other more specific treatment.

More specific topical treatment for **chronic stable plaque psoriasis** on extensor surfaces of trunk and limbs involves the use of vitamin D analogues, coal tar p. 1253, dithranol p. 1253, and the retinoid tazarotene p. 1262. However, they can irritate the skin and they are not suitable for the more inflammatory forms of psoriasis; their use should be suspended during an inflammatory phase of psoriasis. The efficacy and the irritancy of each substance varies between patients. If a substance irritates significantly, it should be stopped or the concentration reduced; if it is tolerated, its effects should be assessed after 4 to 6 weeks and treatment continued if it is effective.

**Scalp psoriasis** is usually scaly, and the scale may be thick and adherent; this will require softening with an emollient cream, ointment, or oil. A tar-based shampoo is first-line treatment for scalp psoriasis; a keratolytic, such as salicylic acid, should also be used if there is significant scaling, to allow other treatments to work.

Some preparations prescribed for psoriasis affecting the scalp, combine salicylic acid with coal tar or sulfur. The product should be applied generously, and an adequate quantity should be prescribed. It should be left on for at least an hour, often more conveniently overnight, before washing off. The use of scalp preparations containing a potent corticosteroid or a vitamin D analogue, either alone or in combination, can also be helpful.

**Facial, flexural and genital psoriasis** can be managed with short-term use of a mild or moderate potency topical corticosteroid (a mild potency topical corticosteroid is preferred for the initial treatment of facial psoriasis). Calcipotriol p. 1263 or tacalcitol p. 1264 can be used for longer-term treatment, or if the response to mild or moderate potency topical corticosteroids is inadequate; calcipotriol p. 1263 is more likely to cause irritation. Low strength tar preparations can also be used. Pimecrolimus p. 1255 or tacrolimus p. 1256 by topical application [unlicensed indication] can be used short-term, under specialist supervision, in patients whose condition has not responded adequately to other treatments, or who are intolerant of them.

Widespread unstable psoriasis of erythrodermic or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited using emollients frequently and generously; emollients should be prescribed in quantities of 1 kg or more. More localised acute or subacute inflammatory psoriasis with hot, spreading or itchy lesions, should be treated topically with emollients or with a corticosteroid of moderate potency. Calcipotriol and tacalcitol are analogues of vitamin D that affect cell division and differentiation. Calcitriol is an active form of vitamin D. Vitamin D and its analogues are used first-line for the long-term treatment of plaque psoriasis; they do not smell or stain and they may be more acceptable than tar or dithranol products. Of the vitamin D analogues, tacalcitol and calcitriol are less likely to irritate.

**Coal tar** has anti-inflammatory properties that are useful in chronic plaque psoriasis; it also has antiscaling properties. Crude coal tar (coal tar, BP) is the most effective form, typically in a concentration of 1 to 10% in a soft paraffin base, but few outpatients tolerate the smell and mess. Cleaner extracts of coal tar included in proprietary preparations, are more practicable for home use but they are less effective and improvement takes longer. Contact of coal tar products with normal skin is not normally harmful and they can be used for widespread small lesions; however, irritation, contact allergy, and sterile folliculitis can occur. The milder tar extracts can be used on the face and flexures. Tar baths and tar shampoos are also helpful.

Dithranol is effective for chronic plaque psoriasis. Its major disadvantages are irritation (for which individual susceptibility varies) and staining of skin and of clothing. Dithranol is not generally suitable for widespread small lesions nor should it be used in the flexures or on the face. Proprietary preparations are more suitable for home use; they are usually washed off after 5 to 60 minutes (‘short contact’). Specialist nurses may apply intensive treatment with dithranol paste which is covered by sterile nette dressings and usually retained overnight. Dithranol should be discontinued if even a low concentration causes acute inflammation; continued use can result in the psoriasis becoming unstable.

Tazarotene, a retinoid, has a similar efficacy to vitamin D and its analogues, but is associated with higher incidence of irritation. Although irritation is common, it is minimised by applying tazarotene sparingly to the plaques and avoiding normal skin; application to the face and in flexures should also be avoided. Tazarotene does not stain and is odourless. A topical corticosteroid is not generally suitable for long-term use or as the sole treatment of extensive chronic plaque psoriasis; any early improvement is not usually maintained and there is a risk of the condition deteriorating or of precipitating an unstable form of psoriasis (e.g. erythrodermic psoriasis or generalised pustular psoriasis) on withdrawal. Topical use of potent corticosteroids on widespread psoriasis can also lead to systemic as well as local side-effects. However, topical corticosteroids used short-term may be appropriate to treat psoriasis in specific sites such as the face or flexures (with a mild or moderate corticosteroid), and psoriasis of the scalp, palms, and soles (with a potent corticosteroid). Very potent corticosteroids should only be used under specialist supervision.

Combining the use of a corticosteroid with another specific topical treatment may be beneficial in chronic plaque psoriasis; the drugs may be used separately at different times of the day or used together in a single formulation. Eczema co-existing with psoriasis may be treated with a corticosteroid, or coal tar, or both.
**Phototherapy**

Phototherapy is available in specialist centres under the supervision of a dermatologist. Ultraviolet B (UVB) radiation is usually effective for chronic stable psoriasis and for guttate psoriasis. It may be considered for patients with moderately severe psoriasis in whom topical treatment has failed, but it may irritate inflammatory psoriasis.

**Photochemotherapy** combining long-wave ultraviolet A radiation with a psoralen (PUVA) is available in specialist centres under the supervision of a dermatologist. The psoralen, which enhances the effect of irradiation, is administered either by mouth or topically. PUVA is effective in most forms of psoriasis, including localised palmoplantar, pustular psoriasis. Early adverse effects include phototoxicity and pruritus. Higher cumulative doses exaggerate skin ageing, increase the risk of dysplastic and neoplastic skin lesions, especially squamous cancer, and pose a theoretical risk of cataracts.

Phototherapy combined with coal tar, dithranol, tazarotene, topical vitamin D or vitamin D analogues, or oral acitretin, allows reduction of the cumulative dose of phototherapy required to treat psoriasis.

**Systemic treatment**

**Systemic treatment** is required for severe, resistant, unstable or complicated forms of psoriasis, and it should be initiated only under specialist supervision. Systemic drugs for psoriasis include acitretin and drugs that affect the immune response (such as ciclosporin p. 838 and methotrexate p. 913).

Systemic corticosteroids should be used only rarely in psoriasis because rebound deterioration may occur on reducing the dose.

Acitretin p. 1261, a metabolite of etretinate, is a retinoid (vitamin A derivative); it is prescribed by specialists. The main indication for acitretin is psoriasis, but it is also used in disorders of keratinisation such as severe Darier’s disease (keratosis follicularis), and some forms of ichthyosis. Although a minority of cases of psoriasis respond well to acitretin alone, it is only moderately effective in many cases and it is combined with other treatments. A therapeutic effect occurs after 2 to 4 weeks and the maximum benefit after 4 months. Consideration should be given to stopping acitretin if the response is inadequate after 4 months at the optimum dose. The manufacturers of acitretin do not recommend continuous treatment for longer than 6 months. However, some patients may benefit from longer treatment, provided that the lowest effective dose is used, patients are monitored carefully for adverse effects, and the need for treatment is reviewed regularly.

Acitretin is teratogenic, which remains a risk for 3 years after stopping, acitretin is the least toxic systemic treatment for psoriasis; in women with a potential for child-bearing, the possibility of pregnancy must be excluded before treatment and effective contraception must be used during treatment and for at least 3 years afterwards (oral progestogen-only contraceptives not considered effective).

**Topical treatment**

The vitamin D and analogues, calcipotriol p. 1263, calcitriol p. 1263, and tacalcitol p. 1264 are used for the management of plaque psoriasis. They should be avoided by those with calcium metabolism disorders, and used with caution in generalised pustular or erythrodermic exfoliative psoriasis (enhanced risk of hypercalcaemia).

**Eczema and psoriasis, drugs affecting the immune response**

**Overview**

Drugs affecting the immune response are used for eczema or psoriasis. Systemic drugs acting on the immune system are used under specialist supervision.

Pimecrolimus p. 1255 by topical application is licensed for mild to moderate atopic eczema. Tacrolimus p. 1256 is licensed for topical use in moderate to severe atopic eczema. Both are drugs whose long-term safety is still being evaluated and they should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Treatment of atopic eczema with topical pimecrolimus or topical tacrolimus should be initiated only by prescribers experienced in managing the condition. Topical tacrolimus and pimecrolimus have a role in the treatment of psoriasis.

A short course of a systemic corticosteroid can be given for eczema flares that have not improved despite appropriate topical treatment.

Ciclosporin p. 838 by mouth can be used for severe psoriasis and for severe eczema. Azathioprine p. 836 or mycophenolate mofetil p. 846 are used for severe refractory eczema [unlicensed indication]. Dupilumab p. 1257 is licensed for the treatment of moderate to severe atopic eczema in patients requiring systemic therapy. Dimethyl fumarate p. 853 is licensed for the treatment of moderate to severe plaque psoriasis.

Methotrexate p. 913 can be used for severe psoriasis, the dose being adjusted according to severity of the condition and haematological and biochemical measurements. Folic acid p. 1025 should be given to reduce the possibility of side-effects associated with methotrexate. Folic acid can be given once weekly [unlicensed indication], on a different day from the methotrexate; alternative regimens of folic acid may be used in some settings.

Etanercept p. 1113, adalimumab p. 1108, and infliximab p. 1116 inhibit the activity of tumour necrosis factor (TNFs). They are used for severe plaque psoriasis either refractory to at least 2 standard systemic treatments and phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications; while either etanercept or adalimumab is considered to be the first choice in stable disease, infliximab or adalimumab may be useful when rapid disease control is required. Secukinumab p. 1100 and ixekizumab p. 1259 inhibit the activity of interleukin-17A, brodalumab p. 1257 inhibits the activity of interleukin-17A and guselkumab p. 1258 inhibits the activity of interleukin-23. They are used for moderate to severe plaque psoriasis in patients who are candidates for systemic therapy. Secukinumab is also licensed for psoriatic arthritis and ankylosing spondylitis. Ustekinumab p. 1103 (a monoclonal antibody that inhibits interleukins 12 and 23) can be used for severe plaque psoriasis that has not responded to at least 2 standard systemic treatments and phototherapy, or when these treatments cannot be used because of intolerance or contra-indications.

Adalimumab is also licensed for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in patients who have had inadequate response to conventional systemic therapy. Adalimumab, etanercept, infliximab, ixekizumab and ustekinumab are also licensed for psoriatic arthritis.

**Other drugs used for Eczema and psoriasis**

Apremilast, p. 1119 - Certolizumab pegol, p. 1111
CORTICOSTEROIDS

Topical corticosteroids

Overview
Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), in particular eczema, contact dermatitis, insect stings, and eczema of scabies. Corticosteroids suppress the inflammatory reaction during use; they are not curative and on discontinuation a rebound exacerbation of the condition may occur. They are generally used to relieve symptoms and suppress signs of the disorder when other measures such as emollients are ineffective.

Topical corticosteroids are not recommended in the routine treatment of urticaria; treatment should only be initiated and supervised by a specialist. They should not be used indiscriminately in pruritus (where they will only benefit if inflammation is causing the itch) and are not recommended for acne vulgaris.

Systemic or very potent topical corticosteroids should be avoided or given only under specialist supervision in psoriasis because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). See the role of topical corticosteroids in the treatment of psoriasis.

In general, the most potent topical corticosteroids should be reserved for recalcitrant dermatoses such as chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus, and palmoplantar pustulosis. Potent corticosteroids should generally be avoided on the face and skin flexures, but specialists occasionally prescribe them for use on these areas in certain circumstances.

When topical treatment has failed, intralesional corticosteroid injections may be used. These are more effective than the very potent topical corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing’s syndrome, depending on the area of the body being treated and the duration of treatment. Absorption is greatest where the skin is thin or raw, and from intertriginous areas; it is increased by occlusion.

Choice of formulation
Water-miscible corticosteroid creams are suitable for moist or weeping lesions whereas ointments are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required. Lotions may be useful when minimal application to a large or hair-bearing area is required or for the treatment of exudative lesions. Occlusive polythene or hydrocolloid dressings increase absorption, but also increase the risk of side effects; they are therefore used only under supervision on a short-term basis for areas of very thick skin (such as the palms and soles). The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

In the BNF publications topical corticosteroids for the skin are categorised as ‘mild’, ‘moderately potent’, ‘potent’ or ‘very potent’; the least potent preparation which is effective should be chosen but dilution should be avoided whenever possible.

Absorption through the skin
Mild and moderately potent topical corticosteroids are associated with few side-effects but care is required in the use of potent and very potent corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing’s syndrome, depending on the area of the body being treated and the duration of treatment. Absorption is greatest where the skin is thin or raw, and from intertriginous areas; it is increased by occlusion.

Suitable quantities of corticosteroid preparations to be prescribed for specific areas of the body

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Creams and Ointments</th>
<th>Face and neck</th>
<th>Both hands</th>
<th>Scalp</th>
<th>Both arms</th>
<th>Both legs</th>
<th>Trunk</th>
<th>Groins and genitalia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15 to 30 g</td>
<td>15 to 30 g</td>
<td>15</td>
<td>30 to 60g</td>
<td>100</td>
<td>100</td>
<td>15 to 30 g</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for a single daily application for 2 weeks.

Compound preparations
The advantages of including other substances (such as antibacterials or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation.

The keratolytic effect of salicylic acid p. 1286 facilitates the absorption of topical corticosteroids; however, excessive and prolonged use of topical preparations containing salicylic acid may cause salicylism.

Topical corticosteroid preparation potencies
Potency of a topical corticosteroid preparation is a result of the formulation as well as the corticosteroid. Therefore, proprietary names are shown.

Mild
- Hydrocortisone 0.1–2.5%
- Dioderm
- Mildison
- Synalar 1 in 10 dilution

Mild with antimicrobials
- Canesten HC
- Daktacort
- Econacort
- Fucidin H
- Nystaform-HC
- Terra-Cortril
- Timodine

Moderate
- Betnovate-RD
- Eumovate
- Haelan
- Modrasone
- Synalar 1 in 4 Dilution
- Ultralanum Plain

Moderate with antimicrobials
- Trimovate

Moderate with urea:
- Alphaderm
Skin specialist. Carers of young children should be advised that period to regain control of the condition. A very potent formulation of topical corticosteroids for a short fl... are-up of atopic eczema, it may be appropriate to use more potent preparation as the condition improves. In an acute patient information lea...

Corticosteroids (topical)

Potent
- Beclometasone dipropionate 0.025%
- Betamethasone valerate 0.1%
- Betacap
- Betesil
- Bettamousse
- Betnovate
- Civate
- Diprostone
- Eloxon
- Hydrocortisone butyrate
- Locoid
- Locoid Crelo
- Metosyn
- Mometasone furoate 0.1%
- Nerisone
- Synalar

Potent with antimicrobials
- Aureocort
- Betamethasone and cloquimol
- Betamethasone and neomycin
- Fucibet
- Lotiderm
- Synalar C
- Synalar N

Potent with salicylic acid
- Diprosalic

Very potent
- Clarelux
- Dermovate
- Etrivex
- Nerisone Forte

Very potent with antimicrobials
- Cloetasol with neomycin and nystatin

Use in children
Children, especially infants, are particularly susceptible to side-effects. However, concern about the safety of topical corticosteroids in children should not result in the child being undertreated. The aim is to control the condition as well as possible; inadequate treatment will perpetuate the condition. A mild corticosteroid such as hydrocortisone 0.5% or 1% is useful for treating nappy rash and hydrocortisone 1% for atopic eczema in childhood. A moderately potent or potent corticosteroid may be appropriate for severe atopic eczema on the limbs, for 1–2 weeks only, switching to a less potent preparation as the condition improves. In an acute flare-up of atopic eczema, it may be appropriate to use more potent formulations of topical corticosteroids for a short period to regain control of the condition. A very potent corticosteroid should be initiated under the supervision of a specialist. Carers of young children should be advised that treatment should not necessarily be reserved to ‘treat only the worst areas’ and they may need to be advised that patient information leaflets may contain inappropriate advice for the patient’s condition.

Corticosteroids (topical)

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: CORTICOSTEROID: RARE RISK OF CENTRAL SEROUS CHORIORETINOPATHY WITH LOCAL AS WELL AS SYSTEMIC ADMINISTRATION (AUGUST 2017)

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes. The MHRA recommends that patients should be advised to report any blurred vision or other visual disturbances with corticosteroid treatment given by any route; consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems.

CONTRA-INDICATIONS
- Acne - perioral dermatitis - potent corticosteroids in widespread plaque psoriasis - rosacea (in adults) - untreated bacterial, fungal or viral skin lesions

CAUTIONS
- Avoid prolonged use (particularly on the face) - cautions applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use.
- Dermatoses of infancy, including nappy rash (extreme caution required—treatment should be limited to 5–7 days) (in children) - infection - keep away from eyes.
- Use potent or very potent topical corticosteroids under specialist supervision (in children) - use potent or very potent topical corticosteroids under specialist supervision in psoriasis (can result in rebound relapse, development of generalised pustular psoriasis, and local and systemic toxicity) (in adults)

SIDE-EFFECTS
- Uncommon - Adrenal suppression - hypertrichosis - skin depigmentation (may be reversible)
- Frequency not known - Local reaction

SIDE-EFFECTS, FURTHER INFORMATION
- Side-effects applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use. In order to minimise the side-effects of a topical corticosteroid, it is important to apply it thinly to affected areas only, no more frequently than twice daily, and to use the least potent formulation which is fully effective.

DIRECTIONS FOR ADMINISTRATION
- Topical corticosteroid preparations should be applied no more frequently than twice daily; once daily is often sufficient. Topical corticosteroids should be spread thinly on the skin but in sufficient quantity to cover the affected areas. The length of cream or ointment expelled from a tube may be used to specify the quantity to be applied to a given area of skin. This length can be measured in terms of a fingertip unit (the distance from the tip of the adult index finger to the first crease). One fingertip unit (approximately 500 mg from a tube with a standard 5 mm diameter nozzle) is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers). Mixing topical preparations on the skin should be avoided where possible; several minutes should elapse between application of different preparations.
- In children ‘Wet-wrap bandaging’ increases absorption into the skin, but should be initiated only by a dermatologist and application supervised by a healthcare professional trained in the technique.

PRESCRIBING AND DISPENSING INFORMATION
- The potency of each topical corticosteroid should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

PATIENT AND CARER ADVICE
- Patients or carers should be given advice on how to administer corticosteroid creams and ointments. If a patient is using topical corticosteroids of different potencies, the patient should be told when to use each corticosteroid. Patients and their carers should be reassured that side effects such as skin thinning and systemic effects rarely occur when topical corticosteroids are used appropriately.
**Alclometasone dipropionate**

**INDICATIONS AND DOSE**

Inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

- Alclometasone dipropionate cream 0.05%: moderate

**UNLICENSED USE**

- In children: Licensed for use in children (age range not specified by manufacturer).

**SIDE-EFFECTS**

- Vasodilation

**PATIENT AND CARER ADVICE**

- Patients or carers should be counselled on the application of alclometasone dipropionate cream.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS 15, 28
    - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, propylene glycol
    - Alclometasone dipropionate (Non-proprietary)
    - Alclometasone dipropionate 500 microgram per 1 gram Boots Derma Care Eczema & Dermatitis Flare-Up 0.05% cream
    - 15 gram

**Betamethasone**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

- Betamethasone valerate 0.025% cream and ointment: moderate. Betamethasone valerate 0.1% cream, lotion, ointment, and scalp application: potent. Betamethasone valerate 0.12% foam: potent. Betamethasone dipropionate 0.05% cream, lotion, and ointment: potent.

**UNLICENSED USE**

- In children: Betacap®️, Betnovate®️ and Betnovate-RD®️ are not licensed for use in children under 1 year. Bettamousse®️ is not licensed for use in children under 6 years.

**CAUTIONS**

- Use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression

**INTERACTIONS**

- Appendix 1: corticosteroids

**SIDE-EFFECTS**

- Vasodilatation

**PATIENT AND CARER ADVICE**

- Patient counselling is advised for betamethasone cream, ointment, scalp application and foam (application).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment, foam.

  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS 15, 28
    - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polylsorbates, propylene glycol
    - Betamethasone (RPH Pharmaceuticals AD)
    - Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betamethasone 0.1% cutaneous foam
    - 100 gram
    - £9.75
    - DT = £9.75

  - **Ointment**
    - CAUTIONARY AND ADVISORY LABELS 15, 28
    - Betamethasone (as Betamethasone valerate) 250 microgram per 1 gram
    - 100 gram PDA £2.99 DT = £3.15
    - 100 gram PDA £3.24 DT = £3.37

**Beclometasone dipropionate**

(Beclometasone dipropionate)

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

- Beclometasone dipropionate cream and ointment 0.025%: potent.

**UNLICENSED USE**

- In children: Not licensed for use in children under 1 year.

**INTERACTIONS**

- Appendix 1: corticosteroids

**SIDE-EFFECTS**

- Vasodilatation: vision blurred

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment.

  - **Cream**
    - CAUTIONARY AND ADVISORY LABELS 28
    - Beclometasone dipropionate (Non-proprietary)
    - Beclometasone dipropionate 250 microgram per 1 gram
      - 30 gram  PDA £68.00 DT = £68.00
    - Beclometasone dipropionate 0.025% cream
      - 30 gram  PDA £68.00 DT = £68.00

  - **Ointment**
    - CAUTIONARY AND ADVISORY LABELS 28
    - Beclometasone dipropionate (Non-proprietary)
    - Beclometasone dipropionate 250 microgram per 1 gram
      - 30 gram  PDA £68.00 DT = £68.00
Skin

[0] www.getintopharma.com

**Calcipotriol with betamethasone**

30-May-2017

The properties listed below are those particular to the combination only. For the properties of the components please consider, calcipotriol p. 1263, betamethasone p. 1243.

**INDICATIONS AND DOSE**

**DOVOBET® GEL**

Scalp psoriasis

- **TO THE SKIN**
  - Adult: Apply 1–4 g once daily usual duration of therapy 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, shampoo off after leaving on scalp overnight or during day, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week.

Mild to moderate plaque psoriasis

- **TO THE SKIN**
  - Adult: Apply once daily for 8 weeks; if necessary, treatment may be continued beyond 8 weeks or repeated, on the advice of a specialist, apply to maximum 30% of body surface, when different preparations containing calcipotriol used together.

max. total calcipotriol 5 mg in any one week; maximum 15 g per day

**DOVOBET® OINTMENT**

Stable plaque psoriasis

- **TO THE SKIN**
  - Adult: Apply once daily for 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, apply to maximum 30% of body surface, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week; maximum 15 g per day.

**ENTSTILAR®**

Psoriasis

- **TO THE SKIN**
  - Adult: Apply once daily to be applied to the affected area for up to 4 weeks—consult product literature for further information; maximum 15 g per day

- **CONTRA-INDICATIONS**

**ENTSTILAR®**

Erythrodermic psoriasis - pustular psoriasis

**INTERACTIONS**

- Appendix 1: corticosteroids - vitamin D substances

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (September 2016) that calcipotriol with betamethasone (Entstilar®) is accepted for use within NHS Scotland for the treatment of psoriasis vulgaris.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Butylated hydroxytoluene

- **Dovobet®**
  - Calcipotriol (as Calcipotriol hydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 50 microgram per 1 gram
  - Dovobet ointment | 30 gram (Pst) £15.84 DT = £19.84 | 60 gram (Pst) £39.68 | 120 gram (Pst) £73.86

- **Entstilar®**
  - Calcipotriol (as Calcipotriol monohydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 50 microgram per 1 gram
  - Entstilar 50micrograms/g / 0.5 mg/g cutaneous foam | 60 gram (Pst) £39.68 DT = £39.68 | 120 gram (Pst) £79.36

**Gel**

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Butylated hydroxytoluene

- **Dovobet®**
  - Calcipotriol (as Calcipotriol monohydrate) 50 microgram per 1 gram, Betamethasone (as Betamethasone dipropionate) 50 microgram per 1 gram
  - Dovobet gel | 60 gram (Pst) £37.21 DT = £37.21 | 120 gram (Pst) £69.11

**Clobutasol propionate**

21-Dec-2017

- **INDICATIONS AND DOSE**

**Short-term treatment only of severe resistant inflammatory skin disorders such as calcicritant eczemas unresponsive to less potent corticosteroids**

Psoriasis

- **TO THE SKIN**
  - Child 1-7 years: Apply 1–2 times a day for up to 4 weeks, to be applied thinly
  - Adult: Apply 1–2 times a day for up to 4 weeks, to be applied thinly, maximum 50 g of 0.05% preparation per week
Eczema and psoriasis 1245

**UNLICENSED USE**
- In children. Licensed for use in children (age range not specified by manufacturer).

**PATIENT AND CARER ADVICE**
- Patients or carers should be advised on the application of clobetasone butyrate containing preparations.

**EXCEPTIONS TO LEGAL CATEGORY**
- Cream can be sold to the public for short-term symptomatic treatment and control of patches of eczema and dermatitis (but not seborrhoeic dermatitis) in adults and children over 12 years provided pack does not contain more than 15g.

**MEDIcINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment, paste

**Shampoo**
- **CAUTIONARY AND ADVISORY LABELS** 28
  - Etrivex
  - Clobetasol propionate 500 microgram per 1 gram Etrivex 500 microgram/g shampoo | 125 ml [POD] £19.15 DT = £9.15

**Cream**
- **CAUTIONARY AND ADVISORY LABELS** 28
  - Etrivex
  - Clobetasol propionate 500 microgram per 1 gram Etrivex 0.05% cream | 30 gram [POD] £2.56 DT = £2.69 | 100 gram [POD] £7.51 DT = £7.90
  - Dermovate
  - Clobetasol propionate 500 microgram per 1 gram Dermovate 0.05% cream | 30 gram [POD] £2.69 DT = £2.69 | 100 gram [POD] £7.90 DT = £7.90

**Ointment**
- **CAUTIONARY AND ADVISORY LABELS** 28
  - Etrivex
  - Clobetasol propionate 500 microgram per 1 gram Etrivex 0.05% ointment | 30 gram [POD] £2.56 DT = £2.69 | 100 gram [POD] £7.51 DT = £7.90
  - Dermovate
  - Clobetasol propionate 500 microgram per 1 gram Dermovate 0.05% ointment | 30 gram [POD] £2.69 DT = £2.69 | 100 gram [POD] £7.90 DT = £7.90

**Liquid**
- **CAUTIONARY AND ADVISORY LABELS** 15, 28
  - Dermovate
  - Clobetasol propionate 500 microgram per 1 gram Dermovate 0.05% scalp application | 30 ml [POD] £3.07 DT = £3.07 | 100 ml [POD] £10.42 DT = £10.42
  - Combinations available: Clobetasol propionate with neomycin sulphate and nystatin, p. 1250

**Clobetasone butyrate**

**INDICATIONS AND DOSE**
- **Eczemas and dermatitis of all types**
  - Maintenance between courses of more potent corticosteroids
  - **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**
- Clobetasone butyrate 0.05% cream and ointment: moderate.

**DIFFICORTOLONE VALERATE**

**INDICATIONS AND DOSE**
- Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.3% diflucortolone valerate) | Short-term treatment of severe exacerbations (using 0.3% diflucortolone valerate) | Psoriasis (using 0.3% diflucortolone valerate)
  - **TO THE SKIN**
  - Child 4–17 years: Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60g per week
  - Adult: Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60g per week

**SEVERE INFAMMATORY SKIN DISORDERS**
- Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.1% diflucortolone valerate) | Psoriasis (using 0.1% diflucortolone valerate)
  - **TO THE SKIN**
  - Child: Apply 1–2 times a day for up to 4 weeks, to be applied thinly
  - Adult: Apply 1–2 times a day for up to 4 weeks, to be applied thinly

**POTENCY**
- Diflucortolone valerate 0.1% cream and ointment: potent.
- Diflucortolone valerate 0.3% cream and ointment: very potent.

**UNLICENSED USE**
- In children. Neresine® licensed for use in children (age range not specified by manufacturer); Neresone Forte® not licensed for use in children under 4 years.

www.getintopharma.com
Fludroxy cortide (Flurandrenolone)

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<td>• Fludroxy cortide 0.0125% cream and ointment: moderate</td>
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**HAELAN® TAPE**

**CHRONIC LOCALISED RECALCITRANT DERMATOSES (BUT NOT ACUTE OR WEPPING)**

• **TO THE SKIN**
  » Child: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily
  » Adult: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily

**UNLICENSED USE**

• In children: Licensed for use in children (age range not specified by manufacturer).

**SIDE-EFFECTS**

Cushing’s syndrome - increased risk of infection - vasodilation

**PATIENT AND CARER ADVICE**

Patients or carers should be counselled on application of fludroxy cortide cream and ointment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

<table>
<thead>
<tr>
<th>Combinations available: Flucinolone acetonide with clioquinol, p. 1250 - Flucinolone acetonide with neomycin, p. 1251</th>
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**Flucinolone acetonide**

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**POTENCY**

• Flucinolone acetonide 0.025% cream, gel, and ointment: potent.

**INTERACTIONS**

Appendix 1: flucinolone

**SIDE-EFFECTS**

Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION**

Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for flucinolone acetonide cream, gel and ointment (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

**Fluocinolone acetonide**

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**POTENCY**

• Fluocinolone acetonide 0.00625% cream and ointment: moderate.

• Fluocinolone acetonide 0.025% cream: mild.

**INTERACTIONS**

Appendix 1: fluocinolone

**SIDE-EFFECTS**

Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION**

Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for fluocinolone acetonide cream, gel and ointment (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

**Fluocinolone acetonide with clioquinol, p. 1250 - Flucinolone acetonide with neomycin, p. 1251**

**Flucinolone acetonide**

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**POTENCY**

• Fluocinolone acetonide 0.025% cream, gel, and ointment: potent.

**INTERACTIONS**

Appendix 1: fluocinolone

**SIDE-EFFECTS**

Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION**

Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for fluocinolone acetonide cream, gel and ointment (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

**Fluocinolone acetonide with clioquinol, p. 1250 - Flucinolone acetonide with neomycin, p. 1251**

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**POTENCY**

• Fluocinolone acetonide 0.025% cream, gel, and ointment: potent.

**INTERACTIONS**

Appendix 1: fluocinolone

**SIDE-EFFECTS**

Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION**

Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for fluocinolone acetonide cream, gel and ointment (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

**CAUTIONARY AND ADVISORY LABELS 28**

**Fluocinolone acetonide with clioquinol, p. 1250 - Flucinolone acetonide with neomycin, p. 1251**

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**POTENCY**

• Fluocinolone acetonide 0.025% cream, gel, and ointment: potent.

**INTERACTIONS**

Appendix 1: fluocinolone

**SIDE-EFFECTS**

Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION**

Gel is useful for application to the scalp and other hairy areas.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for fluocinolone acetonide cream, gel and ointment (application).
**SIDE-EFFECTS** Vasodilation

**PATIENT AND CARER ADVICE** Patients or carers should be advised on the application of fluocinonide preparations.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Ointment**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS** May contain Propylene glycol, woolfat and related substances (including lanolin).

**Metosyn FAPG** (Reig Jofre UK Ltd)

Fluocinonide 500 microgram per 1 gram Metosyn FAPG 0.05% ointment | 25 gram (£3.50 DT) = £3.50 | 100 gram (£13.15 DT) = £13.15

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS** May contain Propylene glycol, woolfat and related substances (including lanolin).

**Metosyn FAPG** (Reig Jofre UK Ltd)

Fluocinonide 500 microgram per 1 gram Metosyn FAPG 0.05% cream | 25 gram (£3.96 DT) = £3.96 | 100 gram (£13.34 DT) = £13.34

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**Fluticasone**

21-Dec-2017

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as dermatitis and eczemas unresponsive to less potent corticosteroids

**Psoriasis**

▶ TO THE SKIN

Child: Apply 1–2 times a day, to be applied thinly

Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

Fluticasone cream 0.05%: potent.

Fluticasone ointment 0.005%: potent.

**INTERACTIONS** → Appendix 1: corticosteroids

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on application of fluticasone creams and ointments.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS** May contain Benzyl alcohol, cetostearyl alcohol (including lanolin), propylene glycol, salicylic acid, water.

**Fluticasone propionate 50 microgram per 1 gram Fluticasone** 0.05% cream | 30 gram (£4.24 DT) = £4.24

**Cultivate** (GloxsmithKline UK Ltd)

Fluticasone propionate 50 microgram per 1 gram Cultivate 0.05% cream | 15 gram (£2.27 DT) = £2.27 | 30 gram (£4.24 DT) = £4.24

**Ointment**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS** May contain Propylene glycol

**Cultivate** (GloxsmithKline UK Ltd)

Fluticasone propionate 50 microgram per 1 gram Cultivate 0.005% ointment | 15 gram (£2.27 DT) = £2.27 | 30 gram (£4.24 DT) = £4.24

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**Hydrocortisone**

21-Dec-2017

**DRUG ACTION** Hydrocortisone has equal glucocorticoid and mineralocorticoid activity.

**INDICATIONS AND DOSE** Mild inflammatory skin disorders such as eczemas

▶ TO THE SKIN

Child: Apply 1–2 times a day, to be applied thinly

Adult: Apply 1–2 times a day, to be applied thinly

**POTENCY**

Hydrocortisone cream and ointment 0.5 to 2.5%: mild

**INTERACTIONS** → Appendix 1: corticosteroids

**SIDE-EFFECTS** Vasodilation

**PRESCRIBING AND DISPENSING INFORMATION** When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied. Although Dioderm™ contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP.

**PATIENT AND CARER ADVICE** Patient counselling is advised for hydrocortisone cream and ointment (application).

**PROFESSION SPECIFIC INFORMATION** Dental practitioners’ formulation Hydrocortisone Cream 1% 15 g may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY** Over-the-counter hydrocortisone preparations Skin creams and ointments containing hydrocortisone (alone or with other ingredients) can be sold to the public for the treatment of allergic contact dermatitis, irritant dermatitis, insect bite reactions and mild to moderate eczema in patients over 10 years, to be applied sparingly over the affected area 1–2 times daily for no longer than 1 week. Over-the-counter hydrocortisone preparations should not be sold without medical advice for children under 10 years or for pregnant women; they should not be sold for application to the face, anogenital region, broken or infected skin (including cold sores, acne, and athlete’s foot).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

**Cream**

**CAUTIONARY AND ADVISORY LABELS** 28

**EXCIPIENTS** May contain Benzyl alcohol, cetylstearyl alcohol (including lanolin), propylene glycol, salicylic acid, water.

**Hydrocortisone (Non-proprietary)**

Hydrocortisone 5 mg per 1 gram Hydrocortisone 0.5% cream | 15 gram (£44.00 DT) = £11.01 | 30 gram (£82.02 DT) = £88.00

Hydrocortisone 10 mg per 1 gram Hydrocortisone 1% cream | 15 gram (£105.00 DT) = £10.94 | 30 gram (£233.83 DT) = £11.88

Hydrocortisone 25 mg per 1 gram Hydrocortisone 2.5% cream | 15 gram (£234.00 DT) = £14.15 | 30 gram (£468.00 DT) = £10.74–£18.00

**Dioderm** (Dermal Laboratories Ltd)

Hydrocortisone 1 mg per 1 gram Dioderm 0.1% cream | 30 gram (£23.39 DT) = £2.39

**Milidson Lipocream** (Leo Pharma)

Hydrocortisone 10 mg per 1 gram Milidson Lipocream 1% cream | 30 gram (£41.71 DT) = £11.88

**Ointment**

**CAUTIONARY AND ADVISORY LABELS** 28

**Hydrocortisone (Non-proprietary)**

Hydrocortisone 5 mg per 1 gram Hydrocortisone 0.5% ointment | 15 gram (£44.00 DT) = £5.94 | 30 gram (£122.00 DT) = £88.00

Hydrocortisone 10 mg per 1 gram Hydrocortisone 1% ointment | 15 gram (£105.00 DT) = £10.07 | 30 gram (£233.83 DT) = £2.14

Hydrocortisone 25 mg per 1 gram Hydrocortisone 2.5% ointment | 15 gram (£234.00 DT) = £24.57 | 30 gram (£468.00 DT) = £41.14–£88.00

**Combinations available:** Hydrocortisone with benzoalkonium chlorde, dimethicone and nystatin, p. 1251 - Hydrocortisone with chlorhexidine hydrochloride and nystatin, p. 1251 - Hydrocortisone with clotrimazole, p. 1251 - Hydrocortisone with fusidic acid, p. 1252 - Hydrocortisone with miconazole, p. 1252 - Hydrocortisone with oxytetracycline, p. 1252
**Hydrocortisone butyrate**

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
- Child 2-17 years: Apply 1–2 times a day, to be applied thinly (to scalp in case of lotion)
- Adult: Apply once daily, to be applied thinly (to scalp in case of lotion)

**POTENCY**
- Hydrocortisone butyrate 0.1% cream, ointment, and scalp lotion: potent

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer hydrocortisone butyrate lotion, cream, ointment and scalp lotion.


**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Ointment**
- **CAUTIONARY AND ADVISORY LABELS 28**
- Elocon (Merck Sharp & Dohme Ltd)
- Hydrocortisone butyrate 1 mg per 1 gram Elocon 0.1% ointment | 30 gram (P30) £4.40 DT + £3.40

**Cream**
- **CAUTIONARY AND ADVISORY LABELS 28**
- Betamethasone with clioquinol
- Hydrocortisone butyrate 1 mg per 1 gram Betamethasone valerate 0.1% cream | 30 gram (P30) £6.00 DT + £3.31

**Liquid**
- **CAUTIONARY AND ADVISORY LABELS 15(excluding Lociod Crelo topical emulsion), 28**
- Hydrocortisone butyrate 1 mg per 1 ml Hydrocortisone butyrate 0.1% scalp lotion | 100 ml (P100) £6.83 DT + £6.83

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**Mometasone furoate**

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
- Child 2-17 years: Apply 1–2 times a day, to be applied thinly (to scalp in case of lotion)
- Adult: Apply once daily, to be applied thinly (to scalp in case of lotion)

**POTENCY**
- Mometasone furoate 0.1% cream, ointment, and scalp lotion: potent

**INTERACTIONS** → Appendix 1: corticosteroids

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Cream**
- **CAUTIONARY AND ADVISORY LABELS 28**
- Betamethasone with clioquinol (Non-proprietary)
- Mometasone furoate 1 mg per 1 gram Mometasone 0.1% cream | 30 gram (P30) £6.00 DT + £3.31

**Ointment**
- **CAUTIONARY AND ADVISORY LABELS 28**
- Betamethasone with clioquinol (Non-proprietary)
- Mometasone furoate 1 mg per 1 gram Mometasone 0.1% ointment | 30 gram (P30) £4.80 DT + £3.31

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**Corticosteroids**

**CORTICOSTEROID COMBINATIONS WITH ANTI-INFECTIONES**

**Betamethasone with clioquinol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1243.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

- **TO THE SKIN**
- Child: (consult product literature)
- Adult: (consult product literature)

**POTENCY**
- Betamethasone (as valerate) 0.1% with clioquinol cream and ointment: potent.

**UNLICENSED USE**
- In children Betamethasone and clioquinol preparations is not licensed for use in children under 1 year.

**INTERACTIONS** → Appendix 1: corticosteroids

**PATIENT AND CARER ADVICE** Stains clothing. Patients or carers should be advised on application of betamethasone with clioquinol preparations.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Ointment**
- **CAUTIONARY AND ADVISORY LABELS 28**
- Betamethasone with clioquinol (Non-proprietary)
- Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Clioquinol 30 mg per 1 gram Betamethasone valerate 0.1% | Clioquinol 3% cream | 30 gram (P30) £38.88 DT + £38.88
Betamethasone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1243, clotrimazole p. 1233.

- **INDICATIONS AND DOSE**
  - Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis
  - TO THE SKIN
  - Child: (consult product literature)
  - Adult: (consult product literature)

- **POTENCY**
  - Betamethasone dipropionate 0.064% (=betamethasone 0.5%) with clotrimazole cream: potent.

- **UNLICENSED USE**
  - In children Lotriderm® not licensed for use in children under 12 years.

- **INTERACTIONS** → Appendix 1: antifungals, azoles - corticosteroids

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer betamethasone with clotrimazole cream.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  
  **Cream**
  
  CAUTIONARY AND ADVISORY LABELS 2B
  
  EXCipients: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol
  
  Lotriderm (Merck Sharp & Dohme Ltd)
  
  Betamethasone dipropionate 640 microgram per 1 gram, Clotrimazole 10 mg per 1 gram Lotriderm cream | 30 gram
  
  £6.34 DT = £6.34

Betamethasone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1243, fusidic acid p. 571.

- **INDICATIONS AND DOSE**
  - Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis
  - TO THE SKIN
  - Child: (consult product literature)
  - Adult: (consult product literature)

- **POTENCY**
  - Betamethasone (as valerate) 0.1% with fusidic acid cream: potent.

- **UNLICENSED USE**
  - In children Fucibet® Lipid Cream is not licensed for use in children under 6 years.

- **INTERACTIONS** → Appendix 1: corticosteroids - fusidic acid

- **PATIENT AND CARER ADVICE** Patients or carers should be counselled on application of betamethasone with fusidic acid preparations.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  
  **Cream**
  
  CAUTIONARY AND ADVISORY LABELS 2B
  
  EXCipients: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, hydroxybenzoates (parabens)
  
  Fucibet (LED Pharma)
  
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Fusidic acid 20 mg per 1 gram Fucibet cream | 30 gram
  
  £6.38 DT = £6.38 | 60 gram £12.76 DT = £12.76
  
  Fucibet Lipid cream | 30 gram
  
  £6.74 DT = £6.74

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1243, neomycin sulfate p. 1230.

- **INDICATIONS AND DOSE**
  - Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis
  - TO THE SKIN USING OINTMENT, OR TO THE SKIN USING CREAM
  - Child 2–17 years: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

- **POTENCY**
  - Betamethasone (as valerate) 0.1% with neomycin cream and ointment: potent.

- **INTERACTIONS** → Appendix 1: corticosteroids - neomycin

- **PATIENT AND CARER ADVICE** Patient counselling is advised for betamethasone with neomycin cream and ointment (application).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  
  **Ointment**
  
  CAUTIONARY AND ADVISORY LABELS 2B
  
  Betamethasone with neomycin (Non-proprietary)
  
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Betamethasone valerate 0.1% / Neomycin 0.5% ointment | 30 gram
  
  £38.88 DT = £31.36 | 100 gram £97.00 DT = £104.52

  **Cream**
  
  CAUTIONARY AND ADVISORY LABELS 2B
  
  EXCipients: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol
  
  Betamethasone with neomycin (Non-proprietary)
  
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Betamethasone valerate 0.1% / Neomycin 0.5% cream | 30 gram
  
  £38.88 DT = £31.36 | 100 gram £97.00 DT = £104.52

Betamethasone with salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 1243, salicylic acid p. 1286.

- **INDICATIONS AND DOSE**
  - DIPROSALIC® OINTMENT
  - Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis
  - TO THE SKIN
  - Child: Apply 1–2 times a day, max. 60 g per week
  - Adult: Apply 1–2 times a day, max. 60 g per week

- **POTENCY**
  - Betamethasone (as dipropionate) 0.05% with salicylic acid 3%: potent.

- **DIPROSALIC® SCALP APPLICATION**
  - Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis
  - TO THE SKIN
  - Child: Apply 1–2 times a day, apply a few drops
  - Adult: Apply 1–2 times a day, apply a few drops
### Clobetasol propionate with neomycin sulfate and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, clobetasol propionate p. 1244, neomycin sulfate p. 1230.

#### INDICATIONS AND DOSE

Short-term treatment only of severe resistant inflammatory skin disorders such as calciritant eczemas associated with infection and unresponsive to less potent corticosteroids / Psoriasis associated with infection

- **TO THE SKIN**
- Adult: (consult product literature)

#### POTENCY

- Clobetasol propionate 0.05% with neomycin sulfate and nystatin cream and ointment: very potent.

#### INTERACTIONS

- Appendix 1: neomycin

#### PATIENT AND CARER ADVICE

- Patients or carers should be advised on application of clobetasol propionate, neomycin sulfate and nystatin containing preparations.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Form</th>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>EXCIPIENTS:</th>
<th>Betamethasone (as Betamethasone dipropionate)</th>
<th>Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ointment</td>
<td>2B</td>
<td>May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol</td>
<td>500 microgram per 1 gram, Salicylic acid 30 mg per 1 gram</td>
<td>Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g ointment</td>
</tr>
<tr>
<td>Cream</td>
<td>2B</td>
<td>May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol</td>
<td>500 microgram per 1 ml, Salicylic acid 20 mg per 1 ml</td>
<td>Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g cream</td>
</tr>
</tbody>
</table>

**Fluocinolone acetonide with clioquinol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluocinolone acetonide p. 1246.

#### INDICATIONS AND DOSE

Inflammatory skin disorders such as eczemas associated with infection / Psoriasis associated with infection

- **TO THE SKIN**
- Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

#### POTENCY

- Clioquinol 3% with fluocinolone acetonide 0.025% cream and ointment: potent

#### INTERACTIONS

- Appendix 1: fluocinolone

#### PATIENT AND CARER ADVICE

Patient counselling is advised for clioquinol with fluocinolone acetonide cream and ointment (application). Ointment stains clothing.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Form</th>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>EXCIPIENTS:</th>
<th>Betamethasone (as Betamethasone dipropionate)</th>
<th>Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ointment</td>
<td>2B</td>
<td>May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol</td>
<td>500 microgram per 1 gram, Salicylic acid 30 mg per 1 gram</td>
<td>Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g ointment</td>
</tr>
<tr>
<td>Cream</td>
<td>2B</td>
<td>May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol</td>
<td>500 microgram per 1 ml, Salicylic acid 20 mg per 1 ml</td>
<td>Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units/g cream</td>
</tr>
</tbody>
</table>
Fluocinolone acetonide with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluocinolone acetonide p. 1246, neomycin sulfate p. 1230.

**INDICATIONS AND DOSE**
Inflammatory skin disorders such as eczemas associated with infection | Psoriasis associated with infection
- **TO THE SKIN**
  - Child 1-7 years: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds
  - Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

**POTENCY**
- Fluocinolone acetonide 0.025% with neomycin 0.5% cream and ointment: potent.

**INTERACTIONS** → Appendix 1: fluocinolone · neomycin

**PATIENT AND CARER ADVICE** Patients or carers should be counselled on the application of fluocinolone acetonide with neomycin preparations.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Ointment
- **CAUTIONARY AND ADVISORY LABELS** 28
  - SYNALAR N: May contain Propylene glycol, woolfat and related substances (including lanolin).
  - SYNALAR N (Reg Jofre UK Ltd)
  - Fluocinolone acetonide 250 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram SYNALAR N ointment | 30 gram [POT] £4.36

Hydrocortisone with benzalkonium chloride, dimeticone and nystatin

15-Mar-2016

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, dimeticone p. 1236.

**INDICATIONS AND DOSE**
Mild inflammatory skin disorders such as eczemas associated with infection
- **TO THE SKIN**
  - Child: Apply 3 times a day until lesion has healed, to be applied thinly
  - Adult: Apply 3 times a day until lesion has healed, to be applied thinly

**POTENCY**
- Benzalkonium with dimeticone, hydrocortisone acetate 0.5%, and nystatin cream: mild.

**INTERACTIONS** → Appendix 1: corticosteroids

**PATIENT AND CARER ADVICE** Patients or carers should be advised on application of benzalkonium with dimeticone and hydrocortisone and nystatin preparations.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Cream
- **CAUTIONARY AND ADVISORY LABELS** 28
  - EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), sodium metabisulphite, sorbic acid
  - TIMODINE (Alliance Pharmaceuticals Ltd)
  - Benzalkonium chloride 1 mg per 1 gram, Hydrocortisone 5 mg per 1 gram, Dimeticone 350 100 mg per 1 gram, Nystatin 100000 unit per 1 gram TIMODINE cream | 30 gram [POT] £3.37

Hydrocortisone with chlorhexidine hydrochloride and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, chlorhexidine p. 1277.

**INDICATIONS AND DOSE**
Mild inflammatory skin disorders such as eczemas
- **TO THE SKIN**
  - Child: To be applied thinly (consult product literature)
  - Adult: To be applied thinly (consult product literature)

**POTENCY**
- Hydrocortisone 0.5% with chlorhexidine hydrochloride 1% and nystatin cream: mild
- Hydrocortisone 1% with chlorhexidine hydrochloride 1% and nystatin ointment: mild

**INTERACTIONS** → Appendix 1: corticosteroids

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on application of chlorhexidine hydrochloride with hydrocortisone and nystatin preparations.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

Ointment
- **CAUTIONARY AND ADVISORY LABELS** 28
  - HYDROCORTISONE WITH CHLORHEXIDINE HYDROCHLORIDE AND NYSTATIN (Non-proprietary)
    - Chlorhexidine acetate 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram, Nystatin 100000 unit per 1 gram Nystatin 100,000 units/g / Chlorhexidine acetate 1% / Hydrocortisone 1% ointment | 30 gram [POT] £5.29 DT = £5.29

Cream
- **CAUTIONARY AND ADVISORY LABELS** 28
  - EXCIPIENTS: May contain Benzy1 alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - Hydrocortisone with chlorhexidine hydrochloride and nystatin (Non-proprietary)
    - Hydrocortisone 5 mg per 1 gram, Chlorhexidine hydrochloride 10 mg per 1 gram, Nystatin 100000 unit per 1 gram Nystatin 100,000 units/g / Chlorhexidine hydrochloride 1% / Hydrocortisone 0.5% cream | 30 gram [POT] £5.29 DT + £5.29

Hydrocortisone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, clotrimazole p. 1232.

**INDICATIONS AND DOSE**
Mild inflammatory skin disorders such as eczemas (associated with fungal infection)
- **TO THE SKIN**
  - Child: (consult product literature)
  - Adult: (consult product literature)

**POTENCY**
- Clotrimazole with hydrocortisone 1% cream: mild

**INTERACTIONS** → Appendix 1: antifungals, azoles · corticosteroids

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer clotrimazole with hydrocortisone cream.

**EXCEPTIONS TO LEGAL CATEGORY** A 15-g tube is on sale to the public for the treatment of athlete’s foot and fungal infection of skin folds with associated inflammation in patients 10 years and over.
Hydrocortisone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, fusidic acid p. 571.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **CAUTIONARY AND ADVISORY LABELS** 28
    - EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including ceteryl and stearyl alcohol)
    - Canesten HC (Bayer plc)
      - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram Canesten HC cream | 30 gram | £2.42 DT = £2.42

Hydrocortisone with miconazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, miconazole p. 1233.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **CAUTIONARY AND ADVISORY LABELS** 28
    - EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including ceteryl and stearyl alcohol), polysorbates, potassium sorbate
      - Fucidin H (Fusidic acid / Hydrocortisone) (LEO Pharma)
      - Hydrocortisone acetate 10 mg per 1 gram, Fusidic acid 20 mg per 1 gram Fucidin H cream | 30 gram | £6.02 DT = £6.02
      - 60 gram | £12.05 DT = £12.05

- **INTERACTIONS** → Appendix 1: antifungals, azoles - corticosteroids
- **PATIENT AND CARER ADVICE** Patients or carers should be advised on the application of hydrocortisone with fusidic acid preparations.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Ointment**
    - **CAUTIONARY AND ADVISORY LABELS** 28
      - Daktacort (McNeil Products Ltd, Janssen-Cilag Ltd)
      - Hydrocortisone 10 mg per 1 gram, Miconazole nitrate 20 mg per 1 gram Daktacort ointment | 30 gram | £2.42 DT = £2.42

Hydrocortisone with oxymetazoline

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 1247, oxymetazoline p. 567.

- **INDICATIONS AND DOSE** Mild inflammatory skin disorders such as eczemas
  - TO THE SKIN
    - Child: To be applied thinly (consult product literature)
    - Adult: To be applied thinly (consult product literature)
  - POTENCY
    - Hydrocortisone with oxymetazoline cream: mild
- **INTERACTIONS** → Appendix 1: corticosteroids - oxymetazoline
- **PATIENT AND CARER ADVICE** Patients should be given advice on the application of hydrocortisone with oxymetazoline ointment.

ICHTHAMMOL

- **INDICATIONS AND DOSE** Chronic ichthyosis
  - TO THE SKIN
    - Child 1-17 years: Apply 1–3 times a day
    - Adult: Apply 1–3 times a day
- **UNLICENSED USE** In children No information available.
- **SIDE-EFFECTS** Skin irritation
Ichthammol with zinc oxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, ichthammol p. 1252.

**INDICATIONS AND DOSE**

**Chronic lichenified eczema**
- **TO THE SKIN**
- **Adults:** (consult product literature)

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

**Impregnated dressing**
- **Ichthopaste** (Evolan Pharma AB)
  Ichthopaste bandage 7.5cm × 6m | 1 bandage £3.78

**DERMATOLOGICAL DRUGS** ANTRACEN

**DERIVATIVES**

**Dithranol** (Anthralin)

**INDICATIONS AND DOSE**

**Subacute and chronic psoriasis**
- **TO THE SKIN**
- **Adults:** (consult product literature)

**DITHROCREAM®**

**Subacute and chronic psoriasis**
- **TO THE SKIN**
- **Adults:** For application to skin or scalp, 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for maximum 1 hour (consult product literature)

**MICANOL®**

**Subacute and chronic psoriasis**
- **TO THE SKIN**
- **Adults:** Apply once daily, for application to skin or scalp, to be applied for up to 30 minutes, apply 1% cream, if necessary 3% cream can be used under medical supervision

**CONTRA-INDICATIONS** Acute and pustular psoriasis - hypersensitivity

**CAUTIONS** Avoid sensitive areas of skin - avoid use near eyes

**SIDE-EFFECTS** Skin reactions

**PREGNANCY** No adverse effects reported.

**BREAST FEEDING** No adverse effects reported.

**DIRECTIONS FOR ADMINISTRATION** When applying dithranol, hands should be protected by gloves or they should be washed thoroughly afterwards. Dithranol should be applied to chronic extensor plaques only, carefully avoiding normal skin.

**MICANOL®** At the end of contact time, use plenty of lukewarm (not hot) water to rinse off cream; soap may be used after the cream has been rinsed off; use shampoo before applying cream to scalp and if necessary after cream has been rinsed off.

**PRESCRIBING AND DISPENSING INFORMATION** Treatment should be started with a low concentration such as dithranol 0.1%, and the strength increased gradually every few days up to 3%, according to tolerance.

**PATIENT AND CARER ADVICE** Dithranol can stain the skin, hair and fabrics.

**EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine if dithranol content more than 1%, otherwise may be sold to the public.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Cream**

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol

- **Dithrocream (Dermal Laboratories Ltd)**
  Dithranol 1 mg per 1 gram Dithrocream 0.1% cream | 50 gram | £3.77 DT + £3.77
  Dithranol 2.5 mg per 1 gram Dithrocream 0.25% cream | 50 gram | £4.04 DT + £4.04
  Dithranol 5 mg per 1 gram Dithrocream 0.5% cream | 50 gram | £4.66 DT + £4.66
  Dithranol 10 mg per 1 gram Dithrocream 1% cream | 50 gram | £5.42 DT + £5.42
  Dithranol 20 mg per 1 gram Dithrocream 2% cream | 50 gram | £7.49 DT + £6.79

Combinations available: Coal tar with dithranol and salicylic acid, p. 1254

**Dithranol with salicylic acid and zinc oxide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dithranol above, salicylic acid p. 1286.

**INDICATIONS AND DOSE**

**Subacute and chronic psoriasis**
- **TO THE SKIN**
- **Adult:** (consult local protocol)

**MEDICINAL FORMS** Forms available from special-order manufacturers include: ointment, paste

**DERMATOLOGICAL DRUGS** TARS

**Coal tar**

**INDICATIONS AND DOSE**

**Psoriasis | Chronic atopic eczema**
- **TO THE SKIN USING PASTE**
  - **Child:** Apply 1–3 times a day, start application with low-strength preparations
  - **Adult:** Apply 1–3 times a day, start application with low-strength preparations
- **TO THE SKIN**
  - **Child:** 100 mL/bath, to be added to an adult sized bath; add proportionally less for a child’s bath. Use Coal Tar Solution BP
  - **Adult:** 100 mL/bath, to be added to an adult sized bath. Use Coal Tar Solution BP

**ALPHOSYL 2 IN 1® SHAMPOO**

**Psoriasis | Seborrhoeic dermatitis | Scaling | Itching**
- **TO THE SKIN**
  - **Adult:** Apply every 2–3 days

**Dandruff**
- **TO THE SKIN**
  - **Adult:** Apply 1–2 times a week as required

www.getintopharma.com
**Coal tar with coconut oil and salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253, salicylic acid p. 1286.

**INDICATIONS AND DOSE**

- Scaly scalp disorders | Psoriasis | Seborrhoeic dermatitis | Dandruff | Cradle cap
  - TO THE SKIN USING SHAMPOO
    - Child: Apply daily as required
    - Adult: Apply daily as required

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Shampoo**

- Capasal (Dermal Laboratories Ltd)
  - Salicylic acid 5 mg per 1 gram, Coal tar distilled 10 mg per 1 gram, Coconut oil 10 mg per 1 gram
  - Capasal Therapeutic shampoo | 250 ml (£4.69)

**Coal tar with dithranol and salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253, dithranol p. 1253, salicylic acid p. 1286.

**INDICATIONS AND DOSE**

- Subacute and chronic psoriasis
  - TO THE SKIN
    - Child: Apply up to twice daily
    - Adult: Apply up to twice daily

**UNLICENSED USE**

- In children Psorin® is licensed for use in children (age range not specified by manufacturer).

**MEDICINAL FORMS**

- Forms available from special-order manufacturers include: ointment

**Coal tar with lecithin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253.

**INDICATIONS AND DOSE**

- Psoriasis
  - TO THE SKIN
  - Adult: Apply 1–2 times a day

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS:
NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS

See Emollient and barrier preparations p. 1221.

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Calamine and Coal Tar Ointment BP, consists of calamine 12.5 g, strong coal tar solution 2.5 g, zinc oxide 12.5 g, hydrous wool fat 25 g, white soft paraffin 47.5 g.
ECZEMA AND PSORIASIS

**Coal tar with salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253, salicylic acid p. 1286.

- **INDICATIONS AND DOSE**
  - Psoriasis | Chronic atopic eczema
  - **Adult:** Apply 1–2 times a day
  - **Child:** Apply once weekly as required

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS

See Emollient and barrier preparations p. 1221.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Coal Tar and Salicylic Acid Ointment, BP consists of coal tar 2 g, salicylic acid 2 g, emulsifying wax 11.4 g, white soft paraffin 19 g, coconut oil 54 g, polysorbate ‘80’ 4 g,liquid paraffin 7.6 g.

- **MEDICINAL FORMS**
  - Ointment

**Coal tar with salicylic acid and precipitated sulfur**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253, salicylic acid p. 1286.

- **INDICATIONS AND DOSE**
  - **COCOIS® OINTMENT**
    - Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff
      - **INITIALLY TO THE SKIN USING SCALP OINTMENT**
      - **Child 6-11 years:** Medical supervision required
      - **Child 12-17 years:** Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
      - **Adult:** Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
  - **SEBCO® OINTMENT**
    - Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff
      - **INITIALLY TO THE SKIN USING SCALP OINTMENT**
      - **Child 6-11 years:** Medical supervision required
      - **Child 12-17 years:** Apply as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
      - **Adult:** Apply as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour

- **MEDICINAL FORMS**
  - Ointment

**Pimecrolimus**

- **INDICATIONS AND DOSE**
  - Short-term treatment of mild to moderate atopic eczema (including flares) when topical corticosteroids cannot be used (initiated by a specialist)
    - **TO THE SKIN**
    - **Adult:** Apply twice daily until symptoms resolve (stop treatment if eczema worsens or no response after 6 weeks)
  - Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated by a specialist)
    - **TO THE SKIN**
    - **Adult:** Apply twice daily until symptoms resolve (maximum duration of treatment 4 weeks)

- **UNLICENSED USE**
  - Pimecrolimus is not licensed for short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy.

- **CONTRA-INDICATIONS**
  - Application to malignant or potentially malignant skin lesions - application under occlusion - congenital epidermal barrier defects - contact with eyes - contact with mucous membranes - generalised erythroderma - immunodeficiency - infection at treatment site

- **CAUTIONS**
  - Alcohol consumption (risk of facial flushing and skin irritation) - avoid other topical treatments except emollients at treatment site - UV light (avoid excessive exposure to sunlight and sunlamps)

- **INTERACTIONS**
  - Appendix 1: pimecrolimus

**Coal tar with zinc oxide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1253.

- **INDICATIONS AND DOSE**
  - Psoriasis | Chronic atopic eczema
  - **Adult:** Apply 1–2 times a day
  - **Child:** Apply 1–2 times a day

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (UPDATED DECEMBER 2018): EMOLLIENTS: NEW INFORMATION ABOUT RISK OF SEVERE AND FATAL BURNS WITH PARAFFIN-CONTAINING AND PARAFFIN-FREE EMOLLIENTS

See Emollient and barrier preparations p. 1221.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - No preparations available—when prepared extemporaneously, the BP states Zinc and Coal Tar Paste, BP consists of zinc oxide 6%, coal tar 6%, emulsifying wax 5%, starch 38%, yellow soft paraffin 45%.

- **MEDICINAL FORMS**
  - Ointment, paste

**IMMUNOSUPPRESSANTS > CALCINEURIN INHIBITORS AND RELATED DRUGS**
Side-effects

- Common or very common Increased risk of infection
- Rare or very rare Skin discoloration
- Frequency not known Skin papilloma

Pregnancy
Manufacturer advises avoid; toxicity in animal studies following systemic administration.

Breast-feeding
Manufacturer advises caution; ensure infant does not come in contact with treated areas.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82
  
  Tacrolimus 0.03% ointment to be applied thinly, reduce to once daily or switch to twice weekly.
  
  Topical tacrolimus is an option for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).
  
  Topical tacrolimus is recommended for moderate atopic eczema on the face and neck of children aged 2–16 years. Tacrolimus should be used within its licensed indications.
  
  www.nice.org.uk/TA82

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

- CAUTIONARY AND ADVISORY LABELS 4, 11, 28
- EXCIPIENTS: May contain Benzyl alcohol, ceteareth alcohol (including cetyl and stearyl alcohol), propylene glycol
  
  ▶ Elidel (Meda Pharmaceuticals Ltd)
  
  Pimecrolimus 10 mg per 1 gram. Elidel 1% cream | 30 gram POM £19.69 DT = £38.69 | 60 gram POM £37.41 DT = £74.81 |
  
  100 gram POM £59.07 DT = £59.07

DRUG ACTION

- Tacrolimus is a calcineurin inhibitor.

INDICATIONS AND DOSE

Short-term treatment of moderate to severe atopic eczema (including flares) in patients unresponsive to, or intolerant of conventional therapy (initiated by a specialist)

- TO THE SKIN
  
  Adult: Apply twice daily until lesion clears (consider other treatment if eczema worsens or no improvement after 2 weeks), initially 0.1% ointment to be applied thinly, reduce frequency to once daily or 0.03% ointment if condition allows

Prevention of flares in patients with moderate to severe atopic eczema and experience in treating atopic eczema with systemic therapy (initiated under specialist supervision)

- TO THE SKIN
  
  Adult: Apply twice weekly, 0.1% ointment to be applied thinly, with an interval of 2–3 days between applications, use short-term treatment regimen during an acute flare; review need for preventative therapy after 1 year

Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated under specialist supervision)

- TO THE SKIN
  
  Adult: Apply twice daily until symptoms resolve, 0.1% ointment to be applied thinly, reduce to once daily or switch to 0.03% ointment if condition allows, maximum duration of treatment 4 weeks

UNLICENSED USE

Short-term treatment of facial, flexural, or genital psoriasis is unlicensed.

CONTRA-INDICATIONS

Application to malignant or potentially malignant skin lesions - application under occlusion - avoid contact with eyes - avoid contact with mucous membranes - congenital epidermal barrier defects - generalised erythroderma - immunodeficiency - infection at treatment site

CAUTIONS

- UV light (avoid excessive exposure to sunlight and sunlamps)

INTERACTIONS

▶ Appendix 1: tacrolimus

SIDE-EFFECTS

- Common or very common Alcohol intolerance - increased risk of infection - sensation abnormal - skin reactions
- Uncommon Lymphadenopathy
- Frequency not known Malignancy - neoplasms

ALLERGY AND CROSS-SENSITIVITY

Contra-indicated if history of hypersensitivity to macrolides.

Pregnancy

Manufacturer advises avoid unless essential; toxicity in animal studies following systemic administration.

Breast-feeding

Avoid - present in breast milk (following systemic administration).

Hepatic impairment

Manufacturer advises caution in hepatic failure.

PATIENT AND CARER ADVICE

Avoid excessive exposure to UV light including sunlight.

NATIONAL FUNDING/ACCESS DECISIONS

NICE decisions

- Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82
  
  Topical tacrolimus is an option for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).
  
  Topical tacrolimus is recommended as an option for the second-line treatment for moderate to severe atopic eczema in adults and children over 2 years. Tacrolimus should be used within its licensed indications.
  
  www.nice.org.uk/guidance/TA82

Scottish Medicines Consortium (SMC) decisions

The Scottish Medicines Consortium has advised (April 2010) that tacrolimus 0.1% ointment (Protopic®) is accepted for restricted use within NHS Scotland for the prevention of flares in patients aged 16 years and over with moderate-to-severe atopic eczema in accordance with the licensed indications; initiation of treatment is restricted to doctors (including general practitioners) with a specialist interest and experience in treating atopic eczema with immunomodulatory therapy.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Ointment

- CAUTIONARY AND ADVISORY LABELS 4, 11, 28
- EXCIPIENTS: May contain Beeswax
  
  ▶ Tacrolimus (Non-proprietary)
  
  Tacrolimus (as Tacrolimus monohydrate) 1 mg per gram
  
  1 gram Tacrolimus 0.1% ointment | 30 gram POM £20.74–£25.92 DT = £55.92 | 60 gram POM £37.82–£47.28 DT = £47.28
  
  ▶ Protopic (LEO Pharma)
  
  Tacrolimus (as Tacrolimus monohydrate) 300 microgram per gram
  
  1 gram Protopic 0.03% ointment | 30 gram POM £23.33 DT = £23.33 | 60 gram POM £42.55 DT = £42.55
  
  Tacrolimus (as Tacrolimus monohydrate) 1 mg per gram
  
  1 gram Protopic 0.1% ointment | 30 gram POM £25.92 DT = £25.92 | 60 gram POM £47.28 DT = £47.28
IMMUNOSUPPRESSANTS > INTERLEUKIN INHIBITORS

**Brodalumab**

- **DRUG ACTION** Brodalumab is a recombinant human monoclonal antibody that binds with high affinity to interleukin-17RA and blocks the activity of pro-inflammatory cytokines.

- **INDICATIONS AND DOSE**
  - **Moderate-to-severe plaque psoriasis (under expert supervision)**
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: 210 mg every week for 3 doses, followed by 210 mg every 2 weeks, consider discontinuing treatment if no response after 16 weeks

- **CONTRA-INDICATIONS**
  - Active Crohn’s disease - clinically significant active infection

- **CAUTIONS**
  - Chronic infection - history of Crohn’s disease (monitor for exacerbations) - history of depressive disorders (discontinue if new or worsening symptoms develop) - history of recurrent infection - history of suicidal ideation or behaviour (discontinue if new or worsening symptoms develop)

- **SIDE-EFFECTS**
  - Common or very common: Headache, fatigue, injection site pain, myalgia
  - Uncommon: Meningitis, Crohn’s disease, arthralgia

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer advises avoid, limitations may exist if they are brought up-to-date with current immunisation schedule before initiating treatment.

- **INTERACTIONS**
  - Appendix 1: monoclonal antibodies

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Kyntheum (LEO Pharma): 280 mg/2 ml injection pre-filled syringes | 2 pre-filled disposable injection | £1,280.00

**Dupilumab**

- **DRUG ACTION** Dupilumab is a recombinant human monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling; these cytokines are involved in atopic eczema.

- **INDICATIONS AND DOSE**
  - **Moderate-to-severe atopic eczema (specialist use only)**
    - **BY SUBCUTANEOUS INJECTION**
    - Adult: Initially 600 mg, followed by 300 mg every 2 weeks, if the psoriasis has not responded adequately, as defined:
      - a 75% reduction in the PASI score (PASI 75) from when treatment started, or
      - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI, or these options are contra-indicated or not tolerated, and
      - the manufacturer provides the drug with the discount agreed in the patient access scheme.

- **SIDE-EFFECTS**
  - Common: Headache, nasopharyngitis, injection site reactions

- **CAUTIONS**
  - Asthma—consult product literature: helminth infection

**BNF 78**

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**Ecema and psoriasis**

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**1258 Inflammatory skin conditions**

**Guselkumab**

**06-Jul-2018**

- **DRUG ACTION** Guselkumab is a recombinant human monoclonal antibody that binds selectively to interleukin-23 and blocks the activity of pro-inflammatory cytokines.

- **INDICATIONS AND DOSE**
  - **Moderate-to-severe plaque psoriasis (specialist use only)**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Initially 100 mg, then 100 mg after 4 weeks, then maintenance 100 mg every 8 weeks, consider discontinuation if no response after 16 weeks

- **CONTRA-INDICATIONS** Clinically significant active infection

- **CAUTIONS** Risk of infection

- **CAUTIONS, FURTHER INFORMATION**
  - Risk of infection: Manufacturer advises consider anti-tuberculosis therapy before initiation of guselkumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Manufacturer advises consider completion of appropriate immunisations according to current guidelines before initiating treatment (consult product literature for appropriate interval between vaccination and administration of guselkumab).

- **INTERACTIONS** → Appendix 1: monoclonal antibodies

- **SIDE-EFFECTS**
  - Common or very common: Arthralgia, diarrhoea, headache, increased risk of infection, urticaria

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception in women of childbearing potential during treatment and for at least 12 weeks after treatment.

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid during treatment and for up to 12 weeks after discontinuing treatment—no information available.

- **PRE-TREATMENT SCREENING** Manufacturer advises that patients should be evaluated for tuberculosis infection before treatment.

- **MONITORING REQUIREMENTS** Manufacturer advises monitor for signs and symptoms of active tuberculosis during and after treatment.

- **DIRECTIONS FOR ADMINISTRATION** Manufacturer advises to avoid injecting into areas of the skin that show psoriasis. Patients may self-administer Tremfya 
  - after appropriate training in subcutaneous injection technique.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Manufacturer advises to record the brand name and batch number after each administration.

- **HANDLING AND STORAGE** Manufacturer advises store in a refrigerator (2–8°C) and protect from light.

- **PATIENT AND CARER ADVICE**
  - Manufacturer advises patients and their carers should be advised to seek medical attention if signs or symptoms of infection occur (monitor closely and suspend treatment if infection is clinically significant or unresponsive to treatment). Self-administration: Manufacturer advises patients may self-administer following training in subcutaneous injection technique.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE decisions**
  - Guselkumab is recommended as an option for treating moderate to severe plaque psoriasis in adults, only if:
    - the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a
Dermatology Life Quality Index (DLQI) of more than 10, and
- the disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contra-indicated or not tolerated, and
- the manufacturer provides the drug according to the commercial arrangement.

Stop guselkumab treatment at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
- a 75% reduction in the PASI score (PASI 75) from when treatment started, or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta452

**SCOTTISH MEDICINES CONSORTIUM (SMC) DECISIONS**

SMC No. 1340/18

The Scottish Medicines Consortium has advised (June 2018) that guselkumab (Tremfya®) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to conventional systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Tremfya (Janssen-Cilag Ltd)**
  - Guselkumab 100 mg per 1 ml Tremfya 100 mg/1 ml solution for injection pre-filled pens | 1 pre-filled disposable injection | £2,250.00
  - Tremfya 100 mg/1 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £2,250.00

**Ixeikizumab**

26-Jun-2017

**DRUG ACTION** Ixeikizumab is a human monoclonal antibody that binds to interleukin-17A and inhibits the release of pro-inflammatory cytokines and chemokines.

**INDICATIONS AND DOSE**

Moderate-to-severe plaque psoriasis (under expert supervision) / Psoriatic arthritis with concomitant moderate-to-severe plaque psoriasis (under expert supervision)

- **BY SUBCUTANEOUS INJECTION**
  - **Adults** Initially 160 mg for 1 dose, followed by 80 mg after 2 weeks, then 80 mg every 2 weeks for 5 further doses (at weeks 4, 6, 8, 10 and 12), then maintenance 80 mg every 4 weeks, consider discontinuation of treatment if no response after 16–20 weeks

Psoriatic arthritis (under expert supervision)

- **BY SUBCUTANEOUS INJECTION**
  - **Adults** Initially 160 mg for 1 dose, then maintenance 80 mg every 4 weeks, consider discontinuation of treatment if no response after 16–20 weeks

**CONTRA-INDICATIONS** Active infections (including active tuberculosis)

**CAUTIONS** Chronic infection—monitor carefully and discontinue if serious, unresponsive infection develops
- Crohn’s disease · Ulcerative colitis

**FURTHER INFORMATION**

- Severe hypersensitivity reactions
  - Severe hypersensitivity reactions have been reported—discontinue treatment immediately if symptoms occur.
- Latent tuberculosis
  - Manufacturer advises that patients with latent tuberculosis should complete anti-tuberculosis therapy before starting ixekizumab.
- Inflammatory bowel disease
  - Manufacturer advises to monitor closely for exacerbation.

**INTERACTIONS**

- Common or very common
  - Increased risk of infection · Nausea · Oropharyngeal pain
- Uncommon
  - Conjunctivitis · Neutropenia · Skin reactions · Thrombocytopenia
- Frequency not known
  - Angioedema · Dyspnoea · Hypersensitivity (occasionally late-onset) · Inflammatory bowel disease

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises effective contraception during treatment and for at least 10 weeks after treatment in women of childbearing potential.

**PREGNANCY**

Manufacturer advises avoid—limited information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**DIRECTIONS FOR ADMINISTRATION**

Manufacturer advises to avoid injecting into areas of the skin that show psoriasis; injection sites may be alternated. Patients may self-administer Taltz® after appropriate training in subcutaneous injection technique.

**HANDLING AND STORAGE**

Manufacturer advises store in a refrigerator (2–8°C).

**PATIENT AND CARER ADVICE**

Self-administration if appropriate, patients and their carers should be given training in subcutaneous injection technique.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE DECISIONS**

- Ixeikizumab for treating moderate to severe plaque psoriasis (April 2017) NICE TA442
  - Ixeikizumab (Taltz®) is recommended as an option for treating plaque psoriasis only if:
    - the disease is severe, defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of 10 or more;
    - the disease has not responded to standard systemic therapies (e.g. ciclosporin, methotrexate and PUVA) or these treatments are contra-indicated or not tolerated, and
    - the manufacturer provides ixekizumab with the discount agreed in the patient access scheme
  - Ixeikizumab should be discontinued if there is an inadequate response at 12 weeks.

Patients currently receiving ixekizumab, whose disease does not meet the above criteria, should have the option to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta442

- Ixeikizumab for treating active psoriatic arthritis after inadequate response to DMARDs (August 2018) NICE TA537
  - Ixeikizumab (Taltz®) alone, or with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:
    - it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for...
the treatment of psoriatic arthritis (TA199 recommendations 1.1 and 1.2), or
- the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after the first 12 weeks, or
- TNF-alpha inhibitors are contra-indicated but would otherwise be considered (as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

Ixekizumab is only recommended if the manufacturer provides it according to the commercial arrangement.

Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta537

Scottish Medicines Consortium (SMC) decisions

SMC No. 1223/17

The Scottish Medicines Consortium has advised (April 2017) that ixekizumab (Taltz®) is accepted for restricted use within NHS Scotland for the treatment of moderate-to-severe plaque psoriasis only in patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland, or a list price that is equivalent or lower.

SMC No. SMC2097

The Scottish Medicines Consortium has advised (October 2018) that ixekizumab (Taltz®) is accepted for restricted use within NHS Scotland, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults whose disease has not responded adequately to at least two conventional disease-modifying anti-rheumatic drugs given either alone or in combination, and who have had an inadequate response to a tumour necrosis factor inhibitor.

This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Polysorbates

- Taltz (Eli Lilly and Company Ltd)
- Ixekizumab 80 mg per 1 ml Taltz 80mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £1,125.00 (Hospital only)
- Ixekizumab 80mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection £1,125.00 (Hospital only)

**Tildrakizumab**

**DRUG ACTION** Tildrakizumab is a recombinant human monoclonal antibody that specifically binds to interleukin-23 and inhibits the release of pro-inflammatory cytokines and chemokines.

**INDICATIONS AND DOSE**

**Moderate-to-severe plaque psoriasis (under expert supervision)**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 100 mg, then 100 mg after 4 weeks, then maintenance 100 mg every 12 weeks, consider discontinuation if no response after 28 weeks, in patients with a high disease burden, or with a body weight > 90kg, a dose of 200 mg may provide greater efficacy

**CONTRA-INDICATIONS** Clinically significant active infection

**CAUTIONS** Chronic infection · history of recurrent infection · recent serious infection

**CAUTIONS, FURTHER INFORMATION**

- Risk of infection  Manufacturer advises consider anti-tuberculosis therapy before initiation of tildrakizumab in patients with a history of tuberculosis, in whom an adequate course of treatment cannot be confirmed.

- Manufacturer advises consider completion of immunisations according to current guidelines before initiating treatment (consult product literature for appropriate interval between vaccination and administration of tildrakizumab).

**INTERACTIONS** → Appendix 1: monoclonal antibodies

**SIDE-EFFECTS**

- Common or very common Back pain · diarrhoea · headache · increased risk of infection · nausea

**CONCEPTION AND CONTRACEPTION**  Manufacturer advises that women of childbearing potential should use effective contraception during treatment and for at least 17 weeks after stopping treatment.

**PREGNANCY**  Manufacturer advises avoid—limited information available.

**BREAST FEEDING**  Manufacturer advises avoid—limited information available.

**PRE-TREATMENT SCREENING**  Manufacturer advises patients should be evaluated for tuberculosis infection before treatment.

**MONITORING REQUIREMENTS**  Manufacturer advises monitor for signs and symptoms of active tuberculosis during and after treatment.

**DIRECTIONS FOR ADMINISTRATION**  Manufacturer advises to take the syringe out of the refrigerator at least 30 minutes before administration, and to avoid injecting into areas of the skin that are affected by psoriasis or are tender, bruised, red, hard, thick, or scaly. Patients may self-administer Ilumetri®, after appropriate training in subcutaneous injection technique.

**PRESCRIBING AND DISPENSING INFORMATION**

Tildrakizumab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name, see Biological medicines and Biosimilar medicines, under Guidance on prescribing p. 1; manufacturer advises to record the brand name and batch number after each administration.

**HANDLING AND STORAGE**  Manufacturer advises store in a refrigerator (2–8°C) and protect from light—consult product literature for further information regarding storage outside refrigerator.

**PATIENT AND CARER ADVICE**  Manufacturer advises patients and their carers should be advised to seek medical advice if signs or symptoms of infection occur.

**NATIONAL FUNDING/ACCESS DECISIONS NICE decisions**

- Tildrakizumab for treating moderate to severe plaque psoriasis (April 2019) NICE TA575

Tildrakizumab (Ilumetri®) is recommended as an option for treating plaque psoriasis in adults, only if:

- the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10, and

- the disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contra-indicated or not tolerated, and

- the manufacturer provides the drug according to the commercial arrangement.
Consider stopping tildrakizumab between 12 weeks and 28 weeks if there has not been at least a 50% reduction in the PASI score from when treatment started. Stop tildrakizumab at 28 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
- a 75% reduction in the PASI score (PASI 75) from when treatment started, or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

www.nice.org.uk/guidance/ta575

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
**Excipients:** May contain Polysorbates
- Ilumetri (Almirall Ltd) ▼
  - Tildrakizumab 100 mg per 1 ml Ilumetri 100mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £3,241.00 | 2 pre-filled disposable injection | £6,241.00

**RETINOID AND RELATED DRUGS**

**Acitretin**

**DRUG ACTION** Acitretin is a metabolite of etretinate.

**INDICATIONS AND DOSE**
- Severe extensive psoriasis resistant to other forms of therapy (under expert supervision) / Palmoplantar pustulosis psoriasis (under expert supervision) / Severe congenital ichthyosis (under expert supervision)
  - **BY MOUTH**
    - Adult: Initially 25–30 mg daily for 2–4 weeks, then adjusted according to response to 25–50 mg daily, increased to up to 75 mg daily, dose only increased to 75 mg daily for short periods in psoriasis

- Severe Darier's disease (keratosis follicularis) (under expert supervision)
  - **BY MOUTH**
    - Adult: Initially 10 mg daily for 2–4 weeks, then adjusted according to response to 25–50 mg daily

**CONTRA-INDICATIONS** Hyperlipidaemia

**CAUTIONS** Avoid excessive exposure to sunlight and unsupervised use of sunlamps - diabetes (can alter glucose tolerance—initial frequent blood glucose checks) - do not donate blood during and for 2 years after stopping therapy (teratogenic risk) - in children use only in exceptional circumstances and monitor growth parameters and bone development (premature epiphyseal closure reported) - investigate atypical musculoskeletal symptoms

**INTERACTIONS** ▸ Appendix 1: retinoids

**SIDE-EFFECTS**
- Common or very common Abdominal pain - arthralgia - brittle nails - conjunctivitis - diarrhoea - dry mouth - gastrointestinal disorder - haemorrhage - hair texture abnormal - headache - increased risk of infection - mucosal abnormalities - myalgia - nausea - oral disorders - peripheral oedema - skin reactions - thirst - vomiting - xerophthalmia
- Uncommon Dizziness - hepatic disorders - photosensitivity reaction - vision disorders
- Rare or very rare Bone pain - exostosis - idiopathic intracranial hypertension - peripheral neuropathy
- Frequency not known Angioedema - capillary leak syndrome - drowsiness - dysphonia - flushing - glucose tolerance impaired - granuloma - hearing impairment - hyperhidrosis - malaise - pyogenic granuloma - retinoic acid syndrome - taste altered - tinnitus

**SIDE-EFFECTS, FURTHER INFORMATION**

**Exostosis** Skeletal hyperostosis and extra-osseous calcification reported following long-term treatment with etretinate (of which acitretin is a metabolite) and premature epiphyseal closure in children.

**Benign intracranial hypertension** Discontinue if severe headache, nausea, vomiting, or visual disturbances occur.

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used.

**PREGNANCY** Avoid—teratogenic.

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid in severe impairment; increased risk of toxicity.

**MONITORING REQUIREMENTS**
- Monitor serum-triglyceride and serum-cholesterol concentrations before treatment, 1 month after starting, then every 3 months.
- Check liver function at start, then every 4–6 weeks for 1 year and then every 3 months.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Prescribing for women of child-bearing potential
    - Female of child-bearing potential must be advised on pregnancy prevention.

  - Effective contraception must be used.
    - Oral contraceptives are recommended for patients aged 18 years and over.
    - Female patients must use an effective contraceptive method, which is known to be effective.
    - Women should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception.

  - Exclusion from treatment
    - Patients who are pregnant at the time of treatment or within 3 months of stopping treatment. They should be advised to avoid alcohol during treatment and for 2 months after stopping treatment.

  - Effective contraception must be used.
    - Oral contraceptives are recommended for patients aged 18 years and over.
    - Female patients must use an effective contraceptive method, which is known to be effective.

  - Discontinue if
    - severe headache, nausea, vomiting, or visual disturbances occur.

  - **CAPSULE**
    - **CAUTIONARY AND ADVISORY LABELS** 10, 11, 21
    - **Acitretin (Non-proprietary)**
      - Acitretin 10 mg Acitretin 10mg capsules | 60 capsule | £23.80
      - Acitretin 25 mg Acitretin 25mg capsules | 60 capsule | £55.24

  - **RECOMMENDED DOSE**
    - **Acitretin 10 mg** Neotigason 10mg capsules | 60 capsule | £17.30
      - DT = £23.80
    - **Acitretin 25 mg** Neotigason 25mg capsules | 60 capsule | £43.00
      - DT = £55.24

www.getintopharma.com
Alitretinoin

10-Apr-2019

**INDICATIONS AND DOSE**

Severe chronic hand eczema refractory to potent topical corticosteroids

- **BY MOUTH**
  - Adult (prescribed by or under supervision of a consultant dermatologist): 30 mg once daily; reduced if not tolerated to 10 mg once daily for 12–24 weeks total duration of treatment, discontinue if no response after 12 weeks, course may be repeated in those who relapse.
  - Severe chronic hand eczema refractory to potent topical corticosteroids in patients with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease

- **INTERACTIONS**
  - Manufacturer advises reduce dose to 10 mg once daily with concurrent use of potent inhibitors of CYP3A4, CYP2C8 and moderate inhibitors of CYP2C9.

- **CONTRA-INDICATIONS**
  - Hypervitaminosis A, uncontrolled hyperlipidaemia, uncontrolled hypothyroidism

- **CAUTIONS**
  - Avoid blood donation during treatment and for at least 1 month after stopping treatment.
  - Dry eye syndrome - history of depression

- **INTERACTIONS** → Appendix 1: retinoids

- **SIDE-EFFECTS**
  - Common or very common: Alopeica - anaemia - conjunctivitis - depression - dizziness - dry eye - dry mouth - eye irritation - fatigue - flushing - headache - hypercholesterolaemia - hypertension - hypertriglyceridaemia (risk of pancreatitis if triglycerides above 9 mmol/litre) - joint disorders - myalgia - nausea - oral disorders - skin reactions - tinnitus - vomiting
  - Uncommon: Bone disorders - cataract - dyspepsia - epistaxis - vision disorders
  - Rare or very rare: Idiopathic intracranial hypertension - nail disorder - photosensitivity reaction - vasculitis

- **Frequency not known**
  - Inflammatory bowel disease - mood altered - peripheral oedema - suicidal ideation

SIDE-EFFECTS, FURTHER INFORMATION: Dry eyes: Dry eyes may respond to lubricating eye ointment or tear replacement therapy.

**Benign intracranial hypertension**

Discontinue treatment if headache, nausea, vomiting, papilloedema, or visual disturbances occur.

- **CONCEPTION AND CONTRACEPTION**
  - Effective contraception must be used.
  - Pregnancy prevention: In women of child-bearing potential, exclude pregnancy 1 month before treatment, up to 3 days before treatment, every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment — perform pregnancy test in the first 3 days of the menstrual cycle.
  - Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods.

- **PREGNANCY**
  - Avoid — teratogenic.

- **BREAST FEEDING**
  - Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises avoid — limited information available.

- **RENAL IMPAIRMENT**
  - Manufacturer advises avoid in severe impairment — no information available.

- **MONITORING REQUIREMENTS**
  - Monitor serum lipids (more frequently in those with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease) — discontinue if uncontrolled hyperlipidaemia.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Prescribing for women of child-bearing potential. Each prescription for alitretinoin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription.
  - Alitretinoin is teratogenic and must not be given to women of child-bearing potential unless they practise effective contraception and then only after detailed assessment and explanation by the physician.

- **PATIENT AND CARER ADVICE**
  - A patient information leaflet should be provided.

- **Conception and contraception**
  - Women of child-bearing potential must be counselled on pregnancy prevention.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE decisions**
    - **Alitretinoin for the treatment of severe chronic hand eczema** (August 2009)
      - **NICE TA177**
        - Alitretinoin (Toctino®) is recommended for the treatment of severe chronic hand eczema in adults that has not responded to potent topical corticosteroids. Treatment should be stopped as soon as an adequate response has been achieved (hands clear or almost clear), or if the eczema remains severe after 12 weeks, or if an adequate response has not been achieved by 24 weeks.
        - [www.nice.org.uk/guidance/ta177](http://www.nice.org.uk/guidance/ta177)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - **CAUTIONARY AND ADVISORY LABELS** 10, 11, 21
      - **Toctino** (Stiefel Laboratories (UK) Ltd)
        - **Alitretinoin 10 mg**
          - **Toctino 10 mg capsules** | 30 capsule | PCT | £493.72 DT + £493.72
        - **Alitretinoin 30 mg**
          - **Toctino 30 mg capsules** | 30 capsule | PCT | £493.72 DT + £493.72

- **Tazarotene**

  **INDICATIONS AND DOSE**

  Mild to moderate plaque psoriasis affecting up to 10% of skin area

- **TO THE SKIN**
  - Adult: Apply once daily usually for up to 12 weeks, apply in the evening

- **CAUTIONS**
  - Avoid contact with eczematous skin - avoid contact with eyes - avoid contact with face - avoid contact with hair-covered scalp - avoid contact with inflamed skin - avoid contact with intertriginous areas

- **INTERACTIONS** → Appendix 1: retinoids

- **SIDE-EFFECTS**
  - Common or very common: Paraesthesia - skin reactions

SIDE-EFFECTS, FURTHER INFORMATION: Local irritation is more common with higher concentration and may require treatment interruption.
SALICYLIC ACID AND DERIVATIVES

Salicylic acid with zinc oxide

- **INDICATIONS AND DOSE**
  - **TO THE SKIN**
  - Adults: Apply twice daily

- **CAUTIONS**
  - Avoid broken skin - avoid inflamed skin
  - Salicylate toxicity may occur particularly if applied on large areas of skin or neonatal skin.

- **SIDE-EFFECTS**
  - Skin reactions

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Zinc and Salicylic Acid Paste BP is also referred to as Lassar Paste. When prepared extemporaneously, the BP states Zinc and Salicylic Acid Paste, BP (Lassar’s Paste) consists of zinc oxide 24%, salicylic acid 2%, starch 24%, white soft paraffin 50%.

- **MEDICINAL FORMS**
  - Forms available from special-order manufacturers include: paste

VITAMINS AND TRACE ELEMENTS

- **VITAMIN D AND ANALOGUES**

  **Calcipotriol**
  (1,25-Dihydroxycholecalciferol)

- **INDICATIONS AND DOSE**
  - **TO THE SKIN**
  - Adults: Apply twice daily, not more than 35% of body surface to be treated daily; maximum 30 g per day

- **CONTRA-INDICATIONS**
  - Do not apply under occlusion - patients with calcium metabolism disorders
  - Erythodermic exfoliative psoriasis (enhanced risk of hypercalcaemia) - generalised pustular psoriasis (enhanced risk of hypercalcaemia)

- **INTERACTIONS**
  - Appendix 1: vitamin D substances

- **SIDE-EFFECTS**
  - Common or very common Skin reactions
  - Uncommon Increased risk of infection
  - Rare or very rare Hypercalcaemia - hypercalciuria - photosensitivity reaction

- **PREGNANCY**
  - Manufactures advise avoid unless essential.

- **BREAST FEEDING**
  - No information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturers advise avoid in severe impairment (no information available).

- **PATIENT AND CARER ADVICE**
  - Advice on application: Patient information leaflet for Dovonex® ointment advises liberal application. However, patients should be advised of maximum recommended weekly dose.
  - Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **EXCIPIENTS**
  - May contain Disodium edetate, propylene glycol, polyisorbates
  - Zorac (Allergan Ltd)

- **PATIENT INFORMATION**
  - Manufactures advise avoid.

- **CONTRA-INDICATIONS**
  - Vitamin D substances

- **INTERACTIONS**
  - Appendix 1: vitamin D substances

- **SIDE-EFFECTS**
  - Common or very common Skin reactions
  - Uncommon Increased risk of infection
  - Rare or very rare Hypercalcaemia - hypercalciuria - photosensitivity reaction

- **PREGNANCY**
  - Manufactures advise avoid unless essential.

- **BREAST FEEDING**
  - No information available.

- **HEPATIC IMPAIRMENT**
  - Manufactures advise avoid in severe impairment (no information available).

- **PATIENT AND CARER ADVICE**
  - Advice on application: Patient information leaflet for Dovonex® ointment advises liberal application. However, patients should be advised of maximum recommended weekly dose.
  - Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

- **EXCIPIENTS**
  - May contain Disodium edetate, propylene glycol, polyisorbates
  - Zorac (Allergan Ltd)

- **PATIENT INFORMATION**
  - Manufactures advise avoid.

- **CONTRA-INDICATIONS**
  - Vitamin D substances

- **INTERACTIONS**
  - Appendix 1: vitamin D substances

- **SIDE-EFFECTS**
  - Common or very common Skin reactions
  - Uncommon Increased risk of infection
  - Rare or very rare Hypercalcaemia - hypercalciuria - photosensitivity reaction

- **PREGNANCY**
  - Manufactures advise avoid unless essential.

- **BREAST FEEDING**
  - No information available.

- **HEPATIC IMPAIRMENT**
  - Manufactures advise avoid in severe impairment (no information available).

- **PATIENT AND CARER ADVICE**
  - Advice on application: Patient information leaflet for Dovonex® ointment advises liberal application. However, patients should be advised of maximum recommended weekly dose.
  - Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas.
Limited evidence suggests that oxybutynin hydrochloride p. 778 [unlicensed indication] can be used to treat hyperhidrosis in patients whose symptoms are not adequately managed through lifestyle modifications and antiperspirants.

In more severe cases specialists use glycopyrronium bromide below as a 0.05% solution in the iontophoretic treatment of hyperhidrosis of plantar and palmar areas. Botox® contains botulinum toxin type A complex p. 407 and is licensed for use intradermally for severe hyperhidrosis of the axillae unresponsive to topical antiperspirant or other antihidrotic treatment.

### Antimuscarinics

#### Glycopyrronium bromide (Glycopyrrolate)

**INDICATIONS AND DOSE**

Iontophoretic treatment of hyperhidrosis

- **TO THE SKIN**
- Adult: Only 1 site to be treated at a time, maximum 2 sites treated in any 24 hours, treatment not to be repeated within 7 days (consult product literature)

**CONTRA-INDICATIONS**

Infected sites should be avoided. Infected sites may include inflammation, eczema, infection, and systemic effects unlikely with topical use.

**SIDE-EFFECTS**

Abdominal discomfort, eating disorder, pain, paraesthesia

**INTERACTIONS**

Appendix 1: glycopyrronium

**CONTRA-INDICATIONS, FURTHER INFORMATION**

The possibility of systemic side-effects should be considered; however, glycopyrronium is poorly absorbed and systemic effects are unlikely with topical use.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- Curatoderm (Almirall Ltd)

<table>
<thead>
<tr>
<th>Product</th>
<th>Strength</th>
<th>Manufacturer</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curatoderm 4 microgram/g ointment</td>
<td>30 g</td>
<td>£13.40</td>
<td>£13.40</td>
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<tr>
<td>Curatoderm 4 microgram/g lotion</td>
<td>30 ml</td>
<td>£12.73</td>
<td>£12.73</td>
</tr>
</tbody>
</table>

### Perspiration

#### Hyperhidrosis

**Overview**

Aluminium chloride hexahydrate below is a potent antiperspirant used in the treatment of hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.
5 Pruritus

Topical local antipruritics

Overview

Pruritus may be caused by systemic disease (such as obstructive jaundice, endocrine disease, chronic renal disease, iron deficiency, and certain malignant diseases), skin disease (e.g. psoriasis, eczema, urticaria, and scabies), drug hypersensitivity, or as a side-effect of opioid analgesics. Where possible, the underlying causes should be treated. An emollient may be of value where the pruritus is associated with dry skin. Pruritus that occurs in otherwise healthy elderly people can also be treated with an emollient. Levomenthol cream p. 1266 can be used to relieve pruritus; it exerts a cooling effect on the skin. Local antipruritics have a role in the treatment of pruritus in palliative care. Preparations containing crotamiton below are sometimes used but are of uncertain value. Preparations containing calamine are often ineffective.

A topical preparation containing doxepin 5% p. 1266 is licensed for the relief of pruritus in eczema; it can cause drowsiness and there may be a risk of sensitisation.

Pruritus is common in biliary obstruction, especially in acute exudative dermatoses and intractable pruritus where sedation is desirable. Calamine preparations are of little value for the treatment of insect stings or bites.

Topical local anaesthetics are indicated for the relief of local pain. Preparations may be absorbed, especially through mucosal surfaces, therefore excessive application should be avoided and they should preferably not be used for more than 3 days; not generally suitable for young children and are less suitable for prescribing.

Topical antihistamines should be avoided in eczema and are not recommended for longer than 3 days. They are less suitable for prescribing.

Other drugs used for Pruritus

Alimemazine tartrate, p. 282 • Cetirizine hydrochloride, p. 279 • Chlorphenamine maleate, p. 283 • Coal tar with calamine, p. 1254 • Hydroxyzine hydrochloride, p. 285 • Levocetirizine hydrochloride, p. 281

Calamine with zinc oxide

15-Jan-2019

• INDICATIONS AND DOSE

Pruritus

➢ TO THE SKIN
➢ Child: (consult product literature)
➢ Adult: (consult product literature)

15-Jan-2019

• CONTRA-INDICATIONS

Avoid application of preparations containing zinc oxide prior to x-ray (zinc oxide may affect outcome of x-ray)

• LESS SUITABLE FOR PRESCRIBING

Less suitable for prescribing.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

CAUTIONARY AND ADVISORY LABELS 15

➢ Calamine with zinc oxide (Non-proprietary)

Phenoxyethanol 5 mg per 1 gram, Zinc oxide 30 mg per 1 gram, Calamine 40 mg per 1 gram, Cetomacrogol emulsifying wax 50 mg per 1 gram, Self-emulsifying glyceryl monostearate 50 mg per 1 gram, Liquid paraffin 200 mg per 1 gram Aqueous calamine cream

100 gram G51 £1.43 DT = £1.43

Liquids

➢ Calamine with zinc oxide (Non-proprietary)

Phenol liquefied 5 mg per 1 ml, Sodium citrate 5 mg per 1 ml, Bentonite 30 mg per 1 ml, Glycerol 50 mg per 1 ml, Zinc oxide 50 mg per 1 ml, Calamine 150 mg per 1 ml

Calamine lotion

200 ml G35 £0.94–£1.09 DT = £1.09

Crotamiton

• INDICATIONS AND DOSE

Pruritus (including pruritus after scabies)

➢ TO THE SKIN
➢ Child 1 month–2 years (on doctor’s advice only): Apply once daily
➢ Child 3–17 years: Apply 2–3 times a day
➢ Adult: Apply 2–3 times a day

• CONTRA-INDICATIONS

Acute exudative dermatoses

• CAUTIONS

Avoid use in buccal mucosa - avoid use near eyes - avoid use on broken skin - avoid use on very inflamed skin - use on doctor’s advice for children under 3 years

• PREGNANCY

Manufacturer advises avoid, especially during the first trimester—no information available.

• BREAST FEEDING

No information available; avoid application to nipple area.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Beeswax, cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, hydroxybenzoates (parabens)

➢ Eurax (GloxsmithKline Consumer Healthcare)

Crotamiton 100 mg per 1 gram Eurax 10% cream

30 gram G35 £2.50 DT = £2.50

100 gram G51 £4.35 DT = £4.35

www.getintopharma.com
Doxepin

- **INDICATIONS AND DOSE**
  - **Pruritus in eczema**
    - **TO THE SKIN**
    - Child 12-17 years: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day
    - Adult: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day
  - **TAKE CARE** Avoid application to large areas - cardiac arrhythmias - mania - severe heart disease - susceptibility to angle-closure glaucoma - urinary retention
  - **INTERACTIONS** → Appendix 1: tricyclic antidepressants
  - **SIDE-EFFECTS** Constipation - diarrhoea - dizziness - drowsiness - dry eye - dry mouth - dyspepsia - fever - headache - nausea - paraesthesia - skin reactions - suicidal tendencies - taste altered - urinary retention - vision blurred - vomiting
  - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk
  - **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk
  - **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.
  - **PATIENT AND CARER ADVICE** A patient information leaflet should be provided.
  - **Driving and skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving).
  - **Effects of alcohol enhanced.**

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - **CAUTIONARY AND ADVISORY LABELS 2, 10**
    - **EXCIPIENTS:** May contain Benzyl alcohol
    - **Xepin** (Cambridge Healthcare Supplies Ltd)
    - **Doxepin hydrochloride 50 mg per 1 gram** Xepin 5% cream |
      30 gram (P3A) £11.70 DT = £11.70

Menthol and Derivatives

Levomenthol

- **INDICATIONS AND DOSE**
  - **Pruritus**
    - **TO THE SKIN**
    - Adult: Apply 1–2 times a day
  - **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream
    - **AquaSoothe** (Enogen Healthcare Ltd)
      - Menthol 10 mg per 1 gram AquaSoothe 1% cream | 100 gram £3.70 DT = £3.97 | 500 gram £15.43 DT = £16.59
      - Menthol 20 mg per 1 gram AquaSoothe 2% cream | 50 gram £1.86 | 500 gram £15.43 DT = £16.97
    - **Arjus** (Arjus Products Ltd)
      - Menthol 5 mg per 1 gram Arjus 0.5% cream | 500 gram £15.30 DT = £16.07
      - Menthol 10 mg per 1 gram Arjus 1% cream | 100 gram £3.25 DT = £3.97 | 500 gram £15.30 DT = £16.59
      - Menthol 20 mg per 1 gram Arjus 2% cream | 500 gram £15.30 DT = £16.97
    - **Dermacool** (Pern Consumer Products Ltd)
      - Menthol 5 mg per 1 gram Dermacool 0.5% cream | 100 gram £3.85 | 500 gram £16.07 DT = £16.97
      - Menthol 10 mg per 1 gram Dermacool 1% cream | 100 gram £3.97 DT = £3.97 | 250 gram £8.99 | 500 gram £16.59 DT = £16.59

6 Rosacea and acne

Rosacea and Acne

Acne

Treatment of acne should be commenced early to prevent scarring. Patients should be counselled that an improvement may not be seen for at least a couple of months. The choice of treatment depends on whether the acne is predominantly inflammatory or comedonal and its severity.

*Mild to moderate acne* is generally treated with topical preparations. Systemic treatment with oral antibiotics is generally used for *moderate to severe acne* or where topical preparations are not tolerated or are ineffective or where application to the site is difficult. Another oral preparation used for acne is the hormone treatment co-cyproterone p. 1267 (cyproterone acetate with ethinyloestradiol); it is for women only.

*Severe acne*, acne unresponsive to prolonged courses of oral antibacterials, scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe isotretinoin p. 1270 for administration by mouth.

**Acne: topical preparations**

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide p. 1269 or to a topical retinoid. Alternatively, topical application of an antibacterial such as erithromycin p. 539 or clindamycin p. 1268 may be effective for inflammatory acne. If topical preparations prove inadequate, oral preparations may be needed.

**Benzoyl peroxide and azelaic acid**

Benzoyl peroxide is effective in mild to moderate acne. Both comedones and inflamed lesions respond well to benzoyl peroxide. The lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with treatment continued at a reduced frequency of application. If the acne does not respond after 2 months then use of a topical antibacterial should be considered.

Azelaic acid p. 1269 has antimicrobial and antiinflammatory properties. It may be an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face. Some patients prefer azelaic acid because it is less likely to cause local irritation than benzoyl peroxide.

**Topical antibacterials for acne**

For many patients with mild to moderate inflammatory acne, topical antibacterials may be no more effective than topical benzoyl peroxide or tretinoin p. 939. Topical antibacterials are probably best reserved for patients who wish to avoid oral antibacterials or who cannot tolerate them. Topical preparations of erythromycin and clindamycin are effective for inflammatory acne. Topical antibacterials can produce mild irritation of the skin, and on rare occasions cause
sensitisation; gastro-intestinal disturbances have been reported with topical clindamycin. Antibiometric resistance of Propionibacterium acnes is increasing; there is cross-resistance between erythromycin and clindamycin. To avoid development of resistance:

- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid);
- avoid concomitant treatment with different oral and topical antibacterials;
- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl peroxide or azelaic acid may eliminate any resistant propionibacteria);
- do not continue treatment for longer than necessary (however, treatment with a topical preparation should be continued for at least 6 months).

Some manufacturers of topical antibacterial preparations for acne advise that preparations containing alcohol are not suitable for use with benzoyl peroxide.

Topical retinoids and related preparations for acne

Topical tretinoin, its isomer isotretinoin, and adapalene p. 1259 (a retinoid-like drug), are useful for treating comedones and inflammatory lesions in mild to moderate acne. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. Isotretinoin is given by mouth in severe acne.

Other topical preparations for acne

Preparations containing aluminium oxide are not considered beneficial in acne.

A topical preparation of nicotinamide p. 1272 is available for inflammatory acne.

Acne: oral preparations

Systemic antibacterial treatment is useful for inflammatory acne if topical treatment is not adequately effective or if it is inappropriate. Anticomodel sodium treatment (e.g. with topical benzoyl peroxide) may also be required. Either oxytetracycline p. 567 or tetracycline p. 567 is usually given for acne. If there is no improvement after the first 3 months another oral antibacterial should be used.

Maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer.

Doxycycline p. 564 and lymecycline p. 566 are alternatives to tetracycline.

Although minocycline p. 566 is as effective as other tetracyclines for acne, it is associated with a greater risk of lupus erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation; it is given in an once or twice daily dose.

Erythromycin in a twice daily dose is an alternative for the management of acne but propionibacteria strains resistant to erythromycin are becoming widespread and this may explain poor response.

Trimethoprim p. 574 may be used for acne resistant to other antibacterials [unlicensed indication]. Prolonged treatment with trimethoprim may depress haematopoiesis; it should generally be initiated by specialists.

Concomitant use of different topical and systemic antibacterials is undesirable owing to the increased likelihood of the development of bacterial resistance.

Hormone treatment for acne

Co-cyprindiol (cyproterone acetate with ethinylestradiol) contains an anti-androgen. It is licensed for use in women with moderate to severe acne that has not responded to topical therapy or oral antibacterials, and for moderately severe hirsutism. Although it is an effective hormonal contraceptive, it should not be used solely for contraception.

Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some women with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.

**Oral retinoid for acne**

The retinoid isotretinoin reduces sebum secretion. It is used for the systemic treatment of nodulo-cystic and conglutate acne, severe acne, scarring, acne which has not responded to an adequate course of a systemic antibacterial, or acne which is associated with psychological problems. It is also useful in women who develop acne in the third or fourth decades of life, since late onset acne is frequently unresponsive to antibacterials.

Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist. It is given for at least 16 weeks; repeat courses are not normally required.

Side-effects of isotretinoin include severe dryness of the skin and mucous membranes, nose bleeds, and joint pains. The drug is teratogenic and must not be given to women of child-bearing age unless they practise effective contraception (oral progestogen-only contraceptives not considered effective) and then only after detailed assessment and explanation by the physician. Women must also be registered with a pregnancy prevention programme. Although a causal link between isotretinoin p. 1270 use and psychiatric changes (including suicidal ideation) has not been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.

**Rosacea**

Rosacea is not comedonal (but may exist with acne which may be comedonal). Brimonidine tartrate p. 1273 is licensed for the treatment of facial erythema in rosacea. The pustules and papules of rosacea respond to topical azelaic acid p. 1269, topical ivermectin p. 1273 or to topical metronidazole p. 1230. Alternatively oral administration of oxytetracycline p. 567 or tetracycline p. 567, or erythromycin p. 539, can be used; courses usually last 6–12 weeks and are repeated intermittently. Doxycycline p. 564 can be used [unlicensed indication] if oxytetracycline or tetracycline is inappropriate (e.g. in renal impairment). A modified-release preparation of doxycycline is licensed in low daily doses for the treatment of facial rosacea. Isotretinoin is occasionally given in refractory cases [unlicensed indication]. Camouflagers may be required for the redness.

**6.1 Acne**

**ANTI-ANDROGENS**

**Co-cyprindiol**

- **INDICATIONS AND DOSE**

  Moderate to severe acne in females of child-bearing age refractory to topical therapy or oral antibacterials | Moderately severe hirsutism

  - **BY MOUTH**
    - Females of childbearing potential: 1 tablet daily for 21 days, to be started on day 1 of menstrual cycle; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs), time to symptom remission, at least 3 months; review need for treatment regularly

- **CONTRA-INDICATIONS** Acute porphyrias p. 1058 • gallstones • heart disease associated with pulmonary hypertension or risk of embolus • history during pregnancy of cholestatic jaundice • history during pregnancy of...
Rosacea and acne

- **MEDICINAL FORMS**
  - **Frequency not known** Abdominal cramps, amenorrhoea, pruritus, constipation, nervousness, skin reactions, depression, diarrhea, postmenstrual syndrome, anaemia, chest pain.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal discomfort, nausea.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - **A mixture of cyproterone acetate and ethinylestradiol in the mass proportions 2000 parts to 35 parts, respectively.

- **MEDICINAL FORMS**
  - **Tablet**
    - **Cyproterone Acetate 50 mg**
    - **Ethinylestradiol 35 microgram**
    - **Dianette tablets 35 microgram, Cyproterone acetate 2 mg**
    - **Ethinylestradiol 35 microgram, Cyproterone acetate 2 mg**
    - **Teragezza tablets 35 microgram, Cyproterone acetate 2 mg**

- **ANTIBACTERIALS**
  - **Clindamycin**
    - **INDICATIONS AND DOSE**
      - **Acne vulgaris**
        - **TO THE SKIN**
        - **Child:** Apply twice daily, to be applied thinly.
        - **Adult:** Apply twice daily, to be applied thinly.
    - **INTERACTIONS**
      - **Appendix 1:** clindamycin
      - **SIDE-EFFECTS**
        - **Common or very rare** Cholelithiasis, photosensitivity reaction.
        - **Frequency not known** Abdominal pain, abdominal distension, cholestasis, hepatic disease or cholestasis, jaundice, nausea.

- **MEDICINAL FORMS**
  - **Dianette (Bayer Plc)**
    - **Ethinylestradiol 35 microgram, Cyproterone acetate**
      - **2 mg Dianette tablets 35 microgram**
      - **Teragezza (Morningside Healthcare Ltd)**
      - **Ethinylestradiol 35 microgram, Cyproterone acetate**
      - **2 mg Teragezza 2000 microgram/35 microgram tablets**

- **Clindamycin**
  - **INDICATIONS AND DOSE**
    - **Dianette tablets**
    - **Teragezza tablets**

- **Clindamycin**
  - **TO THE SKIN**
    - **Child:** Apply twice daily.
    - **Adult:** Apply twice daily.

- **INTERACTIONS**
  - **Appendix 1:** clindamycin
  - **SIDE-EFFECTS**
  - **Common or very common** Cholelithiasis, photosensitivity reaction.
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- **Clindamycin**
  - **INDICATIONS AND DOSE**
    - **Dianette tablets**
    - **Teragezza tablets**

- **Clindamycin**
  - **TO THE SKIN**
    - **Child:** Apply twice daily.
    - **Adult:** Apply twice daily.

- **INTERACTIONS**
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  - **INDICATIONS AND DOSE**
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    - **Teragezza tablets**

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  - **TO THE SKIN**
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    - **Adult:** Apply twice daily.

- **INTERACTIONS**
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    - **Teragezza tablets**

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- **INTERACTIONS**
  - **Appendix 1:** clindamycin
  - **SIDE-EFFECTS**
  - **Common or very common** Cholelithiasis, photosensitivity reaction.
  - **Frequency not known** Abdominal pain, abdominal distension, cholestasis, hepatic disease or cholestasis, jaundice, nausea.
ACNE VULGARIS

INDICATIONS AND DOSAGE

**Acne vulgaris**

- **TO THE SKIN**

  - **Child 12-17 years:** Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations
  - **Adults:** Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations

SIDE-EFFECTS

- **Common or very common** Skin reactions
- **Frequency not known** Facial swelling
  - **SIDE-EFFECTS, FURTHER INFORMATION** Reduce frequency or suspend use until skin irritation subsides and re-introduce at reduced frequency.

PATIENT AND CARER ADVICE

- **May bleach fabrics and hair.**

MEDICINAL FORMS

- **There can be variation in the licensing of different medicines containing the same drug.**

**Liquid**

- **Zinerty (LEO Pharma)**
  - Zinc acetate 12 mg per 1 ml, Erythromycin 40 mg per 1 ml Zinerty lotion | 30 ml \( £25.25 \) | 90 ml \( £50.02 \) DT = £0.02

**Antiseptics and Disinfectants**

Benzoyl peroxide

INDICATIONS AND DOSE

**Acne vulgaris**

- **TO THE SKIN**

  - **Child 12-17 years:** Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations
  - **Adults:** Apply 1–2 times a day, preferably apply after washing with soap and water, start treatment with lower-strength preparations

UNLICENSED USE

- Not licensed for use in treatment of infantile acne.

CAUTIONS

- Avoid contact with broken skin.
- Avoid contact with eyes.
- Avoid contact with mucous membranes.
- Avoid excessive exposure to sunlight.

SIDE-EFFECTS

- **Common or very common** Skin reactions
- **Frequency not known** Facial swelling
  - **SIDE-EFFECTS, FURTHER INFORMATION** Reduce frequency or suspend use until skin irritation subsides and re-introduce at reduced frequency.

PATIENT AND CARER ADVICE

- **May bleach fabrics and hair.**

MEDICINAL FORMS

- **There can be variation in the licensing of different medicines containing the same drug.**

**Liquid**

- **Brevoxyl** (GlaxoSmithKline Consumer Healthcare)
  - Benzoyl peroxide 40 mg per 1 gram Brevoxyl 4% cream | 50 gram \( £4.13 \) DT = £4.13

Gel

- **EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, isopropyl palmitate, propylene glycol
  - **Brevoxyl** (GlaxoSmithKline Consumer Healthcare)
  - Benzoyl peroxide 50 mg per 1 gram Benzoyl peroxide 5% gel | 30 gram \( £5.44 \) DT = £5.44

**Cream**

- **EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, isopropyl palmitate, propylene glycol
  - **Acnecide** (Galdemra (UK) Ltd)
    - Benzoyl peroxide 50 mg per 1 gram Acnecide 5% gel | 30 gram \( £5.44 \) DT = £5.44
    - Acnecide Wash 5% gel | 50 gram \( £5.44 \) DT = £5.44

COMBINATIONS AVAILABLE: **Adapalene with benzoyl peroxide**, p. 1270

**Benzoyl peroxide with clindamycin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, benzoyl peroxide above, clindamycin p. 1268.

INDICATIONS AND DOSE

**Acne vulgaris**

- **TO THE SKIN**

  - **Child 12-17 years:** Apply once daily, dose to be applied in the evening
  - **Adults:** Apply once daily, dose to be applied in the evening

INTERACTIONS

- **Appendix 1: clindamycin**

MEDICINAL FORMS

- **There can be variation in the licensing of different medicines containing the same drug.**

**Gel**

- **EXCIPIENTS:** May contain Disodium edetate
  - **Duac** (Stiefel Laboratories (UK) Ltd)
    - Clindamycin (as Clindamycin phosphate) 10 mg per 1 gram, Benzoyl peroxide 30 mg per 1 gram Duac Once Daily gel (3% and 1%) | 30 gram \( £13.14 \) DT = £13.14 | 60 gram \( £26.28 \) DT = £26.28
  - **Clindamycin (as Clindamycin phosphate) 10 mg per 1 gram, Benzoyl peroxide 50 mg per 1 gram Duac Once Daily gel (5% and 1%) | 30 gram \( £13.14 \) DT = £13.14 | 60 gram \( £26.28 \) DT = £26.28

**DERMATOLOGICAL DRUGS**

**Antiacneals**

Azelaic acid

INDICATIONS AND DOSE

**FINACEA**

- **Facial acne vulgaris**
  - **TO THE SKIN**
    - **Child 12-17 years:** Apply twice daily, discontinue if no improvement after 1 month
    - **Adults:** Apply twice daily, discontinue if no improvement after 1 month

**Papulopustular rosacea**

- **TO THE SKIN**
  - **Adults:** Apply twice daily, discontinue if no improvement after 2 months

**SKINOREN**

- **Acne vulgaris**
  - **TO THE SKIN**
    - **Child 12-17 years:** Apply twice daily
    - **Adults:** Apply twice daily

- **Acne vulgaris in patients with sensitive skin**
  - **TO THE SKIN**
    - **Child 12-17 years:** Apply once daily for 1 week, then apply twice daily
    - **Adults:** Apply once daily for 1 week, then apply twice daily

INTERACTIONS

- Avoid contact with eyes.
- Avoid contact with mouth.
- Avoid contact with mucous membranes.

SIDE-EFFECTS

- **Uncommon** Skin reactions
- **Rare or very rare** Asthma exacerbated - cheilitis
- **Frequency not known** Angioedema - eye swelling

MEDICINAL FORMS

- **There can be variation in the licensing of different medicines containing the same drug.**

**Cream**

- **EXCIPIENTS:** May contain Propylene glycol
  - **Skinoren** (Bayer Plc)
    - Azelaic acid 200 mg per 1 gram Skinoren 20% cream | 30 gram \( £4.49 \) DT = £4.49

**Gel**

- **EXCIPIENTS:** May contain Disodium edetate, polysorbates, propylene glycol
  - **Finacea** (Bayer Plc)
    - Azelaic acid 150 mg per 1 gram Finacea 15% gel | 30 gram \( £7.48 \) DT = £7.48

**RETINOID AND RELATED DRUGS**

**Adapalene**

INDICATIONS AND DOSE

- **Mild to moderate acne vulgaris**
  - **TO THE SKIN**
    - **Child 12-17 years:** Apply once daily, apply thinly in the evening
    - **Adults:** Apply once daily, apply thinly in the evening

www.getintopharma.com
### Unlicensed Use
- In children: Not licensed for use in infantile acne.

### Caution
- Avoid accumulation in angles of the nose - avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin - avoid exposure to UV light (including sunlight, solariums) - avoid in severe acne involving large areas - caution in sensitive areas such as the neck.

### Interactions
- Appendix 1: retinoids

### Conception and Contraception
- Females of childbearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

### Pregnancy
- Avoid.

### Breast Feeding
- Amount of drug in milk probably too small to be harmful; ensure infant does not come in contact with treated areas.

### Patient and Carer Advice
- If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.

### Medicinal Forms
- There can be variation in the licensing of different medicines containing the same drug.

#### Cream
- CAUTIONARY AND ADVISORY LABELS 11
- EXCIPIENTS: May contain Disodium edetate, hydroxybenzoates (parabens)
  - Adapalene (Non-proprietary)
    - Adapalene 1 mg per 1 gram
      - Differin (Galderma (UK) Ltd).
  - Adapalene 1 mg per 1 gram
    - Differin 0.1% cream 45 gram (POM)
      - £16.43 DT = £16.43

#### Gel
- CAUTIONARY AND ADVISORY LABELS 11
- EXCIPIENTS: May contain Disodium edetate, propylene glycol
  - Adapalene (Non-proprietary)
    - Adapalene 1 mg per 1 gram
      - Differin (Galderma (UK) Ltd).
  - Adapalene 1 mg per 1 gram
    - Differin 0.1% gel 45 gram (POM)
      - £16.43 DT = £16.43

### Adapalene with benzoyl peroxide

The properties listed below are those particular to the combination only. For the properties of the components please consider, adapalene p. 1269, benzoyl peroxide p. 1269.

#### Indications and dose
- Acne vulgaris
  - TO THE SKIN
    - Child 9–17 years: Apply once daily, to be applied thinly in the evening
    - Adult: Apply once daily, to be applied thinly in the evening

#### Interactions
- Appendix 1: retinoids

#### Conception and Contraception
- Females of childbearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

#### Patient and Carer Advice
- Gel may bleach clothing and hair.

#### National Funding/Access Decisions
- Scottish Medicines Consortium (SMC) decisions
  - The Scottish Medicines Consortium has advised (March 2014) that Epiduo™ should be restricted for use in mild to moderate facial acne when monotherapy with benzoyl peroxide or adapalene is inappropriate.

### Medicinal Forms
- There can be variation in the licensing of different medicines containing the same drug.

#### Gel
- CAUTIONARY AND ADVISORY LABELS 11
- EXCIPIENTS: May contain Disodium edetate, polysorbates, propylene glycol
  - Epiduo (Galderma (UK) Ltd)
    - Adapalene 1 mg per 1 gram, Benzoyl peroxide 25 mg per 1 gram
      - Epiduo 0.1%/2.5% gel 45 gram (POM) £19.53 DT = £19.53

### Isotretinoin

#### Indications and Dose
- Topical treatment of mild to moderate acne
  - TO THE SKIN
    - Adult: Apply 1–2 times a day, to be applied thinly

#### Special considerations
- Severe acne (under expert supervision) Acne which is associated with psychological problems (under expert supervision). Acne which has not responded to an adequate course of a systemic antibacterial (under expert supervision). Acne with scarring (under expert supervision). Systemic treatment of nodulo-cystic and conglobate acne (under expert supervision)

#### By mouth
- Adult: Initially 500 micrograms/kg daily in 1–2 divided doses, increased if necessary to 1 mg/kg daily for 16–24 weeks, repeat treatment course after a period of at least 8 weeks if relapse after first course; maximum 150 mg/kg per course.

### Important safety information
  - An EU-wide review has concluded that on rare occasions, oral isotretinoin, indicated for severe acne, may cause sexual side-effects, including erectile dysfunction and decreased libido.

#### Contra-indications
- With oral use: Hyperlipidaemia, hypervitaminosis A
- With topical use: Perioral dermatitis, rosacea

#### Caution
- With oral use: Avoid blood donation during treatment and for at least 1 month after treatment. Diabetes, dry eye syndrome (associated with risk of keratitis), history of depression, monitor for depression
- With topical use: Allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid - alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application) - avoid accumulation in angles of the nose - avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin - avoid exposure to UV light (including sunlight, solariums) - avoid in severe acne involving large areas - avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics - caution in sensitive areas such as the neck, personal or familial history of skin cancer

#### Interactions
- Appendix 1: retinoids

#### Side-effects
- General side-effects
  - Skin reactions
  - Rare or very rare: Photosensitivity reaction
  - Specific side-effects
    - Common or very common
      - With oral use: Alopecia, anaemia, arthralgia, back pain, cheilitis, dry eye, eye discomfort, eye inflammation, haemorrhage, headache, increased risk of infection

www.getintopharma.com
myalgia - nasal dryness - neutropenia - proteinuria - skin fragility (trauma may cause blistering) - thrombocytopoenia
- thrombocytosis

- Rare or very rare

- Frequency not known
- With oral use Rhabdomyolysis - severe cutaneous adverse reactions (SCARs)

SIDE-EFFECTS, FURTHER INFORMATION
Risk of pancreatitis if triglycerides above 9 mmol/litre—discontinue if uncontrolled hypertriglyceridaemia or pancreatitis.

Discontinue treatment if skin peeling severe or haemorrhagic diarrhoea develops.

Visual disturbances require expert referral and possible withdrawal.

Psychiatric side-effects could require expert referral.

- CONCEPTION AND CONTRACEPTION

Pregnancy prevention

With oral use Effective contraception must be used. In women of child-bearing potential, exclude pregnancy up to 3 days before treatment (start treatment on day 2 or 3 of menstrual cycle), every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle. Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone, but can be used in conjunction with other contraceptive methods. Each prescription for isotretinoin should be limited to a supply of up to 30 days' treatment and dispensed within 7 days of the date stated on the prescription; repeat prescriptions or faxed prescriptions are not acceptable. Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

- With topical use Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

- PREGNANCY

Contra-indicated in pregnancy (teratogenic).

- BREAST FEEDING

Avoid.

- HEPATIC IMPAIRMENT

With oral use Manufacturer advises avoid—limited information available.

- RENAL IMPAIRMENT

Dose adjustments

- With oral use In severe impairment, reduce initial dose (e.g. 10 mg daily) and increase gradually up to 1 mg/kg daily as tolerated.

- MONITORING REQUIREMENTS

With oral use Measure hepatic function and serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised).

- PRESCRIBING AND DISPENSING INFORMATION

Isotretinoin is an isomer of tretinoin.

PATIENT AND CARER ADVICE

- With oral use Warn patient to avoid wax epilation (risk of epidermal stripping), dermabrasion, and laser skin treatments (risk of scarring) during treatment and for at least 6 months after stopping; patient should avoid exposure to UV light (including sunlight) and use sunscreen and emollient (including lip balm) preparations from the start of treatment. Patients and carers should be told how to recognise signs and symptoms of psychiatric disorders such as depression, anxiety, and rarely suicidal thoughts.

- With topical use Patients should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capule

CAUTIONARY AND ADVISORY LABELS 10, 11, 21

- Isotretinoin (non-proprietary) ▼

Isotretinoin 5 mg Isotretinoin 5mg capsules | 30 capsule POM £10.10–£10.15 | 56 capsule POM £14.78 DT = £14.78
Isotretinoin 10 mg Isotretinoin 10mg capsules | 30 capsule POM £14.54 DT = £14.54
Isotretinoin 20 mg Isotretinoin 20mg capsules | 30 capsule POM £20.00 DT = £16.65 | 56 capsule POM £31.08–£37.85
Isotretinoin 40 mg Isotretinoin 40mg capsules | 30 capsule POM £38.96 DT = £38.98

Roaccutane (Roche Products Ltd)

Isotretinoin 10 mg Roaccutane 10mg capsules | 30 capsule POM £14.54 DT = £14.54
Isotretinoin 20 mg Roaccutane 20mg capsules | 30 capsule POM £20.02 DT = £16.65

Isotretinoin with erythromycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, isotretinoin p. 1270, erythromycin p. 539.

- INDICATIONS AND DOSE

Topical treatment of mild to moderate acne

- TO THE SKIN

- Adult: (consult product literature)

- INTERACTIONS

→ Appendix 1: macrolides - retinoids

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gel

CAUTIONARY AND ADVISORY LABELS 11

EXCIPIENTS: May contain Butylated hydroxytoluene

- Isotrexin (Stiefel Laboratories (UK) Ltd)

Isotretinoin 500 microgram per 1 gram, Erythromycin 20 mg per 1 gram Isotrexin gel | 30 gram POM £7.47 DT = £7.47

www.getintopharma.com
Tretinoin with clindamycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, tretinoin p. 939, clindamycin p. 1268.

### INDICATIONS AND DOSE

**Facial acne**
- TO THE SKIN
  - Child 12–17 years: Apply daily, (to be applied thinly at bedtime)
  - Adult: Apply daily, (to be applied thinly at bedtime)

### CONTRA-INDICATIONS

Perioral dermatitis - personal or familial history of skin cancer - rosacea

### CAUTIONS

Allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid - alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application) - avoid accumulation in angles of the nose - avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin - avoid exposure to UV light (including sunlight, solariums) - avoid in severe acne involving large areas - avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics - caution in sensitive areas such as the neck

### SIDE-EFFECTS

Dry skin (discontinue if severe) - eye irritation - oedema - photosensitivity reaction - skin pigmentation change (transient) - skin reactions

### CONCEPTION AND CONTRACEPTION

Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

### PREGNANCY

Contra-indicated in pregnancy.

### BREAST FEEDING

Amount of drug in milk after topical application probably too small to be harmful; ensure infant does not come in contact with treated areas.

### PATIENT AND CARER ADVICE

If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.

Patients and carers should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Gel**

CAUTIONARY AND ADVISORY LABELS 11

EXCIPIENTS: May contain Butylated hydroxytoluene, hydroxybenzoates (parabens), polysorbates

Treclin (Meda Pharmaceuticals Ltd)

Tretinoin 250 microgram per 1 gram, Clindamycin (as Clindamycin phosphate) 10 mg per 1 gram

Treclin 1%/0.025% gel

30 gram [POD] £11.94 DT + £1.94

Tretinoin 250 microgram per 1 gram, Erythromycin 40 mg per 1 gram

Treclin 1%/0.025% gel

30 gram [POD] £11.94 DT + £1.94

VITAMINS AND TRACE ELEMENTS

**VITAMIN B GROUP**

### Nicotinamide

**INDICATIONS AND DOSE**

Inflammatory acne vulgaris

- TO THE SKIN
  - Adult: Apply twice daily, reduced to once daily or on alternate days, dose reduced if irritation occurs

**CAUTIONS**

Avoid contact with eyes - avoid contact with mucous membranes (including nose and mouth) - reduce
6.2 Rosacea

Other drugs used for Rosacea Azelaic acid, p. 1269

ANTHELMINTICS

Ivermectin 17-May-2017

- INDICATIONS AND DOSE
  Papulopustular rosacea
  ► TO THE SKIN
  ► Adult: Apply daily for up to 4 months, the treatment course may be repeated; discontinue if no improvement after 3 months

- INTERACTIONS → Appendix 1: ivermectin
- SIDE-EFFECTS
  - Common or very common Skin reactions
  - PREGNANCY Manufacturer advises avoid—limited information but toxicity following oral use in animal studies
  - BREAST FEEDING Manufacturer advises avoid—limited information but present in milk following oral use
  - HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).
  - DIRECTIONS FOR ADMINISTRATION Manufacturer advises apply thinly to the face only, avoiding contact with eyes, lips and mucosa.
  - PATIENT AND CARER ADVICE Wash hands immediately after use.

- NATIONAL FUNDING/ACCESS DECISIONS
  Scottish Medicines Consortium (SMC) decisions
  The Scottish Medicines Consortium has advised (December 2015) that ivermectin (Soolantra®) is accepted for restricted use within NHS Scotland for the treatment of moderate-to-severe inflammatory lesions of rosacea (papulopustular) where a topical treatment is considered appropriate.

  All Wales Medicines Strategy Group (AWMSG) decisions
  The All Wales Medicines Strategy Group has advised (April 2016) that ivermectin (Soolantra®) is recommended as an option for use within NHS Wales for the topical treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
  - Cream
    CAUTIONARY AND ADVISORY LABELS 28 EXCipients: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, isopropyl palmitate, propylene glycol
    Soolantra (Galderma (UK) Ltd)
    Ivermectin 10 mg per 1 gram Soolantra 10mg/g cream ▶ 30 gram [□] £16.29 DT = £16.29

- SYMPATHOMIMETICS › ALPHA_2-ADRENOCEPTOR AGONISTS
  Brimonidine tartrate 12-Jul-2017
  - DRUG ACTION Brimonidine, an alpha_2-adrenoceptor agonist, is used to reduce erythema in rosacea by cutaneous vasoconstriction.
  - INDICATIONS AND DOSE
    Facial erythema in rosacea
    ► TO THE SKIN
    ► Adult: Apply once daily until erythema subsides, apply thinly, divide dose over forehead, chin, nose, and cheeks, max. 1 g of gel per day
  - DOSE EQUIVALENCE AND CONVERSION
    - 1 g of gel contains 5 mg of brimonidine tartrate (equivalent to 3.3 mg of brimonidine).

- IMPORTANT SAFETY INFORMATION
  MHRA/CHM ADVISE: BRIMONIDINE GEL (MINIRAX®): RISK OF SYSTEMIC CARDIOVASCULAR EFFECTS (JUNE 2017)
  Systemic cardiovascular effects including bradycardia, hypotension, and dizziness have been reported after application of brimonidine gel. To minimise the possibility of systemic absorption, it is important to avoid application to irritated or damaged skin, including after laser therapy.

  MHRA/CHM ADVISE: BRIMONIDINE GEL (MINIRAX®): RISK OF EXACERBATION OF ROSACEA (NOVEMBER 2016)
  Symptom exacerbation has been reported very commonly in patients treated with brimonidine gel. Treatment should be initiated with a small amount of gel (less than the maximum dose) for at least 1 week, then increased gradually, based on tolerability and response. Patients should be counselled on the importance of not exceeding the maximum daily dose, and advised to stop treatment and seek medical advice if symptoms worsen during treatment.

- CAUTIONS Cerebral insufficiency · coronary insufficiency · depression · postural hypotension · Raynaud’s syndrome · severe cardiovascular disease · thromboangiitis obliterans
- INTERACTIONS → Appendix 1: brimonidine
- SIDE-EFFECTS
  - Common or very common Dizziness · dry mouth · flushing · headache · skin reactions
  - Uncommon Angioedema · eyelid oedema · feeling hot · nasal congestion · paraesthesia · peripheral coldness
  - Rare or very rare Bradycardia · hypotension
- PREGNANCY Manufacturer advises avoid—limited information available.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT Manufacturer advises caution (no information available).
- RENAL IMPAIRMENT Manufacturer advises use with caution.
- DIRECTIONS FOR ADMINISTRATION Avoid contact with eyes, mouth, and mucous membranes; avoid use on irritated or damaged skin or open wounds; apply other topical preparations (including cosmetics) only after brimonidine gel has dried on skin.
- PATIENT AND CARER ADVICE Patients should be advised on administration of gel.
- Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving).
Scalp and hair conditions

Overview
Dandruff is considered to be a mild form of seborrheic dermatitis. Shampoos containing antimicrobial agents such as pyrithione zine (which are widely available) and selenium below may have beneficial effects. Shampoos containing tar extracts may be useful and they are also used in psoriasis. Ketoconazole shampoo p. 1233 should be considered for more persistent or severe dandruff or for seborrheic dermatitis of the scalp.

Corticosteroid gels and lotions can also be used. Shampoos containing coal tar with salicylic acid p. 1255 may also be useful. A cream or an ointment containing coal tar with salicylic acid is very helpful in Psoriasis p. 1239 that affects the scalp. Patients who do not respond to these treatments may need to be referred to exclude the possibility of other skin conditions.

Cradle cap in infants may be treated with coconut oil or olive oil applications followed by shampooing.

Hirsutism
Hirsutism may result from hormonal disorders or as a side-effect of drugs such as minoxidil p. 1275, corticosteroids, anabolic steroids, androgens, danazol p. 742, and progestogens.

Weight loss can reduce hirsutism in obese women. Women should be advised about local methods of hair removal, and in the mildest cases this may be all that is required.

Ellorinethine p. 1275 an antiprotoseal coal, inhibits the enzyme ornithine decarboxylase in hair follicles. Topical ellorinethine can be used as an adjunct to laser therapy for facial hirsutism in women.

Co-cyprindiol p. 1267 may be effective for moderately severe hirsutism. Metformin hydrochloride p. 692 is an alternative in women with polycystic ovary syndrome [unlicensed indication]. Systemic treatment is required for 6–12 months before benefit is seen.

Androgenetic alopecia
Finasteride p. 787 is licensed for the treatment of androgenetic alopecia in men. Continuous use for 3–6 months is required before benefit is seen, and effects are reversed 6–12 months after treatment is discontinued.

Topical application of minoxidil may stimulate limited hair growth in a small proportion of adults but only for as long as it is used.

Other drugs used for Scalp and hair conditions
Coal tar,
p. 1253 - Coal tar with lecithin, p. 1254 - Coal tar with salicylic acid and precipitated sulfur, p. 1255

Cetrimide with undecenoic acid

INDICATIONS AND DOSE
Scalp psoriasis | Seborrhoeic dermatitis | Dandruff

TO THE SKIN
- Child: Apply 3 times a week for 1 week, then apply twice weekly
- Adult: Apply 3 times a week for 1 week, then apply twice weekly

MIRVASO®

INDICATIONS AND DOSE
Seborrhoeic scalp conditions associated with dandruff and scaling

TO THE SKIN
- Adult: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required
- Adult: Apply twice weekly for 2 weeks, then apply twice weekly for 2 weeks, then apply as required

VITAMINS AND TRACE ELEMENTS
Selenium

INDICATIONS AND DOSE
Seborrhoeic dermatitis | Dandruff

TO THE SKIN USING SHAMPOO
- Child 5–17 years: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required
- Adult: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required

TO THE SKIN USING SHAMPOO
- Adult: Apply once daily for 7 days, apply to the affected area and leave on for 10 minutes before rinsing off. The course may be repeated if necessary. Diluting with a small amount of water prior to application can reduce irritation

UNLICENSED USE
The use of selenium sulfide shampoo as a lotion for the treatment of pityriasis (tinea) versicolor is an unlicensed indication.

INTERACTIONS
Appendix 1: selenium

PATIENT AND CARER ADVICE
Avoid using 48 hours before or after applying hair colouring, straightening or waving preparations.
7.1 Alopecia

Other drugs used for Alopecia: Finasteride, p. 787

Vasodilators > Vasodilator Antihypertensives

Minoxidil

- Indications and Dose
  - **Regaine® for Men Extra Strength Foam**
    - Androgenetic alopecia
      - To the skin
      - Adult: Apply 0.5 capful twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 16 weeks
  - **Regaine® for Men Extra Strength Solution**
    - Androgenetic alopecia
      - To the skin
      - Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year
  - **Regaine® for Women Regular Strength**
    - Androgenetic alopecia
      - To the skin
      - Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year

- Contra-Indications: Phaeochromocytoma
- Cautions: Avoid contact with broken, infected, shaved, or inflamed skin; avoid contact with eyes; avoid contact with mouth; avoid contact with mucous membranes; avoid inhalation of spray mist; avoid occlusive dressings

CAUTIONS, FURTHER INFORMATION: When used topically systemic effects usually; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

- Interactions: Appendix 1: minoxidil
- Side-Effектs
  - Common or very common: Hair changes
  - Uncommon: Hypotension

SIDE-EFFECTS, FURTHER INFORMATION: When used topically systemic effects unlikely; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

- Pregnancy: Avoid—possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.
- Breast Feeding: Present in milk but not known to be harmful.
- Patient and Carer Advice: Ensure hair and scalp dry before application. Patients and their carers should be advised to wash hands after application of liquid or foam.

7.2 Hirsutism

Other drugs used for Hirsutism: Co-cyprindiol, p. 1267

Antiprotozoals

Eflo르nithine

- Drug Action: An antiprotozoal drug that inhibits the enzyme ornithine decarboxylase in hair follicles.

- Indications and Dose
  - Adjunct to laser therapy for facial hirsutism in women
    - To the skin
    - Adult: Apply twice daily, to be applied thinly, discontinue use if no improvement after 4 months of treatment

- Side-Effects
  - Common or very common: Alopecia - increased risk of infection - paraesthesia - skin reactions
  - Uncommon: Face oedema - flushing - hair changes - oral disorders - skin haemorrhage
  - Rare or very rare: Skin neoplasm

- Pregnancy: Toxicity in animal studies—manufacturer advises avoid.
- Breast Feeding: Manufacturer advises avoid—no information available.
- Patient and Carer Advice: Medicines must be rubbed in thoroughly. Cosmetics may be applied over treated area 5 minutes after eflo르nithine, do not wash treated area for 4 hours after application.

- National Funding/Access Decisions
  - Scottish Medicines Consortium (SMC) decisions
    - SMC No. 159/05
    - The Scottish Medicines Consortium has advised (September 2005) that eflo르nithine 11.5% cream (Vaniqua®) for facial hirsutism be restricted for use in women in whom alternative drug treatment cannot be used.

- Medicinal Forms: There can be variation in the licensing of different medicines containing the same drug.
8 Skin cleansers, antiseptics and desloughing agents

Skin cleansers, antiseptics and desloughing agents

Skin cleansers and antiseptics

Soap or detergent is used with water to cleanse intact skin; emollient preparations such as aqueous cream or emulsifying ointment can be used in place of soap or detergent for cleansing dry skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing chlorhexidine p. 1277 or povidone-iodine below, which should be thoroughly rinsed off, are used. Emollients may also contain antiseptics. Antiseptics such as chlorhexidine or povidone-iodine are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent. Antiseptic solutions containing cetrimide can be used if a detergent effect is also required.

Hydrogen peroxide p. 1278, an oxidising agent, can be used in solutions of up to 6% for skin disinfection, such as cleansing and deodorising wounds and ulcers. Hydrogen peroxide is also available as a cream for superficial bacterial skin infections.

For irrigating ulcers or wounds, lukewarm sterile sodium chloride 0.9% solution is used, but tap water is often appropriate. Potassium permanganate below solution 1 in 10 000, a mild antiseptic with astringent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry.

Desloughing agents

Alginate, hydrogel and hydrocolloid dressings are effective at wound debridement. Sterile larvae (maggots) (available from BioMonde) are also used for managing sloughing wounds and are prescribable on the NHS.

Desloughing solutions and creams are of little clinical value. Substances applied to an open area are easily absorbed and perilesional skin is easily sensitised. Gravitational dermatitis may be complicated by infections, particularly minor wounds and infections, and perivesical skin is easily sensitised. Features of acute alcohol intoxication include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Overdose Features of acute alcohol intoxication include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis.

Emergency treatment of poisoning

For details on the management of poisoning, see Alcohol, under Emergency treatment of poisoning p. 1359.

Antiseptics and disinfectants

Potassium permanganate

- **INDICATIONS AND DOSE**
  - Cleansing and deodorising suppurating eczematous reactions and wounds
    - TO THE SKIN
    - Adult: For wet dressings or baths, use approximately 0.01% (1 in 10 000) solution

- **CAUTIONS** Irritant to mucous membranes
- **DIRECTIONS FOR ADMINISTRATION** Potassium permanganate 0.1% solution to be diluted 1 in 10 to provide a 0.01% (1 in 10 000) solution. With potassium permanganate tablets for solution, 1 tablet dissolved in 4 litres of water provides a 0.01% (1 in 10 000) solution.
- **PATIENT AND CARER ADVICE** Can stain clothing, skin and nails (especially with prolonged use).

Antiseptics and disinfectants

Alcohol (Industrial methylated spirit)

- **INDICATIONS AND DOSE**
  - Skin preparation before injection
    - TO THE SKIN
    - Child: Apply as required
    - Adult: Apply as required

- **CONTRA-INDICATIONS** Neonates
- **CAUTIONS** Avoid broken skin - flammable - patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants

- **SIDE-EFFECTS**
  - Overdose
    - Features of acute alcohol intoxication include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis.
    - For details on the management of poisoning, see Alcohol, under Emergency treatment of poisoning p. 1359.

Antiseptics and disinfectants

Povidone-iodine

- **INDICATIONS AND DOSE**
  - Skin disinfection
    - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

Antiseptics and disinfectants

Potassium permanganate

- **INDICATIONS AND DOSE**
  - Cleansing and deodorising suppurating eczematous reactions and wounds
    - TO THE SKIN
    - Adult: For wet dressings or baths, use approximately 0.01% (1 in 10 000) solution
Skin cleansers, antiseptics and desloughing agents

VIDENE® SURGICAL SCRUB®

Skin disinfection
  TO THE SKIN
  Child: Use as a pre-operative scrub for hand and skin disinfection
  Adult: Use as a pre-operative scrub for hand and skin disinfection

VIDENE® TINCTURE

Skin disinfection
  TO THE SKIN
  Adult: Apply undiluted in pre-operative skin disinfection

CONTRA-INDICATIONS Avoid regular use in patients with thyroid disorders (in adults) - concomitant use of lithium - corrected gestational age under 32 weeks - infants body-weight under 1.5 kg - regular use in neonates

CAUTIONS Broken skin - large open wounds

Cautions, Further Information
  Large open wounds. The application of povidone-iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia and impairment of renal function.

VIDENE® TINCTURE Procedures involving hot wire cautery and diathermy

SIDE-EFFECTS
  Rare or very rare Eye erythema - punctate keratitis
  Frequency not known Cytotoxicity - eye discoloration
  PREGNANCY Sufficient iodine may be absorbed to affect the fetal thyroid in the second and third trimester.

BREAST FEEDING Avoid regular or excessive use.

RENAL IMPAIRMENT Avoid regular application to inflamed or broken skin or mucosa.

EFFECT ON LABORATORY TESTS May interfere with thyroid function tests.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

Spray
  Betadine (Aspire Pharma Ltd)
  Povidone-iodine 25 mg per 1 gram Betadine 2.5% dry powder spray | 100 ml | £9.95 DT + €9.95

Liquid

CAUTIONARY AND ADVISORY LABELS 15 (Only for use with alcoholic solutions)
  Videne (Ecolab Healthcare Division)
  Povidone-iodine 75% surgical scrub solution | 100 ml | £1.97 DT + €1.97
  Povidone-iodine 100% surgical scrub solution | 160 ml | £1.97 DT + €1.97

ANTISEPTICS AND DISINFECTANTS > OTHER

Chlorhexidine

INDICATIONS AND DOSE

CEPTON® LOTION

For skin disinfection in acne
  TO THE SKIN
  Child: (consult product literature)
  Adult: (consult product literature)

CEPTON® SKIN WASH

For use as skin wash in acne
  TO THE SKIN
  Child: (consult product literature)
  Adult: (consult product literature)

HIBITANE® PLUS 5% CONCENTRATE SOLUTION

General and pre-operative skin disinfection
  TO THE SKIN
  Child: (consult product literature)

HIBISCUB®

Pre-operative hand and skin disinfection | General hand and skin disinfection
  TO THE SKIN
  Child: Use as alternative to soap (consult product literature)
  Adult: Use as alternative to soap (consult product literature)

HIBITANE OBSTETRIC®

For use in obstetrics and gynaecology as an antiseptic and lubricant
  TO THE SKIN
  Adult: To be applied to skin around vulva and perineum and to hands of midwife or doctor

HIBI® LIQUID HAND RUB+

Hand and skin disinfection
  TO THE SKIN
  Child: To be used undiluted (consult product literature)
  Adult: To be used undiluted (consult product literature)

HYDREX® SOLUTION

For pre-operative skin disinfection
  TO THE SKIN
  Child: (consult product literature)
  Adult: (consult product literature)

HYDREX® SURGICAL SCRUB

For pre-operative hand and skin disinfection | General hand disinfection
  TO THE SKIN
  Child: (consult product literature)
  Adult: (consult product literature)

UNISEPT®

For cleansing and disinfecting wounds and burns and swabbing in obstetrics
  TO THE SKIN
  Child: (consult product literature)
  Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION

In preterm neonates, use sparingly, monitor for skin reactions, and do not allow solution to pool - risk of severe chemical burns.

CONTRA-INDICATIONS Alcoholic solutions not suitable before diathermy - not for use in body cavities

CAUTIONS Avoid contact with brain - avoid contact with eyes - avoid contact with meninges - avoid contact with middle ear

SIDE-EFFECTS Skin reactions

DIRECTIONS FOR ADMINISTRATION

HIBITANE® PLUS 5% CONCENTRATE SOLUTION For pre-operative skin preparation, dilute 1 in 10 (0.5%) with alcohol 70%. For general skin disinfection, dilute 1 in 100 (0.05%) with water. Alcoholic solutions not suitable for use before diathermy or on neonatal skin.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Cream
  Hibitane Obstetric (Derma UK Ltd)
  Chlorhexidine gluconate 10 mg per 1 gram Hibitane Obstetric 1% cream | 250 ml | £16.95
Chlorhexidine with cetrimide

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1277.

### INDICATIONS AND DOSE

**Skin disinfection such as wound cleansing and obstetrics**
- **TO THE SKIN**
  - Child: To be used undiluted
  - Adult: To be used undiluted

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- Chlorhexidine with cetrimide (Non-proprietary)
  - Chlorhexidine gluconate 1 mg per 1 gram, Cetrimide 5 mg per 1 gram
    - Savlon antiseptic cream
    - 15 gram [GSL £0.90]
  - 30 gram [GSL £1.19] 60 gram [GSL £1.91] 100 gram [GSL £2.78]

**Irrigation solution**
- Chlorhexidine with cetrimide (Non-proprietary)
  - Chlorhexidine acetate 150 microgram per 1 ml, Cetrimide 1.5 mg per 1 ml
    - Sterets Unisept 0.15% irrigation solution 1 litre bottles
      - 1 bottle [P]
  - Sterets Tisept
    - Chlorhexidine gluconate 150 microgram per 1 ml, Cetrimide 1.5 mg per 1 ml
      - Sterets Tisept solution 25ml sachets
      - 25 sachet [P] £5.33 DT = £5.33
      - Sterets Tisept solution 100ml sachets
      - 10 sachet [P] £6.85 DT = £6.85

## Diethyl phthalate with methyl salicylate

### INDICATIONS AND DOSE

**Skin preparation before injection**
- **TO THE SKIN**
  - Adult: Apply to the area to be disinfected

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**
- Diethyl phthalate with methyl salicylate (Non-proprietary)
  - Methyl salicylate 5 ml per 1 litre, Diethyl phthalate 20 ml per 1 litre, Castor oil 25 ml per 1 litre, Industrial methylated spirit
    - 950 ml per 1 litre
    - Surgical spirit
      - 200 ml [GSL £1.17 DT = £1.17]
      - 1000 ml [GSL £3.95]

## Hydrogen peroxide

### DRUG ACTION

Hydrogen peroxide is an oxidising agent.

### INDICATIONS AND DOSE

For skin disinfection, particularly cleansing and deodorising wounds and ulcers
- **TO THE SKIN**
  - Child: Apply 2–3 times a day for up to 3 weeks
  - Adult: Apply 2–3 times a day for up to 3 weeks

### UNLICENSED USE

In children licensed for use in children (age range not specified by manufacturer).

### CONTRA-INDICATIONS

Closed body cavities (in adults) - deep wounds (in adults) - large wounds (in adults) - use as
disinfection agent for surgical instruments (in adults) - use as enema (in adults) - use during surgery (in adults)

- **CAUTIONS** Avoid on eyes - avoid on healthy skin - incompatible with products containing iodine or potassium permanganate
- **PRESCRIBING AND DISPENSING INFORMATION** The BP directs that when hydrogen peroxide is prescribed, hydrogen peroxide solution 6% (20 vols) should be dispensed. Strong solutions of hydrogen peroxide which contain 27% (90 vols) and 30% (100 vols) are only for the preparation of weaker solutions.
- **HANDLING AND STORAGE** Hydrogen peroxide bleaches fabric.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Cream**

- **Crystacide** (Reig Jofre UK Ltd)
  - Hydrogen peroxide 10 mg per 1 gram Crystacide 1% cream | 25 gram | £8.07 DT | £8.07 | 40 gram | £11.62

**Liquid**

- **Hydrogen peroxide (Non-proprietary)**
  - Hydrogen peroxide 60 mg per 1 ml Hydrogen peroxide 6% solution | 200 ml | £0.67 | 500 ml | £1.92 | 2000 ml | £9.33
  - Hydrogen peroxide 90 mg per 1 ml Hydrogen peroxide 9% solution | 200 ml | £0.72
  - Hydrogen peroxide 30 ml per 1 litre Hydrogen peroxide 3% solution | 200 ml | £0.63

- **Proflavine**

  - **INDICATIONS AND DOSE**
    - Infected wounds / infected burns
    - Adults: (consult product literature)

  - **PATIENT AND CARER ADVICE** Stains clothing.

- **MEDICINAL FORMS** Forms available from special-order manufacturers include: liquid

**Irrigation solutions**

- **IRRIGATION SOLUTIONS**
  - Flowfusor sodium chloride 0.9% irrigation solution 120ml bottles (Frenius Kabi Ltd) Sodium chloride 9 mg per 1 ml bottle - NHS indicative price = £1.71 - Drug Tariff (Part Ixa)
  - Irriclens sodium chloride 0.9% irrigation solution aerosol spray (Convatec Ltd) Sodium chloride 9 mg per 1 ml 240 ml - NHS indicative price = £3.60 - Drug Tariff (Part Ixa)
  - Normasol sodium chloride 0.9% irrigation solution 100ml sachets (Molnlycke Health Care Ltd) Sodium chloride 9 mg per 1 ml 10 unit dose - NHS indicative price = £7.97 - Drug Tariff (Part Ixa)
  - Normasol sodium chloride 0.9% irrigation solution 25ml sachets (Molnlycke Health Care Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £6.46 - Drug Tariff (Part Ixa)
  - Sodium chloride 0.9% irrigation solution 20ml Clinipod unit dose (Mayors Healthcare Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.80 - Drug Tariff (Part Ixa)
  - Sodium chloride 0.9% irrigation solution 20ml ISO-POD unit dose (St George’s Medical Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.95 - Drug Tariff (Part Ixa)
  - Sodium chloride 0.9% irrigation solution 20ml Irripod unit dose (Emrosh Healthcare Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.90 - Drug Tariff (Part Ixa)

- **Sodium chloride 0.9% irrigation solution 20ml Sal-e Pods unit dose** (Emrosh Healthcare Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.80 - Drug Tariff (Part Ixa)

- **Sodium chloride 0.9% irrigation solution 20ml unit dose** (Sal-Meds Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.99 - Drug Tariff (Part Ixa)
- **Sodium chloride 0.9% irrigation solution 20ml Steripod unit dose** (Molnlycke Health Care Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £7.06 - Drug Tariff (Part Ixa)
- **Sodium chloride 0.9% irrigation solution 20ml Sterowash unit dose** (Steroplast Healthcare Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £7.36 - Drug Tariff (Part Ixa)
- **Sodium chloride 0.9% irrigation solution 20ml unit dose** (Bell, Sons & Co (Druggists) Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £6.76 - Drug Tariff (Part Ixa)
- **Sodium chloride 0.9% irrigation solution 20ml unit dose** (Crest Medical Ltd) Sodium chloride 9 mg per 1 ml 25 unit dose - NHS indicative price = £4.99 - Drug Tariff (Part Ixa)
- **Stericlens sodium chloride 0.9% irrigation solution aerosol spray** (C D Medical Ltd) Sodium chloride 9 mg per 1 ml 200 ml - NHS indicative price = £2.07 - Drug Tariff (Part Ixa)

- **NHS indicative price = £3.15 - Drug Tariff (Part Ixa)**

### 8.1 Minor cuts and abrasions

#### Minor cuts and abrasions

**Management**

Many preparations traditionally used to manage minor burns, and abrasions have fallen out of favour. Preparations containing camphor and sulphonamides should be avoided. Preparations such as magnesium sulfate paste are now rarely used to treat carbuncles and boils as these are best treated with antibiotics.

Cetrimide is used to treat minor cuts and abrasions and proflavine above may be used to treat infected wounds or burns, but its use has now been largely superseded by other antiseptics or suitable antibacterials. The effervescent effect of hydrogen peroxide per. 1278 is used to clean minor cuts and abrasions.

Flexible collodion (see castor oil with collodion and clophophy, p. 1280) may be used to seal minor cuts and wounds that have partially healed; skin tissue adhesives are used similarly, and also for additional suture support.

#### Glycerol with magnesium sulfate and phenol

- **INDICATIONS AND DOSE**
  - Treat carbuncles and boils
  - To the skin
  - Adult: To be applied under dressing

- **DIRECTIONS FOR ADMINISTRATION** Paste should be stirred before use.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Paste**

- Glycerol with magnesium sulfate and phenol (Non-proprietary)
  - Phenol 5 mg per 1 gram, Magnesium sulfate dried 450 mg per 1 gram
  - Glycerol 550 mg per 1 gram Magnesium sulfate paste | 25 gram | £0.16–£1.24 | 50 gram | £0.91–£2.48 DT = £2.48
9 Skin disfigurement

Camouflagers

Overview
Disfigurement of the skin can be very distressing to patients and may have a marked psychological effect. In skilled hands, or with experience, camouflage cosmetics can be very effective in concealing scars and birthmarks. The depigmented patches in vitiligo are also very disfiguring and camouflage creams are of great cosmetic value.

Opaque cover foundation or cream is used to mask skin pigment abnormalities; careful application using a combination of dark- and light-coloured cover creams set with powder helps to minimise the appearance of skin deformities.

Borderline substances
The preparations marked ‘ACBS’ can be prescribed on the NHS for postoperative scars and other deformities and as adjunctive therapy in the relief of emotional disturbances due to disfiguring skin disease, such as vitiligo.

10 Sun protection and photodamage

Sunscreen

Sunscreen preparations
Solar ultraviolet irradiation can be harmful to the skin. It is responsible for disorders such as polymorphic light eruption, solar urticaria, and it provokes the various cutaneous porphyrias. It also provokes (or at least aggravates) skin lesions of lupus erythematosus and may aggravate rosacea and some other dermatoses. Certain drugs, such as demeclocycline, phenothiazines, or amiodarone, can cause photosensitivity. All these conditions (as well as sunburn) may occur after relatively short periods of exposure to the sun. Solar ultraviolet irradiation may provoke attacks of recurrent herpes labialis (but it is not known whether the effect of sunlight exposure is local or systemic).

The effects of exposure over longer periods include ageing changes and more importantly the initiation of skin cancer.

Solar ultraviolet radiation is approximately 200–400 nm in wavelength. The medium wavelengths (290–320 nm, known as UVB) cause sunburn. The long wavelengths (320–400 nm, known as UVA) are responsible for many photosensitivity reactions and photodermatoses. Both UVA and UVB contribute to long-term photodamage and to the changes responsible for skin cancer and ageing.

Sunscreen preparations contain substances that protect the skin against UVA and UVB radiation, but they are no substitute for covering the skin and avoiding sunlight. The sun protection factor (SPF, usually indicated in the preparation title) provides guidance on the degree of...
 protección offered against UVB; it indicates the multiples of protection provided against burning, compared with unprotected skin; for example, an SPF of 8 should enable a person to remain 8 times longer in the sun without burning. However, in practice, users do not apply sufficient sunscreen product and the protection is lower than that found in experimental studies.

Some manufacturers use a star rating system to indicate the protection against UVA relative to protection against UVB for sunscreen products. However, the usefulness of the star rating system remains controversial. The EU Commission (September 2006) has recommended that the UVA protection factor for a sunscreen should be at least one-third of the sun protection factor (SPF); products that achieve this requirement will be labelled with a UVA logo alongside the SPF classification. Preparations that also contain reflective substances, such as titanium dioxide, provide the most effective protection against UVA.

Sunscreen preparations may rarely cause allergic reactions. For optimum photoprotection, sunscreen preparations should be applied thickly and frequently (approximately 2 hourly). In photodermatoses, they should be used from spring to autumn. As maximum protection from sunlight is desirable, preparations with the highest SPF should be prescribed.

### Ingredient nomenclature in sunscreen preparations

<table>
<thead>
<tr>
<th>rINN</th>
<th>INCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiloxate</td>
<td>isomethyl p-methoxycinnamate</td>
</tr>
<tr>
<td>avobenzone</td>
<td>butyl methoxydibenzoylmethane</td>
</tr>
<tr>
<td>bemotrizol</td>
<td>bis-ethylhexyloxyphenol methoxyphenyl triazine</td>
</tr>
<tr>
<td>bisocristole</td>
<td>methylene bis-benzotriazolyl tetramethylbutylphenol</td>
</tr>
<tr>
<td>ecamsule</td>
<td>terephthalyldene dicamphor sulfonic acid</td>
</tr>
<tr>
<td>ensulizole</td>
<td>phenylbenzimidazole sulfinic acid</td>
</tr>
<tr>
<td>enzacamene</td>
<td>4-methylbenzylidene camphor</td>
</tr>
<tr>
<td>octinoxate</td>
<td>octyl (or ethylhexyl) methoxyphenyl triamine</td>
</tr>
<tr>
<td>octocrylene</td>
<td>octocrylene</td>
</tr>
<tr>
<td>oxybenzone</td>
<td>benzophenone-3</td>
</tr>
</tbody>
</table>

The European Commission Cosmetic Products Regulation (EC) 1223/2009 requires the use of INCI (International Nomenclature of Cosmetic Ingredients) for cosmetics and sunscreens. This table includes the rINN and the INCI synonym for the active ingredients of sunscreen preparations in the BNF.

### Borderline substances

*Anthelios®* XL SPF 50+ Melt-in cream; *Sunsense®* Ultra; *Uvistar®* Lipscreen SPF 50; and *Uvistar®* Suncream SPF 30 and 50 (see Borderline substances) are regarded as drugs when prescribed for skin protection against ultraviolet radiation in abnormal cutaneous photosensitivity. Preparations with SPF less than 30 should not normally be prescribed.

### Photodamage

#### Overview

Patients should be advised to use a high-SPF sunscreen and to minimise exposure of the skin to direct sunlight or sun lamps.

Topical treatments can be used for actinic keratosis. An emollient may be sufficient for mild lesions. Diclofenac sodium gel below is suitable for the treatment of superficial lesions in mild disease. Fluorouracil cream p. 1282 is effective against most types of non-hypertrophic actinic keratosis, a solution containing fluorouracil with salicylic acid p. 1282 is available for the treatment of low or moderately thick hyperkeratotic actinic keratosis. Imiquimod p. 1285 is used for lesions on the face and scalp when cryotherapy or other topical treatments cannot be used. Fluorouracil and imiquimod produce a more marked inflammatory reaction than diclofenac sodium but lesions resolve faster. A short course of ingenol mebutate p. 1282 is licensed for the treatment of non-hypertrophic actinic keratosis; response to treatment can usually be assessed 8 weeks after the course. Photodynamic therapy in combination with methyl-5-aminolevulinate cream (Metvix®, available from Galderma) or 5-aminolaevulnic acid gel (Ameluz®, available from Spirit Healthcare) is used in specialist centres for treating superficial and confluent, non-hypertrophic actinic keratosis when other treatments are inadequate or unsuitable; it is particularly suitable for multiple lesions, for periorbital lesions, or for lesions located at sites of poor healing. Imiquimod or topical fluorouracil is used for treating superficial basal cell carcinomas. Photodynamic therapy in combination with methyl-5-aminolevulinate cream is used in specialist centres for treating superficial, nodular basal cell carcinomas when other treatments are unsuitable.

### ANALGESICS > NON-Steroidal ANTI-INFLAMMATORY DRUGS

#### Diclofenac sodium

**INDICATIONS AND DOSE**

**SOLARAZE®**

**Actinic keratosis**

- **TO THE SKIN**
- **Adult:** Apply twice daily for 60–90 days, to be applied thinly; maximum 8 g per day
- **INTERACTIONS**
- **Common or very common** Conjunctivitis - muscle tone increased - oedema - rash (discontinue) - sensation abnormal - skin reactions - skin ulcer
- **Uncommon** Abdominal pain - alopecia - diarrhoea - eye pain - haemorrhage - lacrimation disorder - nausea - seborrhoea
- **Rare or very rare** Acute kidney injury - asthma - hypersensitivity - photosensitivity reaction - rash pustular
- **Frequency not known** Hair colour changes

**SIDE-EFFECTS. FURTHER INFORMATION**

Topical application of large amounts of diclofenac can result in systemic effects.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**PREGNANCY** Patient packs for topical preparations carry a warning to avoid during pregnancy.

**BREAST FEEDING** Patient packs for topical preparations carry a warning to avoid during breast-feeding.
**1282 Sun protection and photodamage**

**DIRECTIONS FOR ADMINISTRATION** For topical preparations, apply with gentle massage only.

**PATIENT AND CARER ADVICE** For topical preparations, patients and their carers should be advised to wash hands immediately after use. Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Gel**
- **Excipients**: May contain Benzyl alcohol, fragrances, propylene glycol
- **Solaraze** (Almirall Ltd)
  - Diclofenac sodium 30 mg per 1 gram Solaraze 3% gel | 50 gram [POM] £36.30 DT = £36.30 | 100 gram [POM] £76.60

**SIDE-EFFECTS**
- **Common or very common**: Alopecia - diarrhoea - mucositis - nausea - neutropenia - skin reactions - stomatitis - thrombocytopenia - vomiting
- **Uncommon**: Dizziness - headache
- **Rare or very rare**: Abdominal pain - chills - diarrhoea - haemorrhagic fever - leucocytosis - pancytopenia - skin irritation (use a topical corticosteroid for severe discomfort associated with inflammatory reactions) - skin ulcer
- **Frequency not known**: Conjunctival irritation - excessive tearing - ketariosis - taste altered
- **Conception and contraception**: Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 888.
- **Pregnancy**: Manufacturers advise avoid (teratogenic).
- **Breast feeding**: Manufacturers advise avoid.
- **Handling and storage**: Caution in handling—irritant to tissues.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- **Excipients**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates, propylene glycol
- **Efudix** (Meda Pharmaceuticals Ltd)
  - Fluorouracil 50 mg per 1 gram Efudix 5% cream | 40 gram [POM] £32.90 DT = £32.90

**Fluorouracil with salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluorouracil above, salicylic acid p. 1286.

**INDICATIONS AND DOSE**

**Low or moderately thick hyperkeratotic actinic keratosis**
- **To the skin**
  - **Adult**: Apply once daily for up to 12 weeks, reduced to 3 times a week if severe side effects occur and until side-effects improve, to be applied to the affected area, if treating area with thin epidermis, reduce frequency of application and monitor response more often; maximum area of skin treated at one time, 25 cm² (e.g. 5 cm × 5 cm)

**INTERACTIONS** → Appendix 1: fluorouracil

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Actikerall solution**
- **CAUTIONARY AND ADVISORY LABELS**: 15
- **Fluorouracil 5 mg/g, Salicylic acid 100 mg/g Actikerall 5mg/g / 100mg/g cutaneous solution** | 25 ml [POM] £38.30 DT = £38.30

**PROTEIN KINASE C ACTIVATORS**

**Ingenol mebutate**

**INDICATIONS AND DOSE**

**Actinic keratosis on face and scalp**
- **To the skin**
  - **Adult**: Apply once daily for 3 days, use the 150 microgram/g gel

**Actinic keratosis on trunk and extremities**
- **To the skin**
  - **Adult**: Apply once daily for 2 days, use the 500 microgram/g gel

**CAUTIONS**
- Avoid contact with broken skin - avoid contact with eyes - avoid contact with inside of ears - avoid contact with inside of nostrils - avoid contact with lips - avoid occlusive dressings on treated area

**SIDE-EFFECTS**
- **Common or very common**: Headache - infection - local reaction - oedema - pain - skin reactions
- **Uncommon**: Parasthesia - skin ulcer
- **Pregnancy**: Not absorbed from skin, but manufacturer advises avoid.
- **Breast feeding**: Not absorbed from skin; ensure infant does not come in contact with treated area for 6 hours after application.

**DIRECTIONS FOR ADMINISTRATION** One tube covers skin area of 25 cm². Allow gel to dry on treatment area for 15 minutes. Avoid washing or touching the treated area for 6 hours after application; after this time, area may be washed with mild soap and water. Avoid use immediately after shower or less than 2 hours before bedtime.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Gel**
- **CAUTIONARY AND ADVISORY LABELS**: 15
- **Excipients**: May contain Benzyl alcohol
- **Picato** (LEO Pharma)
  - **Ingenol mebutate 150 microgram per 1 gram Picato 150micrograms/g gel | 1.41 gram [POM] £65.00 DT = £65.00**
  - **Ingenol mebutate 500 microgram per 1 gram Picato 500micrograms/g gel | 0.94 gram [POM] £65.00 DT = £65.00**
11 Superficial soft-tissue injuries and superficial thrombophlebitis

Topical circulatory preparations

Overview
These preparations are used to improve circulation in conditions such as bruising, superficial thrombophlebitis, chilblains and varicose veins but are of little value. Chilblains are best managed by avoidance of exposure to cold; neither systemic nor topical vasodilator therapy is established as being effective.

HEPARINOIDS

Heparinoid

- INDICATIONS AND DOSE
  Superficial thrombophlebitis | Bruising | Haematoma
  - TO THE SKIN
  - Adult: Apply up to 4 times a day

- CONTRA-INDICATIONS
  Should not be used on large areas of skin, broken or sensitive skin, or mucous membranes

- LESS SUITABLE FOR PRESCRIBING
  Hirudoid is less suitable for prescribing.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  **Cream**
  **EXCIPIENTS**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens)
  **Hirudoid (Genus Pharmaceuticals Ltd)**
  Heparinoid 3 mg per 1 gram Hirudoid 0.3% cream | 50 gram
  £3.99 DT = £3.99

- Gel
  **EXCIPIENTS**: May contain Fragrances, propylene glycol
  **Hirudoid (Genus Pharmaceuticals Ltd)**
  Heparinoid 3 mg per 1 gram Hirudoid 0.3% gel | 50 gram
  £3.99 DT = £3.99

12 Warts and calluses

Warts and calluses

Overview
Warts (verrucas) are caused by a human papillomavirus, which most frequently affects the hands, feet (plantar warts), and the anogenital region; treatment usually relies on local tissue destruction. Warts may regress on their own and treatment is required only if the warts are painful, unsightly, persistent, or cause distress.

Preparations of salicylic acid p. 1286, formaldehyde p. 1284, glutaraldehyde p. 1284 or silver nitrate p. 1285 are available for purchase by the public; they are suitable for the removal of warts on hands and feet. Salicylic acid is a useful keratolytic which may be considered first-line; it is also suitable for the removal of corns and calluses. Preparations of salicylic acid in a collodion base are available but some patients may develop an allergy to colophony in the formulation; collodion should be avoided in children allergic to elastic adhesive plaster. Cryotherapy causes pain, swelling, and blistering, and may be no more effective than topical salicylic acid in the treatment of warts.

Anogenital warts
The treatment of anogenital warts (condylomata acuminata) should be accompanied by screening for other sexually transmitted infections. Podophyllotoxin p. 1284 (the major active ingredient of podophylum) may be used for soft, non-keratinised external anogenital warts. Patients with a limited number of external warts or keratinised lesions may be better treated with cryotherapy or other forms of physical ablation.

Imiquimod cream p. 1285 is licensed for the treatment of external anogenital warts; it may be used for both keratinised and non-keratinised lesions. It is also licensed for the treatment of superficial basal cell carcinoma and actinic keratosis. Camellia sinensis ointment below is licensed for the treatment of external anogenital warts.

Inosine pranobex p. 633 is licensed for adjunctive treatment of genital warts but it has been superseded by more effective drugs.

ANTINEOPLASTIC DRUGS > PLANT ALKALOIDS

**Camellia sinensis**

- **DRUG ACTION**
  Camellia sinensis is an extract from green tea leaves. The exact mechanism of action is not known; non-clinical studies have shown inhibition of the growth of activated keratinocytes, and anti-oxidative effects at the site of application.

- **INDICATIONS AND DOSE**
  Warts (external genital and perianal) in immunocompetent patients
  - TO THE LESION
  - Adult: Apply up to 250 mg 3 times a day until complete clearance of warts (maximum 16 weeks), do not exceed treatment period even if new warts develop; maximum 750 mg per day

  DOSE EQUIVALENCE AND CONVERSION
  - 250 mg is equivalent to 0.5 cm of ointment.

  **CAUTIONS**
  - Avoid broken skin
  - Avoid contact with eyes
  - Avoid contact with lips
  - Avoid contact with mouth
  - Avoid contact with nostrils
  - Avoid inflamed skin
  - Uncircumcised males (risk of phimosis)
  - Vulvar region

  **SIDE-EFFECTS**
  - **Uncommon**
    - Balanoposthitis
    - Increased risk of infection
    - Lymphatic abnormalities
    - Necrosis
    - Painful sexual intercourse
    - Phimosis
    - Skin reactions
    - Urinary disorders
  - **Frequency not known**
    - Urinary tract stenosis
    - Vaginal discharge

  **CONCEPTION AND CONTRACEPTION**
  Manufacturer advises Catephen may weaken condoms and vaginal diaphragms—alternative methods of contraception should be considered.

  **PREGNANCY**
  Manufacturer advises avoid—toxicity in animal studies.

  **BREAST FEEDING**
  Manufacturer advises risk to infant cannot be excluded—no information available.

  **HEPATIC IMPAIRMENT**
  Manufacturer advises avoid in severe impairment (limited information available).

  **DIRECTIONS FOR ADMINISTRATION**
  Manufacturer advises apply to each wart, ensuring a thin layer is left on the wart.

  **NATIONAL FUNDING/ACCESS DECISIONS**
  **Scottish Medicines Consortium (SMC) decisions**
  The Scottish Medicines Consortium has advised (April 2016) that camellia sinensis (green tea) leaf extract (Catephen®)
is accepted for restricted use within NHS Scotland for the treatment of external genital and perianal warts in patients not suitable for podophyllotoxin or who have not responded to treatment with podophyllotoxin.

**All Wales Medicines Strategy Group (AWMSG) decisions**

The All Wales Medicines Strategy Group has advised (October 2016) that green tea leaf extract (camellia sinensis), (Catephen \(^{\text{®}}\)), is recommended for restricted use within NHS Wales for the treatment of external genital and perianal warts in patients not suitable for podophyllotoxin or who have not responded to treatment with podophyllotoxin.

### Podophyllotoxin

**INDICATIONS AND DOSE**

**CONDYLONE**

*Condyloma acuminata affecting the penis or the female external genitalia*

- **TO THE LESION**
  - Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of five 3-day treatment courses, direct medical supervision for lesions in the female and for lesions greater than 4 cm\(^2\) in the male, maximum 50 single applications (‘loops’) per session (consult product literature)

**WARTICON \(^{\text{®}}\) CREAM**

*Condyloma acuminata affecting the penis or the female external genitalia*

- **TO THE LESION**
  - Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses, direct medical supervision for lesions greater than 4 cm\(^2\)

**WARTICON \(^{\text{®}}\) LIQUID**

*Condyloma acuminata affecting the penis or the female external genitalia*

- **TO THE LESION**
  - Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses, direct medical supervision for lesions greater than 4 cm\(^2\), maximum 50 single applications (‘loops’) per session (consult product literature)

**CAUTIONS**

Avoid normal skin. Avoid open wounds. Keep away from face. Very irritant to eyes.

**SIDE-EFFECTS**

Balanoposthitis. Skin irritation.

**PREGNANCY**

Avoid.

**BREAST FEEDING**

Avoid.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), sorbic acid

- **Wartinon** (Phoenix Labs Ltd)
  - Podophyllotoxin 1.5 mg per 1 gram Wartinon 0.15% cream | 5 gram £17.83

**Liquid**

CAUTIONARY AND ADVISORY LABELS

- **Condylone** (Takeda UK Ltd)
  - Podophyllotoxin 5 mg per 1 ml Condylone 0.5% solution | 3.5 ml £14.49 DT = £14.49
  - Wartinon (Phoenix Labs Ltd)
  - Podophyllotoxin 5 mg per 1 ml Wartinon 0.5% solution | 3 ml £14.86

**ANTISEPTICS AND DISINFECTANTS**

### Formaldehyde

**INDICATIONS AND DOSE**

*Warts, particularly plantar warts*

- **TO THE LESION**
  - Child: Apply twice daily
  - Adult: Apply twice daily

**UNLICENSED USE**

In children. Licensed for use in children (age range not specified by manufacturer).

**CAUTIONS**

Impaired peripheral circulation. Not suitable for application to anogenital region. Not suitable for application to face. Not suitable for application to large areas. Patients with diabetes at risk of neuropathic ulcers. Protect surrounding skin and avoid broken skin. Significant peripheral neuropathy.

**SIDE-EFFECTS**


**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Glutaraldehyde**

**INDICATIONS AND DOSE**

*Warts, particularly plantar warts*

- **TO THE LESION**
  - Child: Apply twice daily
  - Adult: Apply twice daily

**UNLICENSED USE**

In children. Licensed for use in children (age range not specified by manufacturer).

**CAUTIONS**

Not for application to anogenital areas. Not for application to face. Not for application to mucosa. Protect surrounding skin.

**SIDE-EFFECTS**

Rare or very rare. Severe cutaneous adverse reactions (SCARs).

**FREQUENCY NOT KNOWN**

Rash. Skin irritation. (Discontinue if severe)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Paint**

- **Glutarol** (Dermal Laboratories Ltd)
  - Glutaraldehyde 100 mg per 1 ml Glutarol 10% cutaneous solution | 10 ml £14.59 DT = £2.07
ANTISEPTICS AND DISINFECTANTS › OTHER

Silver nitrate

- INDICATIONS AND DOSE
  Common warts
    - TO THE LESION
      - Child: Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
      - Adult: Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
  Verrucas
    - TO THE LESION
      - Child: Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
      - Adult: Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
  Umbilical granulomas
    - TO THE SKIN
      - Child: Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin
      - Adult: Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin

- UNLICENSED USE
  - In children: No age range specified by manufacturer.
  - CAUTIONS
    - Avoid broken skin - not suitable for application to ano-genital region - not suitable for application to face - not suitable for application to large areas - protect surrounding skin
  - SIDE-EFFECTS
    - Rare or very rare: Argyria - methaemoglobinemia
  - PATIENT AND CARER ADVICE
    - Patients should be advised that silver nitrate may stain fabric.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Stick
    - Avoca (Bray Group Ltd)
      - Silver nitrate 400 mg per 1 gram: Avoca 40% silver nitrate pencils | 1 applicator [P] £1.13 DT = £1.13
      - Silver nitrate 750 mg per 1 gram: Avoca 75% silver nitrate applicators | 100 applicator [P] £47.82
      - Avoca 75% silver nitrate applicators with thick handles | 50 applicator [P] £47.19
      - Silver nitrate 950 mg per 1 gram: Avoca 95% silver nitrate applicators | 100 applicator [P] £51.17
      - Avoca 95% silver nitrate pencils | 1 applicator [P] £2.56 DT = £3.08
      - Avoca wart and verruca treatment set | 1 applicator [P] £3.08 DT = £3.08

ANTIVIRALS › IMMUNE RESPONSE MODIFIERS

Imiquimod

- INDICATIONS AND DOSE
  ALDARA ®
  Warts (external genital and perianal)
    - TO THE LESION
      - Adult: Apply 3 times a week until lesions resolve (maximum 16 weeks), to be applied thinly at night
  Superficial basal cell carcinoma
    - TO THE LESION
      - Adult: Apply daily for 5 nights of each week for 6 weeks, to be applied to lesion and 1 cm beyond it, assess response 12 weeks after completing treatment
  Actinic keratosis
    - TO THE LESION
      - Adult: Apply 3 times a week for 4 weeks, to be applied to lesion at night, assess response after a 4 week treatment-free interval; repeat 4-week course if lesions persist, maximum 2 courses
  ZYCLARA ™
  Actinic keratosis
    - TO THE SKIN
      - Adult: Apply once daily for 2 weeks, to be applied at bedtime to lesion on face or balding scalp, repeat course after a 2-week treatment-free interval, assess response 8 weeks after second course; maximum 2 sachets per day

- CAUTIONS
  - Autoimmune disease - avoid broken skin - avoid contact with eyes - avoid contact with lips - avoid contact with nostrils - avoid open wounds - immunosuppressed patients - not suitable for internal genital warts - uncircumcised males (risk of phimosis or stricture of foreskin)
  - SIDE-EFFECTS
    - Common or very common: Appetite decreased - arthralgia - asthenia - headaches - increased risk of infection - lymphadenopathy - myalgia - nausea - pain
    - Rare or very rare: Autoimmune disorder exacerbated
    - Frequency not known: Alopecia - cutaneous lupus erythematosus - severe cutaneous adverse reactions (SCARs)
  - CONCEPTION AND CONTRACEPTION
    - May damage latex condoms and diaphragms.
  - PREGNANCY
    - No evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution.
  - BREAST FEEDING
    - No information available.
  - DIRECTIONS FOR ADMINISTRATION
    - ZYCLARA ™: Important Should be rubbed in and allowed to stay on the treated area for 8 hours, then washed off with mild soap and water.
    - ALDARA ®: Important Should be rubbed in and allowed to stay on the treated area for 6–10 hours for warts or for 8 hours for basal cell carcinoma and actinic keratosis, then washed off with mild soap and water (uncircumcised males treating warts under foreskin should wash the area daily). The cream should be washed off before sexual contact.
Salicylic acid with lactic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid above.

### INDICATIONS AND DOSE

**CUPLEX®**

**Plantar and mosaic warts | Corns | Calluses**

- **TO THE LESION**
  - **Child:** Apply once daily, treatment may need to be continued for up to 3 months
  - **Adult:** Apply once daily, treatment may need to be continued for up to 3 months

**DUOFILM®**

**Plantar and mosaic warts**

- **TO THE LESION**
  - **Adult:** Apply daily, treatment may need to be continued for up to 3 months
  - **SALACTOL®**

**Warts, particularly plantar warts | Verrucas | Corns | Calluses**

- **TO THE LESION**
  - **Adult:** Apply daily, treatment may need to be continued for up to 3 months

**SALATAC®**

**Warts | Verrucas | Corns | Calluses**

- **TO THE LESION**
  - **Adult:** Apply daily, treatment may need to be continued for up to 3 months

### PRESCRIBING AND DISPENSING INFORMATION

Preparations of salicylic acid in a collodion basis (Cuplex® and Salactol®) are available but some patients may develop an allergy to colophony in the formulation.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Paint

**CAUTIONARY AND ADVISORY LABELS** 15

- **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates
  - **Aldara®** (Meda Pharmaceuticals Ltd)
    - Imiquimod 50 mg per 1 gram Aldara 5% cream 250mg sachets | 12 sachet £46.60 DT + £46.60
  - **Zyclara®** (Meda Pharmaceuticals Ltd)
    - Imiquimod 37.5 mg per 1 gram Zyclara 3.75% cream 250mg sachets | 28 sachet £54.75 DT + £54.75

### SALICYLIC ACID AND DERIVATIVES

#### Salicylic acid

**INDICATIONS AND DOSE**

**OCCLUSAL®**

**Common and plantar warts**

- **TO THE LESION**
  - **Child:** Apply daily, treatment may need to be continued for up to 3 months
  - **Adult:** Apply daily, treatment may need to be continued for up to 3 months

**VERRUGON®**

**For plantar warts**

- **TO THE LESION**
  - **Child:** Apply daily, treatment may need to be continued for up to 3 months
  - **Adult:** Apply daily, treatment may need to be continued for up to 3 months

### UNLICENSED USE

- **In children** Not licensed for use in children under 2 years.
- **CAUTIONS** Avoid broken skin - impaired peripheral circulation - not suitable for application to anogenital region - not suitable for application to face - not suitable for application to large areas - patients with diabetes at risk of neuropathic ulcers - significant peripheral neuropathy
- **SIDE-EFFECTS** Skin irritation
- **PATIENT AND CARER ADVICE** Advise patient to apply carefully to wart and to protect surrounding skin (e.g. with soft paraffin or specially designed plaster); rub wart surface gently with file or pumice stone once weekly.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**OINTMENT**

- **Verrugon®** (Optima Consumer Health Ltd)
  - **Salicylic acid 500 mg per 1 gram** Verrugon complete 50% ointment | 6 gram £4.44 DT + £4.44

**LIQUID**

- **Occlusal®** (Alliance Pharmaceuticals Ltd)
  - **Salicylic acid 260 mg per 1 ml** Occlusal 26% solution | 10 ml £3.56 DT + £3.56

### www.getintopharma.com
Chapter 14
Vaccines

1 Immunoglobulin therapy

IMMUNE SERA AND IMMUNOGLOBULINS IMMAUOGLOBULINS

Immunoglobulins

Passive immunity

Immunity with immediate protection against certain infective organisms can be obtained by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. The duration of this passive immunity varies according to the dose and the type of immunoglobulin. Passive immunity may last only a few weeks; when necessary, passive immunisation can be repeated. Antibodies of human origin are usually termed immunoglobulins. The term antiserum is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins. Reactions are theoretically possible after injection of human immunoglobulins but reports of such reactions are very rare.

Two types of human immunoglobulin preparation are available, normal immunoglobulin p. 1290 and disease-specific immunoglobulins.

Human immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma or serum obtained from outside the UK, tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2). A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme in the UK, for further information consult www.ivig.nhs.uk and Clinical Guidelines for Immunoglobulin Use, www.gov.uk/dh.


Availability

Normal immunoglobulin for intramuscular administration is available from some regional Public Health laboratories, with the exception of tetanus immunoglobulin p. 1292 which is available from BPL, hospital pharmacies, or blood transfusion departments. Rabies immunoglobulin p. 1292 is available from the Specialist and Reference Microbiology Division, Public Health England, Colindale. Hepatitis B immunoglobulin p. 1290 required by transplant centres should be obtained commercially.

In Scotland all immunoglobulins are available from the Scottish National Blood Transfusion Service (SNBTS).

In Wales all immunoglobulins are available from the Welsh Blood Service (WBS).

In Northern Ireland all immunoglobulins are available from the Northern Ireland Blood Transfusion Service (NIBTS).

Normal immunoglobulin

Human normal immunoglobulin (‘HNIG’) is prepared from pools of at least 1000 donations of human plasma; it contains immunoglobulin G (IgG) and antibodies to hepatitis A, measles, mumps, rubella, varicella, and other viruses that are currently prevalent in the general population.

Uses

Normal immunoglobulin (containing 10%–18% protein) is administered by intramuscular injection for the protection of susceptible contacts against hepatitis A virus (infectious hepatitis), measles and, to a lesser extent, rubella. Injection of immunoglobulin produces immediate protection lasting several weeks.

Normal immunoglobulin (containing 3%–12% protein) for intravenous administration is used as replacement therapy for patients with congenital agammaglobulinaemia and hypogammaglobulinaemia, and for the short-term treatment of idiopathic thrombocytopenic purpura and Kawasaki disease; it is also used for the prophylaxis of infection following bone-marrow transplantation and in children with symptomatic HIV infection who have recurrent bacterial infections. Normal immunoglobulin for replacement therapy may also be given intramuscularly or subcutaneously, but intravenous formulations are normally preferred.

Intravenous immunoglobulin is also used in the treatment of Guillain-Barré syndrome as an alternative to plasma exchange.

For guidance on the use of intravenous normal immunoglobulin and alternative therapies for certain conditions, consult Clinical Guidelines for Immunoglobulin Use (www.gov.uk/dh).

Hepatitis A

Hepatitis A vaccine p. 1318 is recommended for individuals at risk of infection including those visiting areas where the disease is highly endemic (all countries excluding Northern and Western Europe, North America, Japan, Australia, and New Zealand). In unimmunised individuals, transmission of hepatitis A is reduced by good hygiene. Intramuscular normal immunoglobulin is no longer recommended for prophylaxis in travellers.

Public Health England recommends the use of normal immunoglobulin in addition to hepatitis A vaccine for prevention of infection in close contacts (of confirmed cases
of hepatitis A) who are 60 years of age or over, have chronic liver disease (including chronic hepatitis B or C infection), or HIV infection (with a CD4 count < 200 cells per microlitre), or who are immunosuppressed; normal immunoglobulin should be given as soon as possible, preferably within 14 days of exposure to the primary case. However, normal immunoglobulin can still be given to contacts with chronic liver disease up to 28 days after exposure to the primary case. Hepatitis A vaccine can be given at the same time, but it should be given at a separate injection site.

**Measles**

Intravenous or subcutaneous normal immunoglobulin may be given to prevent or attenuate an attack of measles in individuals who do not have adequate immunity. Patients with congenital immunity who have come into close contact with measles should receive intravenous or subcutaneous normal immunoglobulin as soon as possible after exposure. It is most effective if given within 72 hours but can be effective if given within 6 days.

Subcutaneous or intramuscular normal immunoglobulin should also be considered for the following individuals if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak:

- non-immune pregnant women
- infants under 9 months

Further advice should be sought from the Centre for Infections, Public Health England (tel. (020) 8200 6868).

Individuals with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given measles, mumps and rubella vaccine, live p. 1323 for prophyaxis following exposure to measles.

**Rubella**

Intramuscular immunoglobulin after exposure to rubella does not prevent infection in non-immune contacts and is not recommended for protection of pregnant women exposed to rubella. It may, however, reduce the likelihood of a clinical attack which may possibly reduce the risk to the fetus. Risk of intra-uterine transmission is greatest in the first 11 weeks of pregnancy, between 16 and 20 weeks there is minimal risk of deafness only, after 20 weeks there is no increased risk. Intramuscular normal immunoglobulin should be used only if termination of pregnancy would be unacceptable to the pregnant woman—it should be given as soon as possible after exposure. Serological follow-up of recipients is essential to determine if the woman has become infected despite receiving immunoglobulin.

For routine prophylaxis against Rubella, see measles, mumps and rubella vaccine, live p. 1323.

**Disease-specific immunoglobulins**

Specific immunoglobulins are prepared by pooling the plasma of selected human donors with high levels of the specific antibody required. For further information, see Immunoglobulin Handbook (www.gov.uk/phe).

There are no specific immunoglobulins for hepatitis A, measles, or rubella—normal immunoglobulin p. 1290 is used in certain circumstances. There is no specific immunoglobulin for mumps; neither normal immunoglobulin nor measles, mumps and rubella vaccine, live is effective as post-exposure prophylaxis.

**Hepatitis B immunoglobulin**

Disease-specific hepatitis B immunoglobulin p. 1290 (‘HBIG’) is available for use in association with hepatitis B vaccine p. 1319 for the prevention of infection in laboratory and other personnel who have been accidentally inoculated with hepatitis B virus, and in infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers. Hepatitis B immunoglobulin will not inhibit the antibody response when given at the same time as hepatitis B vaccine but should be given at different sites.

An intravenous and subcutaneous preparation of hepatitis B immunoglobulin is licensed for the prevention of hepatitis B recurrence in HBV-DNA negative patients who have undergone liver transplantation for liver failure caused by the virus.

**Rabies immunoglobulin**

Following exposure of an unimmunised individual to an animal in or from a country where the risk of rabies is high the site of the bite should be washed with soap and water and specific rabies immunoglobulin p. 1292 of human origin administered. All of the dose should be injected around the site of the wound; if this is difficult or the wound has been thoroughly healed it can be given in the anterolateral thigh (remote from the site used for vaccination).

Rabies vaccine p. 1324 should also be given intramuscularly at a different site (for details see rabies vaccine). If there is delay in giving the rabies immunoglobulin, it should be given within 7 days of starting the course of rabies vaccine.

**Tetanus immunoglobulin**

For the management of tetanus-prone wounds, tetanus immunoglobulin p. 1292 should be used in addition to wound cleansing and, where appropriate, antibacterial prophylaxis and a tetanus-containing vaccine. Tetanus immunoglobulin, together with metronidazole p. 542 and wound cleansing, should also be used for the treatment of established cases of tetanus.

**Varicella-zoster immunoglobulin**

Varicella-zoster immunoglobulin p. 1292 (VZIG) is recommended for individuals who are at increased risk of severe varicella (neonates, pregnant women and immunosuppressed individuals with varicella-zoster virus immunoglobulin G antibody less than 150 mIU/mL) and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox (varicella) or shingles (herpes zoster) during the infectious period.

Immunosuppressed patients receiving regular intravenous immunoglobulin replacement therapy only require varicella-zoster immunoglobulin if the most recent dose was administered more than 3 weeks before exposure.

Immunosuppressed patients on long term aciclovir p. 633 or valaciclovir p. 636 prophylaxis will require a temporary increase in their dose following exposure; for patients within 12 months of a stem cell transplant, varicella-zoster immunoglobulin should also be considered.

**Important:** for full details consult Guidance for issuing varicella-zoster immunoglobulin (VZIG) and Immunisation against infectious disease from Public Health England (www.gov.uk).

**Anti-D (RhD) immunoglobulin**

Anti-D (RhD) immunoglobulin p. 1289 is prepared from plasma from rhesus-negative donors who have been immunised against the anti-D-antigen. Anti-D (RhD) immunoglobulin is used to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The objective is to protect any subsequent child from the hazard of haemolytic disease of the newborn.

Anti-D (RhD) immunoglobulin should be administered to the mother following any sensitising episode (e.g. abortion, miscarriage and birth); it should be injected within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be administered. Anti-D (RhD) immunoglobulin is also given when significant fetal-maternal haemorrhage occurs in rhesus-negative women during delivery. The dose of anti-D (RhD) immunoglobulin is determined according to the level of exposure to rhesus-positive blood.

Use of routine antenatal anti-D prophylaxis should be given irrespective of previous anti-D prophylaxis for a
sensitising event early in the same pregnancy. Similarly, postpartum anti-D prophylaxis should be given irrespective of previous routine antenatal anti-D prophylaxis or antenatal anti-D prophylaxis for a sensitising event in the same pregnancy.

Anti-D (Rh) immunoglobulin is also given to women of child-bearing potential after the inadvertent transfusion of rhesus-incompatible blood components and is used for the treatment of idiopathic thrombocytopenia purpura.

MMR vaccine
Measles, mumps and rubella vaccine, live may be given in the postpartum period with anti-D (Rh) immunoglobulin injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.

Anti-D (Rh(D)) immunoglobulin

**INDICATIONS AND DOSE**

To rhesus-negative woman for prevention of Rh(D) sensitisation, following birth of rhesus-positive infant

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units, dose to be administered immediately or within 72 hours; for transplacental bleed of over 4 mL fetal red cells, extra 100–125 units per mL fetal red cells, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh(D) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) up to 20 weeks’ gestation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 250 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh(D) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) after 20 weeks’ gestation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh(D) sensitisation, antenatal prophylaxis

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 500 units, dose to be given at weeks 28 and 34 of pregnancy, if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh(D) sensitisation, antenatal prophylaxis (alternative NICE recommendation)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Females of childbearing potential: 1000–1650 units, dose to be given at weeks 28 and 34 of pregnancy, alternatively 1500 units for 1 dose, dose to be given between 28 and 30 weeks gestation
### Hepatitis B immunoglobulin

#### INDICATIONS AND DOSE

**Prophylaxis against hepatitis B infection**
- **By intramuscular injection**
  - Adult: 500 units, dose to be administered as soon as possible after exposure; ideally within 12–48 hours, but no later than 7 days after exposure

**Prophylaxis against hepatitis B infection, after exposure to hepatitis B virus–contaminated material**
- **By intravenous infusion**
  - Adult: Dose to be administered as soon as possible after exposure, but no later than 72 hours (consult product literature)

**Prevention of hepatitis B in haemodialysed patients**
- **By intravenous infusion**
  - Adult: (consult product literature)

**Prophylaxis against re-infection of transplanted liver**
- **By intravenous infusion**
  - Adult: (consult product literature)

**Prevention of hepatitis B re-infection more than 6 months after liver transplantation in stable HBV-DNA negative patients**
- **By subcutaneous injection**
  - Adult (body-weight up to 75 kg): 500 units once weekly, increased if necessary up to 1000 units once weekly, dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin
  - Adult (body-weight 75 kg and above): 1000 units once weekly, dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin

#### CAUTIONS

- IgA deficiency • Interference with live virus vaccines
- **INTERACTIONS** → Appendix 1: immunoglobulins
- **SIDE-EFFECTS**
  - Uncommon Abdominal pain upper • headache
  - Rare or very rare Cardiac discomfort • fatigue • hypersensitivity • hypertension • hypotension • muscle spasms • nasopharyngitis • oropharyngeal pain • palpitations • skin reactions

**PRESCRIBING AND DISPENSING INFORMATION**

- Vials containing 200 units or 500 units (for intramuscular injection), available from selected Public Health England and NHS laboratories (except for Transplant Centres), also available from BPL.

**HANDLING AND STORAGE**

- Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. **Refrigerated storage** is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE decisions**
  - Routine antenatal anti-D prophylaxis for rhesus-negative women (August 2008) NICE TA156

Routine antenatal anti-D prophylaxis should be offered to all non-sensitised pregnant women who are rhesus negative.

[www.nice.org.uk/TA156](http://www.nice.org.uk/TA156)

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **D-Gam (Bio Products Laboratory Ltd)**
  - Anti-D (RHO) immunoglobulin 500 unit per 1 ml D-Gam Anti-D immunoglobulin 500unit solution for injection vials | 1 vial (PoM) £38.25

- **Anti-D (RHO) immunoglobulin 1500 unit**
  - Anti-D (RHO) immunoglobulin 1500unit solution for injection vials | 1 vial (PoM) £58.00

- **Rhophylac (CSL Behring UK Ltd)**
  - Anti-D (RHO) immunoglobulin 750 unit per 1 ml Rhophylac 1,500units/2ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PoM) £46.50

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### Normal immunoglobulin

**INDICATIONS AND DOSE**

**To control outbreaks of hepatitis A**
- **By deep intramuscular injection**
  - Adult: 500 mg

**Rubella in pregnancy, prevention of clinical attack**
- **By deep intramuscular injection**
  - Females of childbearing potential: 750 mg

**Antibody deficiency syndromes**
- **By subcutaneous infusion**
  - Adult: (consult product literature)

**SUBGAM®**

**Hepatitis A prophylaxis in outbreaks**
- **By intramuscular injection**
  - Adult: 750 mg

**UNLICENSED USE**

**SUBGAM®**

- Subgam® is not licensed for prophylactic use, but due to difficulty in obtaining suitable immunoglobulin products, Public Health England recommends intramuscular use for prophylaxis against Hepatitis A or rubella.

**CONTRA-INDICATIONS**

- Patients with selective IgA deficiency who have known antibody against IgA
PRIVIGEN® Hyperprolinaemia (contains L-proline)
FLEBOGAMMA® DIF Hereditary fructose intolerance (contains sorbitol)
HIZENTRA® Hyperprolinaemia (contains L-proline)
GAMMAPLEX® Hereditary fructose intolerance (contains sorbitol)

CAUTIONS
- Agammaglobulinaemia with or without IgA deficiency - Hypogammaglobulinaemia with or without IgA deficiency - interference with live virus vaccines

CAUTIONS, FURTHER INFORMATION
- Interference with live virus vaccines Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

Rare or very rare

- With subcutaneous use Diarrhoea - dizziness - drowsiness - fatigue - gastrointestinal discomfort - headaches - hypotension - local reaction - myalgia - nausea - pain - skin reactions
- With intramuscular use Chills
- With subcutaneous use Abdominal pain - arthralgia - musculoskeletal stiffness - myalgia - peripheral coldness - tremor

SIDE-EFFECTS
- Common or very common
- With intramuscular use Diarrhoea - dizziness - drowsiness - fatigue - gastrointestinal discomfort - headaches - hypotension - local reaction - myalgia - nausea - pain - skin reactions
- With subcutaneous use Paraesthesia
- Rare or very rare
- With intramuscular use Abdominal pain - arthralgia - musculoskeletal stiffness - myalgia - peripheral coldness - tremor
- Frequency not known

SIDE-EFFECTS, FURTHER INFORMATION
- Adverse reactions are more likely to occur in patients receiving normal immunoglobulin for the first time, or following a prolonged period between treatments, or when a different brand of normal immunoglobulin is administered.
- MONITORING REQUIREMENTS
- Monitor for acute renal failure; consider discontinuation if renal function deteriorates. Intravenous preparations with added sucrose have been associated with cases of renal dysfunction and acute renal failure.

DIRECTIONS FOR ADMINISTRATION
- Preparations for subcutaneous use May be administered by intramuscular injection if subcutaneous route not possible; intramuscular route not for patients with thrombocytopenia or other bleeding disorders.
- GAMUNEX® Use Glucose 5% intravenous infusion if dilution prior to infusion is required.
- KIOVIG® Use Glucose 5% intravenous infusion if dilution prior to infusion is required.

PRESCRIBING AND DISPENSING INFORMATION
- Antibody titres can vary widely between normal immunoglobulin preparations from different manufacturers—formulations are not interchangeable; patients should be maintained on the same formulation throughout long-term treatment to avoid adverse effects.
- With intramuscular use Available from the Centre for Infections and other regional Public Health England offices (for contacts and control of outbreaks only).

HANDLING AND STORAGE
- Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- ELECTROLYTES: May contain Sodium
  - Hizentra (CSL Behring UK Ltd) Normal immunoglobulin human 200 mg per 1 ml Hizentra 2g/10ml solution for injection pre-filled syringes 1 1 pre-filled disposable injection (PRP) £108.00
  - Subgam (Bio Products Laboratory Ltd) Normal immunoglobulin human 160 mg per 1 ml Subgam 1.5g/9.375ml solution for injection vials 1 1 vial (PRP) £75.00
  - Subgam 4g/25ml solution for injection vials 1 1 vial (PRP) £200.00
  - Subgam 2g/12.5ml solution for injection vials 1 1 vial (PRP) £100.00
  - Subgam 4g/6.25ml solution for injection vials 1 1 vial (PRP) £50.00
  - Subgam 75mg/4.6875ml solution for injection vials 1 1 vial (PRP) £37.50

Solution for infusion
- EXCipients: May contain Glucose, maltose, sorbitol, sucrose
  - Normal immunoglobulin (Non-proprietary)
    - Normal immunoglobulin human 100 mg per 1 ml Normal immunoglobulin human 5g/50ml solution for infusion vials 1 1 vial (PRP)
    - Normal immunoglobulin human 2.5g/25ml solution for infusion vials 1 1 vial (PRP)
    - Normal immunoglobulin human 20g/200ml solution for infusion vials 1 1 vial (PRP)
    - Normal immunoglobulin human 10g/100ml solution for infusion vials 1 1 vial (PRP)
    - Normal immunoglobulin human 30g/300ml solution for infusion vials 1 1 vial (PRP)
  - Flebogammadif (Grifols UK Ltd) Normal immunoglobulin human 50 mg per 1 ml Flebogamma DIF 10g/200ml solution for infusion vials 1 1 vial (PRP) £100.00
    - Flebogamma DIF 2.5g/50ml solution for infusion vials 1 1 vial (PRP) £25.00
    - Flebogamma DIF 5g/100ml solution for infusion vials 1 1 vial (PRP) £255.00
    - Flebogamma DIF 500mg/10ml solution for infusion vials 1 1 vial (PRP) £30.00
    - Flebogamma DIF 2g/400ml solution for infusion vials 1 1 vial (PRP) £1,020.00
  - Gammaplex (Bio Products Laboratory Ltd) Normal immunoglobulin human 50 mg per 1 ml Gammaplex 10g/200ml solution for infusion vials 1 1 vial (PRP) £148.00 (Hospital only)
    - Gammaplex 5g/100ml solution for infusion vials 1 1 vial (PRP) £209.00 (Hospital only)
    - Gammaplex 20g/400ml solution for infusion vials 1 1 vial (PRP) £836.00 (Hospital only)
  - Gamunex (Grifols UK Ltd) Normal immunoglobulin human 100 mg per 1 ml Gamunex 10% 1g/10ml solution for infusion vials 1 1 vial (PRP) £42.50
    - Gamunex 10% 10g/100ml solution for infusion vials 1 1 vial (PRP) £425.00
    - Gamunex 10% 20g/200ml solution for infusion vials 1 1 vial (PRP) £850.00
    - Gamunex 10% 5g/50ml solution for infusion vials 1 1 vial (PRP) £212.50
  - Hizentra (CSL Behring UK Ltd) Normal immunoglobulin human 200 mg per 1 ml Hizentra 2g/10ml solution for infusion vials 1 1 vial (PRP) £108.00
    - Hizentra 1g/5ml solution for infusion vials 1 1 vial (PRP) £54.00
    - Hizentra 4g/20ml solution for infusion vials 1 1 vial (PRP) £216.00
  - Kiovig (Baxalta UK Ltd) Normal immunoglobulin human 100 mg per 1 ml Kiovig 5g/50ml solution for infusion vials 1 1 vial (PRP) £245.00
    - Kiovig 20g/200ml solution for infusion vials 1 1 vial (PRP) £980.00
    - Kiovig 10g/100ml solution for infusion vials 1 1 vial (PRP) £490.00
    - Kiovig 30g/300ml solution for infusion vials 1 1 vial (PRP) £1,470.00
    - Kiovig 2.5g/25ml solution for infusion vials 1 1 vial (PRP) £122.50
**1292 Immunoglobulin therapy**

**Tetanus immunoglobulin**

- **INDICATIONS AND DOSE**
  - **Post-exposure prophylaxis**
    - **BY INTRAMUSCULAR INJECTION**
    - **Child:** Initially 250 units, then increased to 500 units, dose is only increased if more than 24 hours have elapsed or there is risk of heavy contamination or following burns.
    - **Adult:** Initially 250 units, then increased to 500 units, dose is only increased if more than 24 hours have elapsed or there is risk of heavy contamination or following burns.
  - **Treatment of tetanus infection**
    - **BY INTRAMUSCULAR INJECTION**
    - **Child:** 150 units/kg, dose may be given over multiple sites.
    - **Adult:** 150 units/kg, dose may be given over multiple sites.

- **CAUTIONS**
  - IgA deficiency.
  - Interference with live virus vaccines.

- **INTERACTIONS**
  - Appendix 1: immunoglobulins.

- **SIDE-EFFECTS**
  - Rare or very rare: Arthralgia, chills, fatigue, fever, headache, hypersensitivity, hypotension, influenza-like illness, malaise, nausea, skin reactions, tachycardia, vomiting.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - The potency of individual batches of rabies immunoglobulin from the manufacturer may vary; potency may also be described differently by different manufacturers. It is therefore critical to know the potency of the batch to be used and the weight of the patient in order to calculate the specific volume required to provide the necessary dose. Available from Specialist and Reference Microbiology Division, Public Health England (also from BPL).

- **HANDLING AND STORAGE**
  - Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Tetanus immunoglobulin (Non-proprietary)**
  - Tetanus immunoglobulin human 250 unit solution for injection vials | 1 vial £170.00

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**Varicella-zoster immunoglobulin**

(=Antivaricella-zoster immunoglobulin)

- **INDICATIONS AND DOSE**
  - **Prophylaxis against varicella infection**
    - **BY DEEP INTRAMUSCULAR INJECTION**
    - **Adult:** 1 g, to be administered as soon as possible—not later than 10 days after exposure, second dose to be given if further exposure occurs more than 3 weeks after first dose, no evidence that effective in severe disease.

- **CAUTIONS**
  - IgA deficiency.
  - Interference with live virus vaccines.

- **INTERACTIONS**
  - Appendix 1: immunoglobulins.

- **SIDE-EFFECTS**
  - Arthralgia, chills, fever, headache, hypersensitivity, hypotension, malaise, nausea, skin reactions, tachycardia, vomiting.
Post-exposure prophylaxis

IMMUNE SERA AND IMMUNOGLOBULINS

ANTITOXINS

Bezlotoxumab

- **Drug Action** Bezlotoxumab is a human monoclonal antitoxin antibody; it binds to *Clostridium difficile* toxin B and neutralises its activity, preventing recurrence of *Clostridium difficile* infection.

- **Indications and Dose** Prevention of recurrence of *Clostridium difficile* infection in patients at high risk of reinfection
  - **By intravenous infusion**
  - Adult: 10 mg/kg for 1 dose, to be administered during the course of antibacterial therapy for *Clostridium difficile* infection

- **Side-effects**
  - Common or very common Dizziness, dyspnoea, fatigue, fever, headache, hypertension, infusion related reaction, nausea
  - Pregnancy Manufacturer advises avoid unless essential—limited information available.
  - Breast Feeding Manufacturer advises avoid—no information available.
  - Directions for administration Manufacturer advises for intravenous infusion (Zinplava®), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute requisite dose to a concentration of 1–10 mg/mL with infusion fluid; give over 60 minutes via a central venous catheter or peripheral catheter using a low-protein binding filter (0.2–5 micron).
  - Handling and storage Manufacturer advises store in a refrigerator (2–8 °C)—consult product literature for further information regarding storage conditions outside refrigerator and after preparation of the infusion.

- **Medical Forms** There can be variation in the licensing of different medicines containing the same drug.

  **Solution for infusion**
  - Excipients: May contain Polysorbates
  - Electrolytes: May contain Sodium
  - **Zinplava (Merck Sharp & Dohme Ltd)**
    - Bezlotoxumab 25 mg per 1 ml

Botulism antitoxin

- **Drug Action** A preparation containing the specific antitoxin globulins that have the power of neutralising the toxins formed by types A, B, and E of *Clostridium botulinum*.

- **Indications and Dose** Post exposure prophylaxis of botulism
  - **By intramuscular injection**
  - Adult: (consult product literature)

- **Side-effects** Hypersensitivity

  **Side-effects, further information** It is essential to read the contra-indications, warnings, and details of sensitivity tests on the package insert. Prior to treatment checks should be made regarding previous administration of any antitoxin and history of any allergic condition, e.g. asthma, hay fever, etc.

- **Pre-Treatment Screening** All patients should be tested for sensitivity (diluting the antitoxin if history of allergy).

- **Prescribing and Dispensing Information** Available from local designated centres, for details see TOXBASE (requires registration) www.toxbase.org. For supplies outside working hours apply to other designated centres or to the Public Health England Colindale duty doctor (Tel (020) 8200 6868). For major incidents, obtain supplies from the local blood bank.

  The BP title Botulinum Antitoxin is not used because the preparation currently in use may have a different specification.

- **Medical Forms** No licensed medicines listed.

Diphtheria antitoxin

(Dip/Ser)

- **Indications and Dose** Passive immunisation in suspected cases of diphtheria
  - **By intravenous infusion**
  - Adult: Dose should be given without waiting for bacteriological confirmation (consult product literature)

- **Cautions**

  **Cautions, further information**
  - Hypersensitivity Hypersensitivity is common after administration; resuscitation facilities should be available. Diphtheria antitoxin is no longer used for prophylaxis because of the risk of hypersensitivity; unimmunised contacts should be promptly investigated and given antibacterial prophylaxis and vaccine.

- **Side-effects**
  - Common or very common Hypersensitivity

- **Pre-Treatment Screening** Diphtheria antitoxin is derived from horse serum and reactions are common; tests for hypersensitivity should be carried out before use.

- **Prescribing and Dispensing Information** Available from Centre for Infections (Tel (020) 8200 6868) or in Northern Ireland from Public Health Laboratory, Belfast City Hospital (Tel (028) 9032 9241).
4 Vaccination

Vaccination, general principles

Active immunity
Active immunity can be acquired by natural disease or by vaccination. Vaccines stimulate production of antibodies and other components of the immune mechanism; they consist of either:

- a live attenuated form of a virus (e.g. measles, mumps and rubella vaccine) or bacteria (e.g. BCG vaccine), or
- inactivated preparations of the virus (e.g. influenza vaccine) or bacteria, or
- detoxified exotoxins produced by a micro-organism (e.g. tetanus vaccine), or
- extracts of a micro-organism, which may be derived from the organism (e.g. pneumococcal vaccine) or produced by recombinant DNA technology (e.g. hepatitis B vaccine).

Live attenuated vaccines usually produce a durable immunity, but not always as long-lasting as that resulting from natural infection.

Inactivated vaccines may require a primary series of injections of vaccine to produce an adequate antibody response, and in most cases booster (reinforcing) injections are required; the duration of immunity varies from months to many years. Some inactivated vaccines are adsorbed onto an adjuvant (such as aluminium hydroxide) to enhance the antibody response.

Vaccines and HIV infection
HIV-positive individuals with or without symptoms can receive the following live vaccines:

- MMR (but avoid if immunity significantly impaired; use of normal immunoglobulin should be considered after exposure to measles), varicella–zoster vaccine against chickenpox (but avoid if immunity significantly impaired—consult product literature; varicella–zoster immunoglobulin should be considered after exposure to chickenpox or herpes zoster), rotavirus;
- and the following inactivated vaccines:
  - anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human papillomavirus, influenza (injection), meningococcal, pertussis, pneumococcal, poliomyelitis, rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive individuals should not receive:

- BCG, influenza nasal spray (unless stable HIV infection and receiving antiretroviral therapy), typhoid (oral), yellow fever (if yellow fever risk is unavoidable, specialist advice should be sought).

The above advice differs from that for other immunocompromised patients; Immunisation Guidelines for HIV-infected Adults issued by British HIV Association (BHIVA) are available at www.bhiva.org and, Immunisation of HIV-infected Children issued by Children’s HIV Association (CHIVA) are available at www.chiva.org.uk

Vaccines and asplenia
The following vaccines are recommended for asplenic patients, those with splenic dysfunction or complement disorders, depending on the age at which their condition is diagnosed:

- Haemophilus influenzae type b with meningococcal group C vaccine p. 1314;
- Influenza vaccine p. 1322;
- Meningococcal groups A with C and W135 and Y vaccine p. 1315 and meningococcal group B vaccine (rDNA, component, adsorbed) p. 1314;
### Routine immunisation schedule

**When to immunise** | **Vaccine given and dose schedule (for details of dose, see under individual vaccines)**
---|---
**Neonates at risk only** | ▶ Bacillus Calmette-Guérin vaccine p. 1313 (at birth, see BCG vaccine p. 1297)
▶ Hepatitis B vaccine p. 1319 (at birth, see Hepatitis B vaccine p. 1300)
**8 weeks** | ▶ Diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine p. 1312 (Infanrix hexa®). First dose
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) p. 1314 (Bexsero®). First dose
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1316 (Prevenar 13®). First dose
▶ Rotavirus vaccine p. 1325 (Rotarix®). First dose
**12 weeks** | ▶ Diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine (Infanrix hexa®). Second dose
▶ Rotavirus vaccine (Rotarix®). Second dose
**16 weeks** | ▶ Diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine (Infanrix hexa®). Third dose
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) (Bexsero®). Second dose
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) (Prevenar 13®). Second dose
**1 year (on or after first birthday)** | ▶ Measles, mumps and rubella vaccine, live p. 1323 (MMR VaxPRO® or Priorix®). First dose
▶ Meningococcal group B vaccine (rDNA, component, adsorbed) (Bexsero®). Single booster dose
▶ Pneumococcal polysaccharide conjugate vaccine (adsorbed) (Prevenar 13®). Single booster dose
▶ Haemophilus influenzae type b with meningococcal group C vaccine p. 1314 (Menitorix®). Single booster dose
**2–10 years on 31st August 2019 (including children in reception class and school years 1, 2, 3, 4, 5, and 6)** | ▶ Influenza vaccine p. 1322 each year from September. Note: live attenuated influenza nasal spray is recommended (Fluenz Tetra®). If contra-indicated and child is in clinical risk group, use inactivated influenza vaccine (see Influenza vaccine p. 1301)
**3 years and 4 months, or soon after** | ▶ Diphtheria with pertussis, poliomyelitis vaccine and tetanus p. 1311 (Repevax®). Single booster dose.
▶ Measles, mumps and rubella vaccine, live (MMR VaxPRO® or Priorix®). Second dose
**11–14 years (females only). First dose of HPV vaccine will be offered to females aged 12–13 years of age in England, Wales, and Northern Ireland, and 11–13 years of age in Scotland. For females aged 15 years and older, see Human papillomavirus vaccine p. 1300.** | ▶ Human papillomavirus vaccines p. 1321 (Gardasil®). 2 doses; second dose 6–24 months after first dose. If a 3-dose course of HPV vaccine has been started, where possible, the course should be completed (2 doses less than 6 months apart does not provide long-term protection). Only Gardasil® is offered as part of the national immunisation programme. Therefore for those females who started the schedule with Cervarix®, but did not complete the vaccination course, the course can be completed with Gardasil®. Ideally one vaccine should be used for the entire course.
**13–15 years** | ▶ Meningococcal groups A with C and W135 and Y vaccine p. 1315 (Nimenrix® or Menveo®). Single booster dose
**13–18 years** | ▶ Diphtheria with poliomyelitis and tetanus vaccine p. 1312 (Revax®). Single booster dose. **Note:** Can be given at the same time as the dose of meningococcal groups A with C and W135 and Y vaccine at 13–15 years of age.
**Females of child-bearing age susceptible to rubella** | ▶ Measles, mumps and rubella vaccine, live females of child-bearing age who have not received 2 doses of a rubella-containing vaccine or who do not have a positive antibody test for rubella should be offered rubella immunisation (using the MMR vaccine)—Exclude pregnancy before immunisation, and avoid pregnancy for one month after vaccination.
**Pregnant females** | ▶ Acellular pertussis-containing vaccine administered as diphtheria with pertussis, poliomyelitis vaccine and tetanus (Boostrix-IPV®). 1 dose from the 16th week of pregnancy, preferably after the fetal anomaly scan (weeks 18–20)
▶ Influenza vaccine (inactivated). Single dose administered from September, regardless of the stage of pregnancy (see Influenza vaccine p. 1301)

### Routine immunisations during adult life

**When to immunise** | **Vaccine given and dose schedule (for details of dose, see under individual vaccines)**
---|---
**Under 25 years, those entering university who are at risk of meningococcal disease** | ▶ Meningococcal groups A with C and W135 and Y vaccine (Nimenrix® or Menveo®). Single dose. **Note:** Should be offered to those aged under 25 years entering university who have not received the meningococcal groups A with C and W135 and Y vaccine over the age of 10 years
**During adult life, if not previously immunised or 5 dose course is incomplete** | ▶ Diphtheria with poliomyelitis and tetanus vaccine
**65 years** | ▶ Pneumococcal polysaccharide vaccine p. 1316
**From 65 years** | ▶ Influenza vaccine (inactivated) Each year from September (see Influenza vaccine p. 1301)
**70 years** | ▶ Varicella-zoster vaccine p. 1326 Single dose
Vaccines

In Scotland information about availability of vaccines can be obtained from a Specialist in Pharmaceutical Public Health. For further details of availability, see under individual publications/the-complete-routine-immunisation-schedule (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Immunisation schedule

Routine immunisations, sources of information


The immunisation schedule reflects advice from ‘The complete routine immunisation schedule’ produced by Public Health England (2018). For the most up to date immunisation schedule see: www.gov.uk/government/publications/the-complete-routine-immunisation-schedule


Vaccines for the immunisation schedule should be obtained from ImmForm at: www.immform.dh.gov.uk

Preterm birth

Babies born preterm should receive all routine immunisations based on their actual date of birth. The risk of apnoea following vaccination is increased in preterm babies, particularly in those born at or before 28 weeks gestational age. If babies at risk of apnoea are in hospital at the time of their first immunisation, they should be monitored for respiratory complications for 48–72 hours after immunisation. If a baby develops apnoea, bradycardia, or desaturation after the first immunisation, the second immunisation should also be given in hospital with similar monitoring.

Individuals with unknown or incomplete immunisation history

For children born in the UK who present with an inadequate or unknown immunisation history, investigation into immunisations received should be carried out. Outstanding doses should be administrated where the routine childhood immunisation schedule has not been completed. For advice on dosing schedules for missed vaccinations, and the immunisation of individuals coming to the UK, consult Chapter 11, The UK immunisation schedule, in Immunisation against infectious disease– ‘The Green Book’. Public Health England, available at: www.gov.uk/government/publications/immunisation-schedule-the-green-book-chapter-11

Immunisations for healthcare and laboratory staff

Vaccine-preventable diseases that can be transmitted from person to person are a risk for staff and patients in healthcare environments, and staff in laboratory environments. Therefore, all staff must be up-to-date with their routine immunisations. In addition, specific immunisations are recommended for certain staff groups due to the risk of acquiring or passing on infection. For detailed recommendations, consult Chapter 12,
**Vaccination 1297**

**Anthrax vaccine**

**Overview**

Anthrax vaccine p. 1312 is made from antigens from inactivated *Bacillus anthracis* adsorbed onto an adjuvant. Anthrax immunisation is indicated for individuals who handle infected animals or process infected animal products where there is a potential risk of occupational exposure to *B. anthracis*. It is also recommended for occupations where workers are at risk of one-off high level exposures to anthrax (e.g. following a deliberate or accidental release of spores).

A 4-dose regimen is used for primary immunisation; a single booster dose should be given at 10-year intervals on up to 3 occasions to workers at potential continuous low level risk of exposure to anthrax. In those with potential intermittent high level exposure, a single booster dose should be offered just before entering situations with a specific high exposure risk. If such opportunities do not arise, a single booster dose should be given at 10-year intervals on up to 3 occasions to sustain protection.

In the event of proven or high probability of exposure to anthrax spores, a single booster dose should be given, in addition to antibacterial prophylaxis, except when a dose has been given in the preceding 12 months.


All suspected cases of anthrax must be notified to the local health protection unit. Where there is a community level outbreak, specialist advice should be sought from Public Health England (tel. 020 8200 4400) or, in Scotland, Health Protection Scotland (tel. 0140 300 1191).

**Useful Resources**


**BCG vaccine**

**Overview**

*Bacillus Calmette-Guérin* vaccine p. 1313 should be given intradermally by operators skilled in the technique.

The expected reaction to successful *Bacillus Calmette-Guérin* vaccine is induration at the site of injection followed by a local lesion which starts as a papule and later ulcerates. A dry dressing may be used if the ulcer discharges, but air should not be excluded.

BCG is recommended for the following groups if BCG immunisation has not previously been carried out and they are negative for tuberculin hypersensitivity:

- neonates, infants, and children under 16 years with a parent or grandparent born in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged under 16 years who were born in, or lived for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged 16–35 years from Sub-Saharan Africa or a country with an incidence of tuberculosis greater than 500 per 100 000;
- contacts aged under 36 years of those with active respiratory tuberculosis (for healthcare or laboratory workers who have had contact with clinical materials or patients with tuberculosis, age limit does not apply);
- healthcare workers and laboratory staff (irrespective of age) who are likely to have contact with patients, clinical materials, or derived isolates; other individuals under 35 years (there is inadequate evidence of protection by BCG vaccine in adults aged over 35 years; however, vaccination is recommended for healthcare workers irrespective of age because of the increased risk to them or their patients) at occupational risk including veterinary and other staff who handle animal species susceptible to tuberculosis, and staff working directly with prisoners, in care homes for the elderly, or in hostels or facilities for the homeless or refugees;
- individuals under 16 years intending to live with local people for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000.

List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at [www.gov.uk/ phe](http://www.gov.uk/phe).

Bladder instillations of BCG are licensed for the management of bladder carcinoma. See also Tuberculosis p. 578 for advice on chemoprophylaxis; for the treatment of infection following vaccination, seek expert advice.

**Tuberculosis Diagnostic Agents**

The Mantoux test is recommended for tuberculin skin testing, but no licensed preparation is currently available. Guidance for healthcare professionals is available at [www.dh.gov.uk/immunisation](http://www.dh.gov.uk/immunisation).

In the Mantoux test, the diagnostic dose is administered by intradermal injection of tuberculin purified protein derivative p. 1294 (PPD). The *Heaf* test (involving the use of multiple-puncture apparatus) is no longer available.

Two interferon gamma release assay (IGRA) tests are also available as an aid in the diagnosis of tuberculosis infection: *QuantiFERON®* TB Gold and *T-SPOT®. TB*. Both tests measure T-cell mediated immune response to synthetic antigens. For further information on the use of interferon gamma release assay tests for tuberculosis, see [www.gov.uk/phe](http://www.gov.uk/phe).

**Useful Resources**

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: [www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book](http://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book).
Botulism antitoxin

Overview
A polyvalent botulism antitoxin p. 1293 is available for the post-exposure prophylaxis of botulism and for the treatment of persons thought to be suffering from botulism. It specifically neutralises the toxins produced by Clostridium botulinum types A, B, and E. It is not effective against infantile botulism as the toxin (type A) is seldom, if ever, found in the blood in this type of infection.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The handbook incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Cholera vaccine

Overview
Oral cholera vaccine p. 1313 contains inactivated Inaba (El-Tor biotype) and Ogawa strains of Vibrio cholerae, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of V. cholerae, serotype O1. Oral cholera vaccine is licensed for adults and children from 2 years of age who are travelling to endemic or epidemic areas on the basis of current recommendations. Immunisation should be completed at least one week before potential exposure. However, there is no requirement for cholera vaccination for international travel. After a full risk assessment, immunisation can be considered for the following individuals:

- relief or disaster aid workers;
- persons with remote itineraries in areas where cholera epidemics are occurring and there is limited access to medical care;
- travellers to potential cholera risk areas, for whom vaccination is considered potentially beneficial;
- individuals at occupational risk, such as laboratory workers who may be regularly exposed to cholera.

For dosing schedule, see cholera vaccine. Immunisation with cholera vaccine does not provide complete protection and all travellers to a country where cholera exists should be warned that scrupulous attention to food, water, and personal hygiene is essential. All suspected cases of cholera must be notified to the local health protection unit. Where there is a community level outbreak, specialist advice should be sought from Public Health England (tel. 020 8200 4400) or, in Scotland, Health Protection Scotland (tel. 0140 300 1191).

Contacts
Contacts of patients with cholera should maintain high standards of personal hygiene to avoid becoming infected. Cholera vaccine should not be used in the management of contacts of cases or in controlling the spread of infection.

Useful Resources

Diphtheria vaccine

Overview
Diphtheria-containing vaccines are prepared from the toxin of Corynebacterium diphtheriae and adsorption on aluminium hydroxide or aluminium phosphate improves antigenicity. The vaccine stimulates the production of the protective antibody. The quantity of diphtheria toxoid in a preparation determines whether the vaccine is defined as 'high dose' or 'low dose'. Vaccines containing the higher dose of diphtheria toxoid are used for primary immunisation of children under 10 years of age. Vaccines containing the lower dose of diphtheria toxoid are used for primary immunisation in adults and children over 10 years. Single-antigen diphtheria vaccine is not available and adsorbed diphtheria vaccine is given as a combination product containing other vaccines.

For primary immunisation of children aged between 2 months and 10 years, vaccination is recommended usually in the form of 3 doses (separated by 1-month intervals) of diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine p. 1312 (Infanrix hexa®) (see Immunisation schedule). In unimmunised individuals aged over 10 years the primary course comprises of 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine.

A booster dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed). Children under 10 years should receive either adsorbed diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine or adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine. Individuals aged over 10 years should receive adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine.

A second booster dose, of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, should be given 10 years after the previous booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed).

Diphtheria-containing vaccines for children over 10 years and adults

A low dose of diphtheria toxoid is sufficient to recall immunity in individuals previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in an individual who is already immune. Preparations containing low dose diphtheria should be used for adults and children over 10 years, for both primary immunisation and booster doses.

Travel
Those intending to travel to areas with a risk of diphtheria infection should be fully immunised according to the UK schedule. If more than 10 years have lapsed since completion of the UK schedule, a dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine should be administered.

Contacts
Staff in contact with diphtheria patients or with potentially pathogenic clinical specimens or working directly with C. diphtheriae or C. ulcerans should receive a booster dose if fully immunised (with 5 doses of diphtheria-containing vaccine given at appropriate intervals); further doses should be given at 10-year intervals if risk persists. Individuals at risk who are not fully immunised should complete the primary course; a booster dose should be given after 5 years and then at 10-year intervals. Adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine is used for this purpose; immunity should be checked by
antibody testing at least 3 months after completion of immunisation.

Advice on the management of cases, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected individuals and their contacts should be determined; those who have been incompletely immunised should complete their immunisation and fully immunised individuals should receive a reinforcing dose. See advice on antibacterial treatment to prevent a secondary case of diphtheria in a non-immune individual.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Haemophilus influenzae type B conjugate vaccine

Overview
Haemophilus influenzae type b (Hib) vaccine is made from capsular polysaccharide; it is conjugated with a protein such as tetanus toxoid to increase immunogenicity, especially in young children. Haemophilus influenzae type b vaccine immunisation is given in combination with diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis vaccine (Infanrix hexa®), as a component of the primary course of childhood immunisation (see Immunisation schedule). For infants under 1 year, the course consists of 3 doses of a vaccine containing Haemophilus influenzae type b component with an interval of 1 month between doses. A booster dose of Haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given at 1 year of age, on or after the child’s first birthday.

Children 1–10 years who have not been immunised against Haemophilus influenzae type b need to receive only 1 dose of Haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine). However, if a primary course of immunisation has not been completed, children born before August 2017 should be given 3 doses of the combined vaccine they were started on. The risk of infection falls sharply in older children and the vaccine is not normally required for children over 10 years.

Haemophilus influenzae type b vaccine may be given to those over 10 years who are considered to be at increased risk of invasive H. influenzae type b disease (such as those with sickle-cell disease or complement deficiency, or those receiving treatment for malignancy).

Invasive Haemophilus influenzae type b disease
After recovery from infection, unimmunised and partially immunised index cases under 10 years of age should complete their age-specific course of immunisation. Previously vaccinated cases under 10 years of age should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if Hib antibody concentrations are low or if it is not possible to measure antibody concentrations. Index cases of any age with asplenia or splenic dysfunction should complete their immunisation according to the recommendations below; fully vaccinated cases with asplenia or splenic dysfunction should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if they received their previous dose over 1 year ago. See also use of rifampicin p. 582 in the prevention of secondary cases of Haemophilus influenzae type b disease.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Hepatitis A vaccine

Overview
Hepatitis A vaccine p. 1318 is prepared from formaldehyde-inactivated hepatitis A virus grown in human diploid cells. Immunisation is recommended for:

- laboratory staff who work directly with the virus;
- staff and residents of homes for those with severe learning difficulties;
- workers at risk of exposure to untreated sewage;
- individuals who work with primates;
- patients with haemophilia or other conditions treated with plasma-derived clotting factors;
- patients with severe liver disease;
- travellers to high-risk areas;
- individuals who are at risk due to their sexual behaviour;
- parenteral drug abusers.

Immunisation should be considered for:

- patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C;
- prevention of secondary cases in close contacts of confirmed cases of hepatitis A, within 14 days of exposure to the primary case (within 8 weeks of exposure to the primary case where there is more than 1 contact in the household).

A booster dose is usually given 6–12 months after the initial dose. A second booster dose can be given 20 years after the previous booster dose to those who continue to be at risk. Specialist advice should be sought on re-immunisation of immunocompromised individuals.

For rapid protection against hepatitis A after exposure or during an outbreak, in adults a single dose of a monovalent vaccine is recommended; for children under 16 years, a single dose of the combined vaccine Ambirix® can also be used.

Public Health England recommends the use of intramuscular normal immunoglobulin p. 1290 in addition to hepatitis A vaccine for prevention of infection in close contacts (of confirmed cases of hepatitis A) who are 60 years of age or over, have chronic liver disease, or HIV infection, or who are immunosuppressed. For further guidance, see Immunoglobulins p. 1287.

Post-exposure prophylaxis is not required for healthy children under 1 year of age, so long as all those involved in nappy changing are vaccinated against hepatitis A. However, children 2–12 months of age can be given a dose of hepatitis A vaccine if it is not possible to vaccinate their carers, or if the child becomes a source of infection to others [unlicensed use]; in these cases, if the child goes on to require long-term protection against hepatitis A after the first birthday, the full course of 2 doses should be given.
Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:

Hepatitis B vaccine
Overview
Hepatitis B vaccine p. 1319 contains inactivated hepatitis B virus surface antigen (HBsAg) adsorbed onto an adjuvant. It is made biosynthetically using recombinant DNA technology.
From August 2017, vaccination against hepatitis B is recommended as part of the routine immunisation schedule. Primary immunisation (see Routine immunisation schedule) requires 3 doses, administered at intervals of 1 month from the age of 2 months, to be given as part of the combined diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine p. 1312 (Infanrix hexa®).
As part of the selective neonatal immunisation programme, vaccination is recommended for neonates whose mothers have had acute hepatitis B during pregnancy or are positive for hepatitis B surface antigen (regardless of e-antigen markers). Hepatitis B vaccination is started immediately after birth with a dose of the monovalent hepatitis B vaccine (no later than 24 hours after delivery), followed by a second dose at 4 weeks; the routine immunisation combination vaccine (Infanrix hexa®) at weeks 8, 12 and 16; and a further dose of the monovalent hepatitis B vaccine at one year of age. Neonates born to highly infectious mothers should also receive hepatitis B immunoglobulin p. 1290 at the same time as the first dose of monovalent hepatitis B vaccine, but administered at a different site—more detailed guidance is given in the handbook Immunisation against Infectious Disease (www.gov.uk/government/publications/hepatitis-b-the-green-book-chapter-18).
Following significant exposure to hepatitis B (e.g. through needle-stick injury or unprotected sex) and for pre-exposure prophylaxis in high-risk groups, an ‘accelerated schedule’ using the single, monovalent hepatitis B vaccine is recommended immediately, with the second dose given 1 month after the initial dose, and the third dose given 2 months after the initial dose. For those at continued high risk following exposure, a fourth dose should be given 12 months after the first dose. More detailed guidance is given in the handbook Immunisation against Infectious Disease.
Specific hepatitis B immunoglobulin can also be indicated for use with the vaccine in those accidentally inoculated and in neonates at special risk of infection. If hepatitis B immunoglobulin is indicated, it should be given as soon as possible, ideally at the same time or within 24 hours of the first dose of vaccine, but not after seven days have elapsed since exposure. See also Hepatitis B immunoglobulin in Immunoglobulins p. 1287.
In the UK, groups at high-risk of hepatitis B include:
• individuals with haemophilia, those receiving regular blood transfusions or blood products, and carers responsible for the administration of such products;
• patients with chronic renal failure including those on haemodialysis. Haemodialysis patients should be monitored for antibodies annually and re-immunised if necessary. Home carers (of dialysis patients) should be vaccinated;
• individuals with chronic liver disease;
• healthcare personnel (including trainees) who have direct contact with blood or blood-stained body fluids or with patients’ tissues;
• laboratory staff who handle material that may contain the virus;
• other occupational risk groups such as morticians and embalmers;
• staff and patients of day-care or residential accommodation for those with severe learning difficulties;
• staff and inmates of custodial institutions;
• those travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods;
• families adopting children from countries with a high or intermediate prevalence of hepatitis B;
• foster carers and their families.
Following a primary course of immunisation, most people do not require a reinforcing dose of a hepatitis B-containing vaccine. A single booster dose should be offered to healthcare workers approximately five years after primary immunisation, to patients on renal dialysis with anti-HBs levels below 10mlU/mL, and at the time of a subsequent significant exposure.
Immunisation does not eliminate the need for commonsense precautions for avoiding the risk of infection from known carriers by the routes of infection which have been clearly established, consult Guidance for Clinical Health Care Workers: Protection against Infection with Blood-borne Viruses (available at www.dh.gov.uk/).
Accidental inoculation of hepatitis B virus-infected blood into a wound, incision, needle-prick, or abrasion may lead to infection, whereas it is unlikely that indirect exposure to a carrier will do so.
A combined hepatitis A and B vaccine p. 1317 is also available.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:

Human papillomavirus vaccine
Overview
Human papillomavirus vaccine is available as a bivalent vaccine (Cervarix® or a quadrivalent vaccine (Gardasil®). Since 2012, only Gardasil® is offered as part of the national immunisation programme. Cervarix® is licensed for use in females for the prevention of cervical cancer and other pre-cancerous lesions caused by human papillomavirus types 16 and 18. Gardasil® is licensed for use in females for the prevention of cervical and anal cancers, genital warts and pre-cancerous genital (cervical, vulvar, and vaginal) and anal lesions caused by human papillomavirus types 6, 11, 16, and 18. The vaccines may also provide limited protection against pre-cancerous and cervical cancer in males; genital warts in males and females; and oropharynx cancers in males.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:

www.getintopharma.com
disease caused by other types of human papillomavirus. The two vaccines are not interchangeable and one vaccine product should be used for an entire course.

Human papillomavirus vaccine will be most effective if given before sexual activity starts. From September 2014, a 2-dose schedule is recommended, as long as the first dose is received before the age of 15 years. The first dose is given to females aged 11 to 14 years, and the second dose is given 6–24 months after the first dose (for the purposes of planning the national immunisation programme, it is appropriate to give the second dose 12 months after the first—see Immunisation schedule). If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more.

Females receiving their first dose aged 15 years or older require a 3-dose schedule (see Cervarix® and Gardasil®), with the second and third doses given 1 and 4–6 months after the first dose; all 3 doses should be given within a 12-month period. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

If a 3-dose course of vaccination had been started before September 2014 in a female aged under 15 years, then where possible this should be completed; the interrupted course should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

Under the national programme in England, females remain eligible to receive the human papillomavirus vaccine up to the age of 18 years if they did not receive the vaccine when scheduled. Where appropriate, immunisation with human papillomavirus vaccine should be offered to females coming into the UK as they may not have been offered protection in their country of origin. The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course.

As the vaccines do not protect against all strains of human papillomavirus, routine cervical screening should continue.

### Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

### Influenza vaccine

#### Overview
While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly altering their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccine p. 1322 in use contain the H and N components of the prevalent strain or strains as recommended each year by the World Health Organization.

The influenza vaccines recommended for immunisation are the adjuvanted trivalent influenza vaccine (inactivated), high dose trivalent influenza vaccine (inactivated), cell-grown quadrivalent influenza vaccine (inactivated), standard egg-grown quadrivalent influenza vaccine (inactivated), and live attenuated influenza vaccine. The choice of vaccine is dependent on the person’s age and contra-indications.

The ideal time for immunisation is between September and early November.

Immunisation is recommended for people at high risk from influenza, and to reduce transmission of infection. Annual immunisation is strongly recommended for individuals aged 6 months and over with the following conditions:

- chronic respiratory disease;
- chronic heart disease;
- chronic liver disease;
- chronic renal disease at stage 3, 4 or 5;
- chronic neurological disease;
- complement disorders;
- diabetes mellitus;
- immunosuppression because of disease (including asplenia or splenic dysfunction) or treatment (including prolonged systemic corticosteroid treatment [for over 1 month at dose equivalents of prednisolone p. 678: adult and child over 20 kg, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily], and chemotherapy);
- HIV infection (regardless of immunostatus);
- morbid obesity (BMI of 40 kg/m² and above).

Annual influenza vaccine is also recommended for:

- children of specific ages, see Immunisation schedule p. 1296;
- all pregnant women (including those who become pregnant during the flu season);
- all adults aged 65 years and over (including those becoming 65 by 31 March 2020);
- residents of nursing or residential homes for the elderly and other long-stay facilities;
- carers of individuals whose welfare may be at risk if the carer falls ill;
- household contacts of immunocompromised individuals;
- frontline health and social care workers.

Children aged 6 months to less than 2 years of age in clinical risk groups should be offered the standard egg-grown quadrivalent inactivated influenza vaccine.

Children aged 2–17 years of age (including those in clinical risk groups) should be offered the live attenuated influenza vaccine, administered as a nasal spray (Fluenz tetra®). The live attenuated vaccine is thought to provide broader protection than inactivated vaccines. If the child is in a clinical risk group and the live attenuated vaccine is contra-indicated or otherwise unsuitable, offer standard egg-grown quadrivalent inactivated influenza vaccine.

Children aged 6 months to less than 9 years of age in clinical risk groups who have not had the influenza vaccine previously should be offered two doses of the appropriate influenza vaccine, four weeks apart.

Adults aged 18 to 64 years of age in clinical risk groups, pregnant females, and other eligible groups should be offered either the standard egg-grown quadrivalent inactivated influenza vaccine or the cell-grown quadrivalent inactivated influenza vaccine.

Adults aged 65 years and over should be offered either the adjuvanted trivalent inactivated influenza vaccine or the cell-grown quadrivalent inactivated influenza vaccine. The high dose trivalent inactivated influenza vaccine is equally suitable but is not eligible for reimbursement under the NHS flu vaccination 2019/2020 programme.

In the 2019/2020 national influenza immunisation programme, annual influenza vaccine will be offered to all children aged 2–10 years on 31st August 2019 (including those in reception class and school years 1, 2, 3, 4, 5, and 6).

For the management of influenza, see Influenza p. 561.

Japanese encephalitis vaccine

Overview

Japanese encephalitis is a mosquito-borne viral encephalitis caused by a Flavivirus. Japanese encephalitis vaccine p. 1323 (JIXARO)® is an inactivated vaccine adsorbed onto an adjuvant. It is recommended for individuals who are going to reside in an area where Japanese encephalitis is endemic or epidemic. Travellers to South and South-East Asia and the Far East should be immunised if staying for a month or longer in endemic areas during the transmission season. Other travellers with shorter exposure periods should also be immunised if the risk is considered sufficient. Immunisation is also recommended for laboratory staff at risk of exposure to the virus.

The primary immunisation course of 2 doses should be completed at least one week before potential exposure to Japanese encephalitis virus.

In adults (aged under 65 years) and children (aged 2 months and over) at ongoing risk (including laboratory staff and long-term travellers), a single booster dose should be given 12 months after the primary immunisation course. A booster dose can be considered in adults aged 65 years and over, but the immune response is lower than in younger adults. For other travellers, a single booster dose should be given within 12–24 months after primary immunisation, before potential re-exposure to the Japanese encephalitis virus. Travellers aged 18–64 years should be offered a second booster dose at 10 years if they remain at risk.

Cases of Japanese encephalitis should be managed with supportive treatment.

Up-to-date information on the risk of Japanese encephalitis in specific countries can be obtained from the National Travel Health Network and Centre.

Useful Resources


National Travel Health Network and Centre

nathac.net

Measles, Mumps and Rubella vaccine

Overview

Measles vaccine has been replaced by a combined measles, mumps and rubella vaccine, live p. 1323 (MMR vaccine).

Measles, mumps and rubella vaccine, live aims to eliminate measles, mumps, and rubella (German measles) and congenital rubella syndrome. Every child should receive two doses of measles, mumps and rubella vaccine, live by entry to primary school, unless there is a valid contra-

indication. Measles, mumps and rubella vaccine, live should be given irrespective of previous measles, mumps, or rubella infection or vaccination.

The first dose of measles, mumps and rubella vaccine, live is given to children at 1 year of age, on or after their first birthday. A second dose is given before starting school at 3 years and 4 months of age, or soon after (see Immunisation Schedule).

Children presenting for pre-school booster who have not received the first dose of measles, mumps and rubella vaccine, live should be given a dose of measles, mumps and rubella vaccine, live followed 3 months later by a second dose.

At school-leaving age or at entry into further education, measles, mumps and rubella vaccine, live immunisation should be offered to individuals of both sexes who have not received 2 doses during childhood. In those who have received only a single dose of measles, mumps and rubella vaccine, live in childhood, a second dose is recommended to achieve full protection. If 2 doses of measles, mumps and rubella vaccine, live are required, the second dose should be given one month after the initial dose. The decision on whether to vaccinate adults should take into consideration their vaccination history, the likelihood of the individual remaining susceptible, and the future risk of exposure and disease.

Measles, mumps and rubella vaccine, live should be used to protect against rubella in seronegative women of childbearing age (see Immunisation Schedule); unimmunised healthcare workers who might put pregnant women and other vulnerable groups at risk of rubella or measles should be vaccinated. Measles, mumps and rubella vaccine, live may also be offered to previously unimmunised and seronegative post-partum women (see measles, mumps and rubella vaccine, live)—vaccination a few days after delivery is important because about 60% of congenital abnormalities from rubella infection occur in babies of women who have borne more than one child. Immigrants arriving after the age of school immunisation are particularly likely to require immunisation.

Contacts

Measles, mumps and rubella vaccine, live may also be used in the control of outbreaks of measles and should be offered to susceptible children aged over 6 months who are contacts of a case, within 3 days of exposure to infection. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measles, mumps and rubella vaccine, live has already been given to a child, then the second dose may be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months of age (or soon after) should still be given. Children aged under 9 months for whom avoidance of measles infection is particularly important (such as those with history of recent severe illness) can be given normal immunoglobulin after exposure to measles; routine measles, mumps and rubella vaccine, live immunisation should then be given after at least 3 months at the appropriate age.

Measles, mumps and rubella vaccine, live is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

Children and adults with impaired immune response should not receive live vaccines (see advice on HIV). If they have been exposed to measles infection they should be given normal immunoglobulin.

Travel

Unimmunised travellers, including children over 6 months, to areas where measles is endemic or epidemic should
receive measles, mumps and rubella vaccine, live. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measles, mumps and rubella vaccine, live has already been given to a child, then the second dose should be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months of age (or soon after) should still be given.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Meningococcal vaccine

Overview
Almost all childhood meningococcal disease in the UK is caused by Neisseria meningitidis serogroups B and C.

Meningococcal group C conjugate vaccine protects only against infection by serogroup C and Meningococcal group B vaccine protects only against infection by serogroup B. The risk of meningococcal disease declines with age—immunisation is not generally recommended after the age of 25 years.

Tetravalent meningococcal vaccines that cover serogroups A, C, W135, and Y are available. Although the duration of protection has not been established, the meningococcal groups A, C, W135, and Y conjugate vaccine is likely to provide longer-lasting protection than the unconjugated meningococcal polysaccharide vaccine. The antibody response to serogroup C in unconjugated meningococcal polysaccharide vaccines in young children may be suboptimal [not currently available in the UK].

Meningococcal group B vaccines, Bexsero®, and Trumenba® are licensed in the UK against infection caused by Neisseria meningitidis serogroup B. The use of Bexsero® is recommended in the Immunisation Schedule. Bexsero® contains 3 recombinant Neisseria meningitidis serogroup B proteins and the outer membrane vesicles from the NZ 98/254 strain, in order to achieve broad protection against Neisseria meningitidis serogroup B. Trumenba® contains 2 recombinant Neisseria meningitidis serogroup B proteins. The proteins are adsorbed onto an aluminium compound to stimulate an enhanced immune response.

Childhood immunisation
Meningococcal group C conjugate vaccine provides long-term protection against infection by serogroup C of Neisseria meningitidis. Immunisation consists of 1 dose given at 12 months of age (as the haemophilus influenzae type b with meningococcal group C vaccine p. 1314) and a second dose given at 13–15 years of age (as the meningococcal groups A with C and W135 and Y vaccine p. 1315) (see Immunisation Schedule).

Meningococcal group B vaccine provides protection against infection by serogroup B of Neisseria meningitidis. Immunisation consists of 1 dose given at 2 months of age, a second dose at 4 months of age, and a booster dose at 12 months of age (see Immunisation Schedule above). Unimmunised children aged under 12 months should be given 1 dose of meningococcal group B vaccine (rDNA, component, adsorbed) p. 1314 followed by a second dose of meningococcal group B vaccine (rDNA, component, adsorbed) two months later. They should then be vaccinated according to the Immunisation Schedule (ensuring at least a two month interval between doses of meningococcal group B vaccines). Unimmunised children aged 12–23 months should be given 2 doses of meningococcal group B vaccine (rDNA, component, adsorbed) separated by an interval of two months if they have received less than 2 doses in the first year of life. Unimmunised children aged 2–9 years should be given a single dose of meningococcal group C vaccine (as the haemophilus influenzae type b with meningococcal group C vaccine) followed by a booster dose of meningococcal groups A with C and W135 and Y vaccine at 13–15 years of age. From 2015, unimmunised individuals aged 10–25 years, including those aged under 25 years who are attending university for the first time, should be given a single dose of meningococcal groups A with C and W135 and Y vaccine; a booster dose is not required.

Patients under 25 years of age with confirmed serogroup C disease, who have previously been immunised with meningococcal group C vaccine, should be offered meningococcal group C conjugate vaccine before discharge from hospital.

Travel
Individuals travelling to countries of risk should be immunised with meningococcal groups A, C, W135, and Y conjugate vaccine, even if they have previously received meningococcal group C conjugate vaccine. If an individual has recently received meningococcal group C conjugate vaccine, an interval of at least 4 weeks should be allowed before administration of the tetravalent (meningococcal groups A, C, W135, and Y) vaccine.

Vaccination is particularly important for those living or working with local people or visiting an area of risk during outbreaks.

Immunisation recommendations and requirements for visa entry for individual countries should be checked before travelling, particularly to countries in Sub-Saharan Africa, Asia, and the Indian sub-continent where epidemics of meningococcal outbreaks and infection are reported. Country-by-country information is available from the National Travel Health Network and Centre (www.nathnac.org/).

Proof of vaccination with the tetravalent meningococcal groups A with C and W135 and Y vaccine is required for those travelling to Saudi Arabia during the Hajj and Umrah pilgrimages (where outbreaks of the W135 strain have occurred).

Contacts
For advice on the immunisation of laboratory workers and close contacts of cases of meningococcal disease in the UK and on the role of the vaccine in the control of local outbreaks, consult Guidance for Public Health Management of Meningococcal Disease in the UK at www.gov.uk/phe. Also see for antibacterial prophylaxis for prevention of secondary cases of meningococcal meningitis.

The need for immunisation of laboratory staff who work directly with Neisseria meningitidis should be considered.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
Pertussis vaccine

Overview
Pertussis vaccine is given as a combination preparation containing other vaccines. Acellular vaccines are derived from highly purified components of Bordetella pertussis. Primary immunisation against pertussis (whooping cough) requires 3 doses of an acellular pertussis-containing vaccine (see Immunisation schedule), given at intervals of 1 to 2 months from the age of 2 months.

All children up to the age of 10 years should receive primary immunisation with a combination vaccine of diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine p. 1312 (Infanrix hexa®).

A booster dose of an acellular pertussis-containing vaccine should ideally be given 3 years after the primary course, although, the interval can be reduced to 1 year if the primary course was delayed. Children aged 1–10 years who have not received a pertussis-containing vaccine as part of their primary immunisation should be offered 1 dose of a suitable pertussis-containing vaccine; after an interval of at least 1 year, a booster dose of a suitable pertussis-containing vaccine should be given. Immunisation against pertussis is not routinely recommended in individuals over 10 years of age.

Vaccination of pregnant women against pertussis

In response to the pertussis outbreak, the UK health departments introduced a temporary programme (October 2012) to vaccinate pregnant women against pertussis, and this programme will continue until further notice. The aim of the programme is to boost the levels of pertussis–specific antibodies that are transferred through the placenta, from the mother to the fetus, so that the newborn is protected before routine immunisation begins at 2 months of age.

Pregnant women should be offered a single dose of acellular pertussis-containing vaccine (as adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine; Boostrix-IPV®) between 16 and 32 weeks of pregnancy. Public Health England has advised (2016) that the vaccine is probably best offered after the fetal anomaly scan at around 18–20 weeks. Pregnant women should be offered a single dose of acellular pertussis-containing vaccine up to the onset of labour if they missed the opportunity for vaccination at 16–32 weeks of pregnancy. A single dose of acellular pertussis-containing vaccine may also be offered to new mothers, who have never previously been vaccinated against pertussis, until the child receives the first vaccination.

While this programme is in place, women who become pregnant again should be offered vaccination during each pregnancy to maximise transplacental transfer of antibody.

Contacts
Vaccination against pertussis should be considered for close contacts of cases with pertussis who have been offered antibacterial prophylaxis. Unimmunised or partially immunised contacts under 10 years of age should complete their vaccination against pertussis. A booster dose of an acellular pertussis-containing vaccine is recommended for contacts aged over 10 years who have not received a pertussis-containing vaccine in the last 5 years and who have not received adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine in the last month.

Side-effects
Local reactions do not contra-indicate further doses.

The vaccine should not be withheld from children with a history to a preceding dose of:

- fever, irrespective of severity;
- persistent crying or screaming for more than 3 hours;
- severe local reaction, irrespective of extent.

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Pneumococcal vaccine

Overview
The pneumococcal polysaccharide conjugate vaccine (adsorbed) p. 1316 and the pneumococcal polysaccharide vaccine p. 1316 protect against infection with Streptococcus pneumoniae (pneumococcus). Both vaccines contain polysaccharide from capsular pneumococci. The pneumococcal polysaccharide vaccine contains purified polysaccharide from 23 capsular types of pneumococcus, whereas the pneumococcal polysaccharide conjugate vaccine (adsorbed) contains polysaccharide from either 10 capsule types (Synflorix®) or 13 capsule types (Prevenar 13®). Both vaccines are inactivated.

Prevenar 13® is the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) used in the childhood Immunisation schedule p. 1296. The schedule consists of 3 doses given at separate intervals. The 23-valent pneumococcal polysaccharide vaccine is recommended for all adults aged 65 years and over, and for adults and children aged 2 years and over in the following at-risk groups:

- asplenia or splenic dysfunction (including homozygous sickle cell disease and coeliac syndrome which could lead to splenic dysfunction);
- chronic respiratory disease (including severe asthma treated with continuous or frequent use of a systemic corticosteroid);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- diabetes mellitus requiring insulin or oral hypoglycaemic drugs;
- immunosuppression because of disease (e.g. HIV infection, and genetic disorders affecting the immune system) or treatment (including prolonged systemic corticosteroid treatment for over 1 month at dose equivalents of prednisolone: adult and child 20 mg and over, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily, and chemotherapy);
- presence of cochlear implant;
- conditions where leakage of cerebrospinal fluid may occur.

The 23-valent pneumococcal polysaccharide vaccine should also be considered for those at risk of occupational exposure to metal fume (e.g. welders). Where possible, the vaccine should be given at least 2 weeks (ideally 4–6 weeks) before splenectomy, chemotherapy, or radiotherapy; patients should be given advice about the increased risk of pneumococcal infection. If it is not possible to vaccinate at least 2 weeks before splenectomy, chemotherapy, or radiotherapy, the vaccine should be given at least 2 weeks after the splenectomy, and at least 3 months after completion of chemotherapy or radiotherapy. For patients with leukaemia or who have had a bone marrow transplant, refer to Chapter 25, Pneumococcal, in Immunisation against infectious disease – The Green Book for vaccination advice. A patient card and Information leaflet
Children diagnosed with at-risk conditions aged 10 years and over and adults

Individuals diagnosed or first presenting with an at-risk condition should be given a single dose of the 23-valent pneumococcal polysaccharide vaccine. No additional 23-valent pneumococcal polysaccharide vaccine is required at 65 years of age.

Severely immunocompromised individuals should be given a single dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) followed by the 23-valent pneumococcal polysaccharide vaccine at least 2 months after, irrespective of their previous pneumococcal vaccinations. If the 23-valent pneumococcal polysaccharide vaccine has already been given, the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) should be given at least 6 months after.

For further information on vaccination in patients with asplenia, see Vaccination, general principles p. 1294.

Revaccination

In individuals with higher concentrations of antibodies to pneumococcal polysaccharides, revaccination with the 23-valent pneumococcal polysaccharide vaccine more commonly produces side effects (e.g. chills, asthenia, and myalgia). Revaccination is therefore not recommended, except for individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and chronic renal disease), where revaccination is recommended every 5 years.

Management of cases

For the management of cases, contacts and outbreaks, refer to Chapter 25, Pneumococcal, in Immunisation against infectious disease—'The Green Book'.

Useful Resources

Recommendations reflect Chapter 25, Pneumococcal, in Immunisation against infectious disease—'The Green Book'.


Poliomyelitis vaccine

Overview

Two types of poliomyelitis vaccines (containing strains of poliovirus types 1, 2, and 3) are available, inactivated poliomyelitis vaccine (for injection) and live (oral) poliomyelitis vaccine. Inactivated poliomyelitis vaccines, only available in combined preparation, is recommended for routine immunisation.

A course of primary immunisation consists of 3 doses of a combined preparation containing inactivated poliomyelitis vaccines, starting at 2 months of age with intervals of 1 month between doses (see Immunisation schedule). A course of 3 doses should also be given to all unimmunised adults; no adult should remain unimmunised against poliomyelitis.

Two booster doses of a preparation containing inactivated poliomyelitis vaccines are recommended, the first before school entry and the second before leaving school (see Immunisation schedule). Further booster doses are only necessary for adults at special risk, such as travellers to endemic areas, or laboratory staff likely to be exposed to the viruses, or healthcare workers in possible contact with cases; booster doses should be given to such individuals every 10 years.

Live (oral) poliomyelitis vaccine is no longer available for routine use; its use may be considered during large outbreaks, but advice should be sought from Public Health England. The live (oral) vaccine poses a very rare risk of vaccine-associated paralytic polio because the attenuated
strain of the virus can revert to a virulent form. For this reason the live (oral) vaccine must not be used for immunosuppressed individuals or their household contacts. The use of inactivated poliomyelitis vaccines removes the risk of vaccine-associated paralytic polio altogether.

Travel
Unimmunised travellers to areas with a high incidence of poliomyelitis should receive a full 3-dose course of a preparation containing inactivated poliomyelitis vaccines. Those who have not been vaccinated in the last 10 years should receive a booster dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine. Information about countries with a high incidence of poliomyelitis can be obtained from www.travax.nhs.uk/ or from the National Travel Health Network and Centre (www.nathnac.org/).

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:

Rabies vaccine

Overview
Rabies vaccine p. 1324 contains inactivated rabies virus cultivated in either human diploid cells or purified chick embryo cells; vaccines are used for pre- and post-exposure prophylaxis.

Pre-exposure prophylaxis
Immunisation should be offered to those at high risk of exposure to rabies—labour staff who handle the rabies virus, those working in quarantine stations, animal handlers, veterinary surgeons and field workers who are likely to be bitten by infected wild animals, certain port officials, and bat handlers. Transmission of rabies by humans has not been recorded but it is advised that those caring for patients with rabies handlers. Information about countries with a high incidence of poliomyelitis can be obtained from www.travax.nhs.uk/ or from the National Travel Health Network and Centre (www.nathnac.org/).

Useful Resources
Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:

Rotavirus vaccine

Overview
Rotavirus vaccine p. 1325 is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection. The recommended schedule consists of 2 doses, the first at 2 months of age, and the second at 3 months of age (see Immunisation schedule). The first dose of rotavirus vaccine must be given between 6–15 weeks of age and the second dose should be given after an interval of at least 4 weeks; the vaccine should not be started in children 15 weeks of age or older. Ideally, the full course should be completed before 16 weeks of age to provide protection before the main burden of disease, and to avoid a temporal
association between vaccination and intussusception; the course must be completed before 24 weeks of age.

The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with immunosuppressed close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus. Carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby’s nappies.

**Useful Resources**

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

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**Smallpox vaccine**

**Overview**

Limited supplies of smallpox vaccine are held at the Specialist and Reference Microbiology Division, Public Health England Colindale (Tel: 020 8209 4400) for the exclusive use of workers in laboratories where pox viruses (such as vaccinia) are handled.

If a wider use of the vaccine is being considered, Guidelines for smallpox response and management in the post-eradication era should be consulted at www.gov.uk/phe.

**Useful Resources**

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

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**Tetanus vaccine**

**Overview**

Tetanus vaccine contains a cell-free purified toxin of Clostridium tetani adsorbed on aluminium hydroxide or aluminium phosphate to improve antigenicity.

Primary immunisation for children under 10 years consists of 3 doses of a combined preparation containing adsorbed tetanus vaccine, with an interval of 1 month between doses (see Routine immunisation schedule). Following routine childhood vaccination, 2 booster doses of a preparation containing adsorbed tetanus vaccine are recommended, the first before school entry and the second before leaving school.

The recommended schedule of tetanus vaccination not only gives protection against tetanus in childhood but also gives the basic immunity for subsequent booster doses. In most circumstances, a total of 5 doses of tetanus vaccine is considered sufficient for long term protection.

For primary immunisation of adults and children over 10 years previously unimmunised against tetanus, 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine are given with an interval of 1 month between doses (see Diphtheria-containing vaccines for children over 10 years and adults).

When an individual presents for a booster dose but has been vaccinated following a tetanus-prone wound, the vaccine preparation administered at the time of injury should be determined. If this is not possible, the booster should still be given to ensure adequate protection against all antigens in the booster vaccine.

Very rarely, tetanus has developed after abdominal surgery; patients awaiting elective surgery should be asked about tetanus immunisation and immunised if necessary.

Parenteral drug abuse is also associated with tetanus; those abusing drugs by injection should be vaccinated if unimmunised—booster doses should be given if there is any doubt about their immunisation status.

All laboratory staff should be offered a primary course if unimmunised.

**Wounds**

Wounds are considered to be tetanus-prone if they are sustained more than 6 hours before surgical treatment or at any interval after injury and are puncture-type (particularly if contaminated with soil or manure) or show much devitalised tissue or are septic or are compound fractures or contain foreign bodies. All wounds should receive thorough cleansing.

- **For clean wounds**: fully immunised individuals (those who have received a total of 5 doses of a tetanus-containing vaccine at appropriate intervals) and those whose primary immunisation is complete (with boosters up to date), do not require tetanus vaccine; individuals whose primary immunisation is incomplete or whose boosters are not up to date require a reinforcing dose of a tetanus-containing vaccine (followed by further doses as required to complete the schedule); non-immunised individuals (or those whose immunisation who is not known or who have been fully immunised but are now immunocompromised) should be given a dose of the appropriate tetanus-containing vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need)

- **For tetanus-prone wounds**: management is as for clean wounds with the addition of a dose of tetanus immunoglobulin given at a different site; in fully immunised individuals and those whose primary immunisation is complete (with boosters up to date) the immunoglobulin is needed only if the risk of infection is especially high (e.g. contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, co-amoxiclav, or metronidazole) may also be required for tetanus-prone wounds.

**Useful Resources**

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

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**Tick-borne encephalitis vaccine**

**Overview**

Tick-borne encephalitis vaccine, inactivated p. 1325 contains inactivated tick-borne encephalitis virus cultivated in chick embryo cells. It is recommended for immunisation of those working in, or visiting, high-risk areas (see International Travel). Those working, walking or camping in warm forested areas of Central and Eastern Europe, Scandinavia, Northern and Eastern China, and some parts of Japan, particularly from April to November when ticks are
Vaccines

1308 Vaccination

most prevalent, are at greatest risk of tick-borne encephalitis. For full protection, 3 doses of the vaccine are required; booster doses are required every 3–5 years for those still at risk. Ideally, immunisation should be completed at least one month before travel.

Useful Resources

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:


Typhoid vaccine

07-Nov-2018

Overview

Typhoid vaccine p. 1217 is available as a Vi capsular polysaccharide (from Salmonella typhi) vaccine for injection and a live, attenuated Salmonella typhi vaccine for oral use.

Typhoid immunisation is advised for:

- travellers to areas where typhoid is endemic and whose planned activities put them at higher risk (country-by-country information is available from the National Travel Health Network and Centre);
- travellers to endemic areas where frequent or prolonged exposure to poor sanitation and poor food hygiene is likely;
- laboratory personnel who, in the course of their work, may be exposed to Salmonella typhi.

Capsular polysaccharide typhoid vaccine is given as a single dose, usually by intramuscular injection. Children under 2 years [unlicensed] may respond suboptimally to the vaccine, but children aged between 1–2 years should be immunised if the risk of typhoid fever is considered high (immunisation is not recommended for infants under 12 months). A single booster dose should be given at 3-year intervals in adults and children over 2 years of age who remain at risk from typhoid fever.

Oral typhoid vaccine is a live, attenuated vaccine contained in an enteric-coated capsule recommended in individuals aged 6 years and over. One capsule taken on alternate days for a total of 3 doses, provides protection 7–10 days after the last dose. If travelling from a non-endemic area to an area where typhoid is endemic, a booster consisting of 3 doses is recommended every 3 years. The oral typhoid vaccine should be avoided in immunosuppressed and HIV-infected individuals.

Prevention of typhoid primarily depends on improving sanitation and water supplies in endemic areas and on scrupulous personal, food and water hygiene.

All suspected cases of typhoid fever must be notified to the local health protection unit. Where there is a community level outbreak, specialist advice should be sought from Public Health England (tel. 020 8200 4400) or, in Scotland, Health Protection Scotland (tel. 0140 300 1191).

Useful Resources


National Travel Health Network and Centre nathac.net

Varicella-zoster vaccine

Overview

The live varicella-zoster vaccine p. 1326, Varilrix® and Varivax®, are licensed for immunisation against varicella (chickenpox) in seronegative individuals. They are not recommended for routine use in children, but can be given to seronegative healthy children over 1 year who come into close contact with individuals at high risk of severe varicella infections. The Department of Health recommends these vaccines for seronegative healthcare workers who come into direct contact with patients. Those with a history of chickenpox or shingles can be considered immune, but healthcare workers with a negative or uncertain history should be tested.

Rarely, the varicella-zoster vaccine virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:

- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy;
- healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the lesions and be allowed to continue working unless in contact with patients at high risk of severe varicella.

National shingles immunisation programme

The aim of the national shingles immunisation programme is to lower the incidence and severity of shingles in older people using the high potency, live varicella-zoster vaccine, Zostavax®. It is recommended that vaccination is routinely offered to people aged 70 years. A catch-up programme has also been rolled out (since 2013) in those aged 70–79 years, as this age group is likely to have the greatest benefit from vaccination.

In the 2016–2017 immunisation programme, varicella-zoster vaccine is recommended in adults who were 70 or 78 years of age on 1st September 2016. Patients who were eligible for vaccination in the first 3 years of the programme but have not been vaccinated against herpes zoster remain eligible until their 80th birthday; this includes patients who were aged 71–73 or 79 on 1st September 2016. Patients who have reached 80 years are no longer eligible for vaccination. A single dose of Zostavax® is likely to give protection for at least 7 years, but the need for, or timing of, a booster dose has not been established. Although Zostavax® is not recommended for the treatment of shingles or post-herpetic neuralgia, it can be given to those with a previous history of shingles; ideally the vaccine should be delayed until systemic antiviral therapy has been completed.

Varicella-zoster immunoglobulin p. 1292 is used to protect susceptible individuals at increased risk of severe varicella infection (see Immunoglobulins p. 1287).

Useful Resources

Advice reflects that in the handbook Immunisation against Infectious Disease (2013), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates. Chapters from the handbook (including updates since 2013) are available at:


Yellow fever vaccine

Overview
Yellow fever vaccine, live p. 1327 is an attenuated preparation of yellow fever virus grown in chick eggs. Yellow fever vaccine, live is recommended for:
- laboratory workers handling infected material;
- individuals aged 9 months or older who are travelling to, or living in areas or countries with a risk of yellow fever transmission;
- individuals aged 9 months or older who are travelling to, or living in countries that require an International Certificate of Vaccination or Prophylaxis (ICVP) for entry (information about countries at risk of yellow fever is available from the National Travel Health Network and Centre).

Children aged under 9 months are at risk of vaccine-associated encephalitis, with the risk being inversely proportional to age. Children aged under 6 months should not be vaccinated. Children aged 6–9 months should only be vaccinated following a detailed risk assessment, and vaccination is generally only recommended if the risk of yellow fever transmission is high (such as during epidemics/epidemics). If travel is unavoidable, seek expert advice on whether to vaccinate.

A single-dose of yellow fever vaccine, live confers life-long immunity against yellow fever disease. Immunisation should be performed at least 10 days before travelling to an endemic area to allow protective immunity to develop and for the ICVP (if required) to become valid.

Reinforcing immunisation is not needed, except for a small subset of individuals at continued risk who may not have developed long-term protection from their initial yellow fever vaccine, live vaccination—seek expert advice.

Yellow fever vaccine, live should be avoided in HIV-infected and immunosuppressed individuals. If the yellow fever risk is unavoidable, consult the British HIV Association (bhiva.org/vaccination-guidelines.aspx) or other specialist advice.

All suspected cases of yellow fever must be notified to the local health protection unit. Where there is a community level outbreak, specialist advice should be sought from Public Health England (tel. 020 8200 4400) or, in Scotland, Health Protection Scotland (tel. 0140 300 1191).

Useful Resources
National Travel Health Network and Centre
nathac.net

Vaccines for travel

Immunisation for travel
See advice on Malaria, treatment p. 613.

No special immunisation is required for travellers to the United States, Europe, Australia, or New Zealand, although all travellers should have immunity to tetanus and poliomyelitis (and childhood immunisations should be up to date); Tick-borne encephalitis vaccine is recommended for immunisation of those working in, or visiting, high-risk areas. Certain special precautions are required in non-European areas surrounding the Mediterranean, in Africa, the Middle East, Asia, and South America.

Travellers to areas that have a high incidence of poliomyelitis or tuberculosis should be immunised with the appropriate vaccine; in the case of poliomyelitis previously immunised travellers may be given a booster dose of a preparation containing inactivated poliomyelitis vaccine. BCG immunisation is recommended for travellers aged under 16 years proposing to stay for longer than 3 months (or in close contact with the local population) in countries with an incidence of tuberculosis greater than 40 per 100,000 (list of countries where the incidence of tuberculosis is greater than 40 cases per 100,000 is available from www.gov.uk/phe); it should preferably be given 3 months or more before departure.

Yellow fever immunisation is recommended for travel to the endemic zones of Africa and South America. Many countries require an International Certificate of Vaccination from individuals arriving from, or who have been travelling through, endemic areas; other countries require a certificate from all entering travellers (consult the Department of Health handbook, Health Information for Overseas Travel, www.dh.gov.uk).

Immunisation against meningococcal meningitis is recommended for a number of areas of the world.

Protection against hepatitis A is recommended for travellers to high-risk areas outside Northern and Western Europe, North America, Japan, Australia and New Zealand. Hepatitis A vaccine is recommended and it is likely to be effective even if given shortly before departure; Public Health England recommends travellers can be vaccinated with hepatitis A vaccine up to the day of travel, and no longer recommends the use of normal immunoglobulin for travel prophylaxis. Special care must also be taken with food hygiene.

Hepatitis B vaccine is recommended for those travelling to areas of high or intermediate prevalence who intend to seek employment as healthcare workers or who plan to remain there for lengthy periods and who may therefore be at increased risk of acquiring infection as the result of medical or dental procedures carried out in those countries. Short-term tourists or business travellers are not generally at increased risk of infection but may put themselves at risk by their sexual behaviour when abroad.

Prophylactic immunisation against rabies is recommended for travellers to enzootic areas on long journeys or to areas out of reach of immediate medical attention.

Travellers who have not had a tetanus booster in the last 10 years and are visiting areas where medical attention may not be accessible should receive a booster dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, even if they have received 5 doses of a tetanus-containing vaccine previously.

Typhoid vaccine is indicated for travellers to countries where typhoid is endemic, but the vaccine is no substitute for personal precautions.

There is no requirement for cholera vaccination as a condition for entry into any country, but oral cholera vaccine should be considered for backpackers and those travelling to situations where the risk is greatest (e.g. refugee camps). Regardless of vaccination, travellers to areas where cholera is endemic should take special care with food hygiene.

Advice on diphtheria, on Japanese encephalitis, and on tick-borne encephalitis is included in Health Information for Overseas Travel.

Food hygiene
In areas where sanitation is poor, good food hygiene is important to help prevent hepatitis A, typhoid, cholera, and other diarrhoeal diseases (including travellers’ diarrhoea). Food should be freshly prepared and hot, and uncooked vegetables (including green salads) should be avoided; only fruits which can be peeled should be eaten. Only suitable
bottled water, or tap water that has been boiled or treated with sterilising tablets, should be used for drinking.

**Information on health advice for travellers**

Health professionals and travellers can find the latest information on immunisation requirements and precautions for avoiding disease while travelling from: www.nathric.org. The handbook, *Health Information for Overseas Travel* (2010), which draws together essential information for health care professionals regarding health advice for travellers, can also be obtained from this website.

Immunisation requirements change from time to time, and information on the current requirements for any particular country may be obtained from the embassy or legation of the appropriate country or from:

- **National Travel Health Network and Centre**
  UCLH NHS Foundation Trust
  3rd Floor Central
  250 Euston Road
  London
  NW1 2PG
  Tel: 0845 602 6712
  (Monday and Friday: 9–11 a.m. and 1–2 p.m., Tuesday to Thursday: 9–11 a.m. and 1–3:30 p.m. For healthcare professionals only)
  www.travelhealthpro.org.uk/

- **Travel Medicine Team**
  Health Protection Scotland
  Meridian Court
  5 Cadogan Street
  Glasgow
  G2 6QE
  Tel: (0141) 300 1130
  (2–4 p.m. Monday to Wednesday, 9:30–11:30 a.m. Friday; for registered TRAVAX users only)
  www.travax.nhs.uk
  (TRAVAX is free for NHS Scotland users (registration required); subscription fee may be payable for users outside NHS Scotland)

- **Welsh Assembly Government**
  Tel: (029) 2082 5397
  (9 a.m.–5:30 p.m. weekdays)

- **Department of Health, Social Services and Public Health**
  Stormont
  Belfast
  BT4 3SQ
  Tel: (028) 9052 2118
  (9 a.m.–5 p.m. weekdays)
  www.dhsspsni.gov.uk

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**VACCINES**

**Vaccines**

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE (UPDATED NOVEMBER 2017)

Following reports of death in neonates who received a live attenuated vaccine after exposure to a tumor necrosis factor alpha (TNF-α) inhibitor in utero, the MHRA has issued the following advice:

- any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible;
- in the case of infants who have been exposed to TNF-α inhibitors and other immunosuppressive biological medicines in utero, PHE advise that any live attenuated vaccination (e.g. BCG vaccine) should be deferred until the infant is age 6 months;
- PHE advise if there is any doubt as to whether an infant due to receive a live attenuated vaccine may be immunosuppressed due to the mother’s therapy, including exposure through breast-feeding, specialist advice should be sought.

**CONTRA-INDICATIONS**

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- Impaired immune response Severely immunosuppressed patients should not be given live vaccines (including those with severe primary immunodeficiency).

**CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

Vaccination may be postponed if the individual is suffering from an acute illness; however, it is not necessary to postpone immunisation in patients with minor illnesses without fever or systemic upset.

- Impaired immune response and drugs affecting immune response Immune response to vaccines may be reduced in immunosuppressed patients and there is also a risk of generalised infection with live vaccines.

Specialist advice should be sought for those being treated with high doses of corticosteroids (dose equivalents of prednisolone: adults, at least 40 mg daily for more than 1 week; children, 2 mg/kg (or more than 40 mg) daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs, and those being treated for malignant conditions with chemotherapy or generalised radiotherapy. Live vaccines should be postponed until at least 3 months after stopping high-dose systemic corticosteroids and at least 6 months after stopping other immunosuppressive drugs or generalised radiotherapy (at least 12 months after discontinuing immunosuppressants following bone-marrow transplantation).


- Predisposition to neurological problems When there is a personal or family history of febrile convulsions, there is an increased risk of these occurring during fever from any cause including immunisation, but this is not a contra-indication to immunisation. In children who have had a seizure associated with fever without neurological deterioration, immunisation is recommended; advice on the management of fever (see Post-immunisation Pyrexia in Infants) should be given before immunisation. When a child has had a convulsion not associated with fever, and the neurological condition is not deteriorating, immunisation is recommended.

Children with stable neurological disorders (e.g. spina bifida, congenital brain abnormality, and peri-natal hypoxic-ischaemic encephalopathy) should be immunised according to the recommended schedule.

When there is a still evolving neurological problem, including poorly controlled epilepsy, immunisation should be deferred and the child referred to a specialist. Immunisation is recommended if a cause for the neurological disorder is identified. If a cause is not identified, immunisation should be deferred until the condition is stable.

- **SIDE-EFFECTS**

  **Common or very common**
  - Appetite decreased · arthralgia (frequency not known in elderly) · diarrhoea (uncommon in elderly) · dizziness (uncommon in elderly) · fatigue · fever · headache · irritability · lymphadenopathy (uncommon in elderly) · malaise · myalgia · nausea

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www.getintopharma.com
UNLICENSED USE Infanrix-IPV + HIB® not licensed for use in children over 36 months; Pediacel® not licensed in children over 4 years. However, the Department of Health recommends that these be used for children up to 10 years.

SIDE-EFFECTS

Common or very common Crying abnormal - drowsiness - restlessness

Uncommon Cough - extensive swelling of vaccinated limb - increased risk of infection - rhinorrhoea

Frequency not known Angioedema - apnoea - hypotonic-hyporesponsiveness episode - seizure

SIDE EFFECTS, FURTHER INFORMATION The incidence of local and systemic reactions is lower with acellular pertussis vaccines than with whole-cell pertussis vaccines used previously.

Compared with primary vaccination, injection site reactions are more common with booster doses of vaccines containing acellular pertussis.

Public Health England has advised (2016) that the vaccine should not be withheld from children with a history to a preceding dose of: fever, irrespective of severity; hypotonic-hyporesponsive episodes; persistent crying or screaming for more than 3 hours; severe local reaction, irrespective of extent.

PRESCRIBING AND DISPENSING INFORMATION Available as part of childhood schedule from health organisations or ImmForm.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Powder and suspension for suspension for injection Infanrix-IPV + Hib® (GlaxoSmithKline UK Ltd) Infanrix-IPV + Hib® vaccine powder and suspension for suspension for injection 0.5ml pre-filled syringes 1 pre-filled disposable injection £2.26.

Vaccines with pertussis, poliomyelitis vaccine and tetanus

INDICATIONS AND DOSE

First booster dose

By intramuscular injection

Child 3-9 years: 0.5 mL, to be given 3 years after primary immunisation

Vaccination of pregnant women against pertussis (using low dose vaccines)

By intramuscular injection

Females of childbearing potential: 0.5 mL for 1 dose

SIDE-EFFECTS

Common or very common Abdominal pain

Uncommon Apathy (in children) - asthma - chills - drowsiness (very common in children) - dry throat (in children) - extensive swelling of vaccinated limb (very common in children) - oral herpes - pain - paraesthesia - sleep disorder (in children)
**1312 Vaccination**

- **Frequency not known** Angioedema - asthenia - hypotonic-hyporesponsive episode - seizure

**SIDE-EFFECTS, FURTHER INFORMATION** The incidence of local and systemic reactions is lower with acellular pertussis vaccines than with whole-cell pertussis vaccines used previously.

Compared with primary vaccination, injection site reactions are more common with booster doses of vaccines containing acellular pertussis.

Public Health England has advised (2016) that the vaccine should not be withheld from children with a history to a preceding dose of: fever, irrespective of severity; hypotonic-hyporesponsive episodes; persistent crying or screaming for more than 3 hours; severe local reaction, irrespective of extent.

- **PREGNANCY** Contra-indicated in pregnant women with a history of encephalopathy of unknown origin within 7 days of previous immunisation with a pertussis-containing vaccine. Contra-indicated in pregnant women with a history of transient thrombocytopenia or neurological complications following previous immunisation against diphtheria or tetanus.

**PRESCRIBING AND DISPENSING INFORMATION** Pregnant women should be vaccinated using low dose vaccines (brands may include Boostrix-IPV® or Repevax®).

Available as part of childhood immunisation schedule from health organisations or ImmForm.

Available for vaccination of pregnant women from ImmForm.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin, polymyxin b, streptomycin

- **Boostrix-IPV®** (GlaxoSmithKline UK Ltd)
  - Boostrix-IPV suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PFS) | £22.74 DT + £20.00
- **Repevax** (Sanofi Pasteur)
  - Repevax vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PFS) | £20.00 DT + £20.00

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**Diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b vaccine**

**INDICATIONS AND DOSE**

Primary immunisation (first dose)

- BY DEEP INTRAMUSCULAR INJECTION
  - Child 2 months: 0.5 mL for 1 dose

Primary immunisation (second dose)

- BY DEEP INTRAMUSCULAR INJECTION
  - Child 3 months: 0.5 mL for 1 dose, preferably administer at a different injection site to that of first dose

Primary immunisation (third dose)

- BY DEEP INTRAMUSCULAR INJECTION
  - Child 4 months: 0.5 mL for 1 dose, preferably administer at a different injection site to that of second dose

**SIDE-EFFECTS**

- Common or very common Anxiety - crying abnormal
- Uncommon Cough - drowsiness - extensive swelling of vaccinated limb - increased risk of infection
- Rare or very rare Angioedema - apnoea - hypotonic-hyporesponsive episode - seizure - swelling - thrombocytopenia

**PRESCRIBING AND DISPENSING INFORMATION** Available as part of childhood schedule from health organisations or ImmForm.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and suspension for suspension for injection**

**EXCIPIENTS:** May contain Neomycin, polymyxin b

- **Infanrix Hexa** (GlaxoSmithKline UK Ltd)
  - Infanrix Hexa vaccine powder and suspension for suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PFS) | £25.00

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**VACCINES** BACTERIAL VACCINES

**Anthrax vaccine**

**INDICATIONS AND DOSE**

Immunisation against anthrax

- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: Initially 0.5 mL every 3 weeks for 3 doses, followed by 0.5 mL after 6 months, to be administered in the deltoid region

Booster

- BY DEEP INTRAMUSCULAR INJECTION
  - Adult: 0.5 mL every 10 years for up to 3 doses, to be administered in deltoid region
Bacillus Calmette-Guérin vaccine (BCG Vaccine)

**INDICATIONS AND DOSE**

**Immunisation against tuberculosis**

- **BY INTRADERMAL INJECTION**
  - Child 1-11 months: 0.05 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.
  - Child 1-17 years: 0.1 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.
  - Adult: 0.1 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.

**CONTRA-INDICATIONS**

Generalised septic skin conditions. A lesion-free site should be used to administer BCG vaccine to patients with eczema.

**CAUTIONS**

A lesion-free site should be used to administer BCG vaccine to patients with eczema. When BCG is given to infants, there is no need to delay routine primary immunisations. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of regional lymphadenitis.

**INTERACTIONS**

Appendix 1: live vaccines

**SIDE-EFFECTS**

- Rare or very rare: Increased risk of infection - osteitis

**PRE-TREATMENT SCREENING**

Apart from children under 6 years, any person being considered for BCG immunisation must first be given a skin test for hypersensitivity to tuberculin protein (see tuberculin purified protein derivative p. 1294). A skin test is not necessary for a child under 6 years provided that the child has not stayed for longer than 3 months in a country with an incidence of tuberculosis greater than 40 per 100,000, the child has not had contact with a person with tuberculosis, and there is no family history of tuberculosis within the last 5 years.

**DIRECTIONS FOR ADMINISTRATION**

Intradermal injection technique. Skin is stretched between thumb and forefinger and needle (size 25G or 26G) inserted (bevel upwards) for about 3 mm into superficial layers of dermis (almost parallel with surface). Needle should be short with short bevel (can usually be seen through epidermis during insertion). Tense raised, blanched bleb showing tips of hair follicles is sign of correct injection; 7 mm bleb ≥ 0.1 mL injection, 3 mm bleb ≥ 0.05 mL injection; if considerable resistance not felt, needle too deep and should be removed and reinserted before giving more vaccine.

**PRESCRIBING AND DISPENSING INFORMATION**

Available from health organisations or direct from ImmForm (Secretary of State for Health) (SSI brand, multidose vial with diluent).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

EXCIPIENTS: May contain Thiomersal

- Anthrax vaccine (Non-proprietary) Anthrax vaccine (alum precipitated sterile filtrate) suspension for injection 0.5mL ampoules | 5 ampoule

- BioThrax (Secretary of State for Health) BioThrax suspension for injection 5mL multidose vials | 1 vial

£751.71 | 300 vial £225,513.09

**BioThrax**

Preparedness and Response (Porton Down).

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Cholera vaccine

**INDICATIONS AND DOSE**

**Immunisation against cholera**

- **BY MOUTH**
  - Child 2-5 years: 1 dose every 1-6 weeks for 3 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure.
  - Child 6-17 years: 1 dose every 1-6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure.
  - Adult: 1 dose every 1-6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure.

**Booster**

- **BY MOUTH**
  - Child 2-5 years: A single booster dose can be given within 6 months after primary course, if more than 6 months have elapsed since the last vaccination, the primary course should be repeated.
  - Child 6-17 years: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated.
  - Adult: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated.

**CONTRA-INDICATIONS**

Acute gastro-intestinal illness.

**INTERACTIONS**

Appendix 1: cholera vaccine

**SIDE-EFFECTS**

- Uncommon: Gastrointestinal discomfort - gastrointestinal disorders.
- Rare or very rare: Chills - cough - dehydration - drowsiness - hyperhidrosis - increased risk of infection - insomnia - pulmonary reaction - syncope - taste altered - throat pain.
- Frequency not known: Angioedema - asthenia - dyspnoea - hypertension - influenza like illness - lymphadenitis - pain - paraesthesia - sputum increased.

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www.getintopharma.com
Haemophilus influenzae type b with meningococcal group C vaccine

**INDICATIONS AND DOSE**

Booster dose (for infants who have received primary immunisation with a vaccine containing *Haemophilus influenzae* type b component) and primary immunisation against *Neisseria meningitidis*

- **BY INTRAMUSCULAR INJECTION**
  - Child 12-13 months: 0.5 mL for 1 dose
  - Immunisation against *Neisseria meningitidis* in an unimmunised patient
    - **BY INTRAMUSCULAR INJECTION**
      - Child 1-9 years: 0.5 mL for 1 dose

Booster dose (for children who have not been immunised against *Haemophilus influenzae* type b): Booster dose after recovery from *Haemophilus influenzae* type b disease (for index cases previously vaccinated, with low Hib antibody concentration or if it is not possible to measure antibody concentration)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-9 years: 0.5 mL for 1 dose

Booster dose after recovery from *Haemophilus influenzae* type b disease (for fully vaccinated index cases with asplenia or splenic dysfunction, if previous dose received over 1 year ago)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-7 years: 0.5 mL for 1 dose
  - Adult: 0.5 mL for 1 dose

Booster dose (for patients diagnosed with asplenia, splenic dysfunction or complement deficiency at under 2 years of age)

- **BY INTRAMUSCULAR INJECTION**
  - Child 2-7 years: 0.5 mL for 1 dose, this booster dose should be given after the second birthday, this is the second dose of haemophilus influenzae type B vaccine combined with meningococcal group C conjugate vaccine (the first dose is given during the routine immunisation schedule)

Meningococcal group B vaccine (rDNA, component, adsorbed)

**INDICATIONS AND DOSE**

**BEXSERO®**

Immunisation against *Neisseria meningitidis*, primary immunisation

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 2 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants), for information about the use of paracetamol for prophylaxis of post-immunisation pyrexia, see paracetamol p. 444.
  - Child 4 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants), for information about the use of paracetamol for prophylaxis of post-immunisation pyrexia, see paracetamol p. 444.

Immunisation against *Neisseria meningitidis*, primary immunisation booster dose

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 12-23 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)

Immunisation against *Neisseria meningitidis*, primary immunisation (in unimmunised patients)

- **BY DEEP INTRAMUSCULAR INJECTION**
  - Child 6-11 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5 mL given between 1–2 years of age and at least 2 months after completion of primary immunisation, injected preferably into deltoid region (or anterolateral thigh in infants)

  - Child 12-23 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5 mL given 12–24 months after completion of primary
Vaccination 1315

Meningococcal groups A with C and W135 and Y vaccine

**INDICATIONS AND DOSE**

**MENVEO**

Primary immunisation against *Neisseria meningitidis*

- **BY INTRAMUSCULAR INJECTION**
  - Child 13-15 years: 0.5 mL for 1 dose, dose preferably injected into deltoid region

Immunisation against *Neisseria meningitidis* in an unimmunised patient

- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL for 1 dose, booster dose is not required
  - Adult 18-24 years: 0.5 mL for 1 dose, booster dose is not required

Immunisation against *Neisseria meningitidis* in those at risk of exposure to prevent invasive disease

- **BY INTRAMUSCULAR INJECTION**
  - Child 3-11 months: 0.5 mL every month for 2 doses, dose preferably injected into deltoid region
  - Child 1-17 years: 0.5 mL for 1 dose, dose preferably injected into deltoid region
  - Adult: 0.5 mL for 1 dose, dose preferably injected into deltoid region

Patients attending university for the first time (who have not received the routine meningococcal groups A with C and W135 and Y conjugate vaccine over the age of 10 years)

- **BY INTRAMUSCULAR INJECTION**
  - Adult 18-24 years: 0.5 mL for 1 dose

**NIMENRIX**

Primary immunisation against *Neisseria meningitidis*

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-17 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region

Immunisation against *Neisseria meningitidis* in an unimmunised patient

- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL for 1 dose, booster dose is not required
  - Adult 18-24 years: 0.5 mL for 1 dose, booster dose is not required

Immunisation against *Neisseria meningitidis* in those at risk of exposure

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-17 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region (or anterolateral thigh in children 12–23 months), then 0.5 mL after continued →

Meningococcal group C vaccine

**INDICATIONS AND DOSE**

Patients with confirmed serogroup C disease (who have previously been immunised)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-17 years: 0.5 mL for 1 dose, dose to be given before discharge from hospital
  - Adult 18-24 years: 0.5 mL for 1 dose, dose to be given before discharge from hospital

**SIDE-EFFECTS**

- **Common or very common** Anxiety (in children) · cough (in children) · crying (in children) · drowsiness (in children) · gastrointestinal discomfort (in children) · hyperhidrosis (in children) · increased risk of infection (in children)
  - **Uncommon** Chills · eyelid oedema (in children) · flushing (in children) · influenza like illness (rare in children) · joint stiffness (in children)
  - **Rare or very rare** Circulatory collapse (in children)
  - **Frequency not known** Angioedema · apnoea · asthena (uncommon in children) · dyspnoea · hypotonic-hyporesponsiveness episode · immune thrombocytopenic purpura · meningism (but no evidence that vaccine causes meningococcal C meningitis) · musculoskeletal stiffness (uncommon in children) · nasal congestion (uncommon in children) · oedema (uncommon in children) · pain (very common in children) · respiratory disorders (uncommon in children) · seizures (uncommon in children) · sensation abnormal (uncommon in children) · sleep disorders (very common in children) · Stevens-Johnson syndrome · syncope (uncommon in children)

**PRESCRIBING AND DISPENSING INFORMATION**

Available as part of childhood immunisation schedule from www.immform.dh.gov.uk.

**MATERIALS**

Available as pre-filled syringes 0.5 mL for 1 dose.

**SPACES**

Available as pre-filled syringes 10 mL for 1 dose.

**EXCIPIENTS**

- May contain kanamycin

**PRECAUTIONS**

- Use with caution in those with known hypersensitivity to the vaccine or any component.

**CONTRAINDICATIONS**

- Do not use in those with a previous severe allergic reaction to the vaccine.

**SIDE-EFFECTS**

- Common or very common: Crying abnormal (in children) · drowsiness (in children) · hypotonic-hyporesponsiveness episode

**PRECAUTIONS**

- Use with caution in those with known hypersensitivity to the vaccine or any component.

**CONTRAINDICATIONS**

- Do not use in those with a previous severe allergic reaction to the vaccine.

**SIDE-EFFECTS**

- Common or very common: Crying abnormal (in children) · drowsiness (in children) · hypotonic-hyporesponsiveness episode

**PRECAUTIONS**

- Use with caution in those with known hypersensitivity to the vaccine or any component.

**CONTRAINDICATIONS**

- Do not use in those with a previous severe allergic reaction to the vaccine.
Vaccines

1. Vaccination

1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of *Neisseria meningitidis* serogroup A infection

- Adult: 0.5 mL for 1 dose, to be injected preferably into deltoid region, then 0.5 mL after 1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of *Neisseria meningitidis* serogroup A infection

**Patients attending university for the first time (who have not received the routine meningococcal groups A with C and W135 and Y conjugate vaccine over the age of 10 years)**

- **BY INTRAMUSCULAR INJECTION**
  - Adult 18–24 years: 0.5 mL for 1 dose

**INDICATIONS AND DOSE**

**PREVENAR 13 ®**

- **INDICATIONS AND DOSE**
  - Primary immunisation against pneumococcal infection [first dose]
    - **BY INTRAMUSCULAR INJECTION**
      - Child 2 months: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants under 1 year
  - Primary immunisation against pneumococcal infection [second dose]
    - **BY INTRAMUSCULAR INJECTION**
      - Child 4 months: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants under 1 year
  - Primary immunisation against pneumococcal infection [booster dose]
    - **BY INTRAMUSCULAR INJECTION**
      - Child 1 year: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants under 1 year; deltoid muscle is preferred in older children
  - Immunisation against pneumococcal infection [in patients who are unimmunosuppressed or partially immunised]
    - **BY INTRAMUSCULAR INJECTION**
      - Child 3–11 months: 0.5 mL for 2 doses, given 2 months apart (interval may be reduced to 1 month to ensure immunisation schedule is completed), followed by 0.5 mL for 1 dose on their first birthday, given at least 2 months after the last dose. Anterolateral thigh is preferred site of injection in infants under 1 year
      - Child 12–23 months: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in children

**UNLICENSED USE**

- **MENVEO ®**
  - In children *Menveo®* is not licensed for use in children under 2 years.

**SIDE-EFFECTS**

- **Common or very common** Drowsiness
- **Uncommon** Crying - insomnia - numbness - pain in extremity
- **Frequency not known** Extensive swelling of vaccinated limb

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - **Menveo** (GlucoSmithKline UK Ltd) Menveo vaccine powder and solvent for solution for injection 0.5ml vials | 1 vial | £30.00
  - **Nimenrix** (Pfizer Ltd) Nimenrix vaccine powder and solvent for solution for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection | £30.00 DT
- **£30.00**

**Pneumococcal polysaccharide conjugate vaccine (adsorbed)**

01-May-2019

**Immunisation against pneumococcal infection [immunised patients at increased risk]**

- **BY INTRAMUSCULAR INJECTION**
  - Child 14 months–17 years: 0.5 mL for 1 dose, given at least 2 months after primary immunisation booster dose, deltoid muscle is preferred site of injection in children
  - Adult: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in adults

**Immunisation against pneumococcal infection [unimmunised or partially immunised patients at increased risk]**

- **BY INTRAMUSCULAR INJECTION**
  - Child 3–11 months: 0.5 mL for 2 doses, given 2 months apart (interval may be reduced to 1 month to ensure immunisation schedule is completed), followed by 0.5 mL for 1 dose on their first birthday, given at least 2 months after the last dose, followed by 0.5 mL for 1 dose, given at least 2 months after the last dose. Anterolateral thigh is preferred site of injection in infants under 1 year
  - Adult: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in adults

**SYNFLORIX ®**

Immunisation against pneumococcal infection

- **BY INTRAMUSCULAR INJECTION**
  - Child 6 weeks–4 years: Deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants (consult product literature)

**UNLICENSED USE**

- **PREVENAR 13 ®** The dose in BNF publications may differ from that in product literature.

**CONTRA-INDICATIONS** Concomitant use of high potency varicella-zoster vaccine (*Zostavax®*) with pneumococcal polysaccharide vaccine (in adults)

**SIDE-EFFECTS**

- **Common or very common** Drowsiness
- **Uncommon** Apnoea - crying abnormal - extensive swelling of vaccinated limb
- **Rare or very rare** Angioedema - hypotonic-hyporesponsiveness episode - Kawasaki disease - seizure

**PRESCRIBING AND DISPENSING INFORMATION**

**PREVENAR 13 ®** Available as part of childhood immunisation schedule from ImmForm www.immform.dh.gov.uk.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Suspension for injection**
  - **Prevenar** (Pfizer Ltd) Prevenar 13 vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection | £49.10 | 10 pre-filled disposable injection | £481.00
  - **Synflorix** (GlucoSmithKline UK Ltd) Synflorix vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection | £27.60

**Pneumococcal polysaccharide vaccine**

01-May-2019

**INDICATIONS AND DOSE**

Primary immunisation against pneumococcal infection

- **BY INTRAMUSCULAR INJECTION**
  - Elderly: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in adults
Immunisation against pneumococcal infection [in patients at increased risk]

- By intramuscular injection
  - Child 2-7 years: 0.5 mL for 1 dose, dose should be administered at least 2 months after the last dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed), deltoid muscle is preferred site of injection in children and adults
  - Adult: 0.5 mL for 1 dose, deltoid muscle is preferred site of injection in adults, primary immunisation with the pneumococcal polysaccharide vaccine is not required when these patients reach 65 years of age

Immunisation against pneumococcal infection [revaccination; booster dose in patients with no spleen, splenic dysfunction or chronic kidney disease]

- By intramuscular injection
  - Child 7-17 years: 0.5 mL every 5 years, deltoid muscle is preferred site of injection in children and adults
  - Adult: 0.5 mL every 5 years, deltoid muscle is preferred site of injection in adults

**SIDE-EFFECTS**

- Angioedema - arthrosis - asthenia - chills - febrile seizure - haemolytic anaemia - injected limb mobility decreased - leucocytosis - lymphadenitis - nerve disorders - paraesthesia - peripheral oedema - thrombocytopenia

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Pneumococcal polysaccharide vaccine (Non-proprietary)
  - Pneumovax 23 (Merck Sharp & Dohme Ltd)
  - Pneumovax 23 solution for injection 0.5 mL pre-filled syringes | 1 pre-filled disposable injection (POA) £16.80

Typhoid vaccine

**INDICATIONS AND DOSE**

**Immunisation against typhoid fever in children at high risk of typhoid fever**

- By intramuscular injection
  - Child 12-23 months: 0.5 mL for 1 dose, dose should be given at least 2 weeks before potential exposure to typhoid infection, response may be suboptimal

**Immunisation against typhoid fever**

- By intramuscular injection
  - Child 2-7 years: 0.5 mL for 1 dose, dose should be given at least 2 weeks before potential exposure to typhoid infection
  - Adult: 0.5 mL for 1 dose, dose should be given at least 2 weeks before potential exposure to typhoid infection
  - By mouth
  - Child 6-17 years: 1 capsule every 2 days for 3 doses (on days 1, 3, and 5)
  - Adult: 1 capsule every 2 days for 3 doses (on days 1, 3, and 5)

**UNLICENSED USE**

- With intramuscular use in children Not licensed for use in children under 2 years.

**CONTRA-INDICATIONS**

- With oral use Acute gastro-intestinal illness

**INTERACTIONS**

- Appendix 1: live vaccines

**SIDE-EFFECTS**

- Common or very common
  - With oral use Gastrointestinal discomfort - influenza like illness

- Rare or very rare
  - With oral use Asthenia - back pain - chills - flatulence - paraesthesia
  - Frequency not known
  - With parental use Abdominal pain - asthma - shock - syncope

**DIRECTIONS FOR ADMINISTRATION**

Capsule should be taken one hour before a meal. Swallow as soon as possible after placing in mouth with a cold or lukewarm drink.

**HANDLING AND STORAGE**

- With oral use It is important to store capsules in a refrigerator.

**PATIENT AND CARER ADVICE**

- With oral use Patients or carers should be given advice on how to administer and store typhoid vaccine capsules.

**VACCINES > VIRAL VACCINES**

**Hepatitis A and B vaccine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1318, hepatitis B vaccine p. 1319.

**INDICATIONS AND DOSE**

**AMBRIX**

Immunisation against hepatitis A and hepatitis B infection (primary course)

- By intramuscular injection
  - Child 1-15 years: Initially 1 mL for 1 dose, then 1 mL after 6–12 months for a dose, the deltoid region is the preferred site of injection in children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**TWINRIX**

Immunisation against hepatitis A and hepatitis B infection (primary course)

- By intramuscular injection
  - Child 16-17 years: Initially 1 mL every month for 2 doses, then 1 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
  - Adult: Initially 1 mL every month for 2 doses, then 1 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
Vaccination

Immunisation against hepatitis A and hepatitis B infection—accelerated schedule for travellers departing within 1 month

- **BY INTRAMUSCULAR INJECTION**
  - Child 16-17 years: Initially 1 ml for 1 dose, then 1 ml after 7 days for 1 dose, then 1 ml after 14 days for 1 dose, then 1 ml for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection; not to be injected into the buttck (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)
  - Adult: Initially 1 ml for 1 dose, then 1 ml after 7 days for 1 dose, then 1 ml after 14 days for 1 dose, then 1 ml for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection; not to be injected into the buttck (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**TWINRIX® PAEDIATRIC**

Immunisation against hepatitis A and hepatitis B infection (primary course)

- **BY INTRAMUSCULAR INJECTION**
  - Child 1-15 years: Initially 0.5 ml every month for 2 doses, then 0.5 ml after 5 months for 1 dose, the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttck (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**IMPORTANT SAFETY INFORMATION**

Ambirix® and Twinrix® are not recommended for post-exposure prophylaxis following percutaneous needlestick, ocular, or mucous membrane exposure to hepatitis B virus.

**PRESCRIBING AND DISPENSING INFORMATION**

**TWINRIX® ADULT** Primary course should be completed with Twinrix® (single component vaccines given at appropriate intervals may be used for booster dose).

**TWINRIX® PAEDIATRIC** Primary course should be completed with Twinrix® (single component vaccines given at appropriate intervals may be used for booster dose).

**AMBIRIX®** Primary course should be completed with Ambirix® (single component vaccines given at appropriate intervals may be used for booster dose).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

**EXCIPIENTS:** May contain Neomycin

- **Ambirix** (GliaxSmithKline UK Ltd)
  - Ambirix vaccine suspension for injection 1ml pre-filled syringes | 1 pre-filled disposable injection £31.18 DT = £31.18
  - **Twinrix** (GliaxSmithKline UK Ltd)
  - Twinrix Paediatric vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £20.79 DT = £20.79 Twinrix Adult vaccine suspension for injection 1ml pre-filled syringes | 1 pre-filled disposable injection £33.31 DT = £33.31 | 10 pre-filled disposable injection £335.13

**SIDE-EFFECTS**

- **Common or very common** Asthenia (uncommon in children) - pain (uncommon in children)
- **Uncommon** Anxiety (in children) - chills (in adults) - cough - crying (in children) - ear pain (rare in children)
Hepatitis A with typhoid vaccine

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1318, typhoid vaccine p. 1317.

- **INDICATIONS AND DOSE**

  **HEPATYRIX®**

  Immunisation against hepatitis A and typhoid infection (primary course)
  - **BY INTRAMUSCULAR INJECTION**
    - Child 15-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines
    - Adult: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

  **VIATIM®**

  Immunisation against hepatitis A and typhoid infection (primary course)
  - **BY INTRAMUSCULAR INJECTION**
    - Child 16-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

  **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Suspension for injection**

  EXCIPIENTS: May contain Neomycin
  - **VAQTA** (Sanofi Pasteur)
    - ViATIM vaccine suspension for injection 1 mL pre-filled syringes | 1 pre-filled disposable injection (PSI) £35.76 DT + £35.76

  **Hepatitis B vaccine**

  - **INDICATIONS AND DOSE**

    **ENERIX B®**

    Immunisation against hepatitis B infection
    - **BY INTRAMUSCULAR INJECTION**
      - Child 1 month–15 years: 10 micrograms for 1 dose, then 10 micrograms after 1 month for 1 dose, followed by 10 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
      - Child 16-17 years: 20 micrograms for 1 dose, then 20 micrograms after 1 month for 1 dose, followed by 20 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
      - Adult: 20 micrograms for 1 dose, then 20 micrograms after 1 month for 1 dose, followed by 20 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

  Immunisation against hepatitis B infection (accelerated schedule)
  - **BY INTRAMUSCULAR INJECTION**
    - Neonate: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), this dose should not be given to neonates born to hepatitis B surface antigen positive mother.
    - Child 1 month–15 years: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, anterolateral thigh is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
    - Child 16-17 years: 20 micrograms every month for 3 doses, followed by 20 micrograms after 10 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
    - Adult: 20 micrograms every month for 3 doses, followed by 20 micrograms after 10 months for 1 dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
Immunisation against hepatitis B infection, alternative accelerated schedule
▶ BY INTRAMUSCULAR INJECTION
- Child 11-15 years: 20 micrograms for 1 dose, followed by 20 micrograms after 6 months, this schedule is not suitable if high risk of infection between doses or if compliance with second dose uncertain, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule in exceptional cases, e.g. for travellers departing within 1 month)
▶ BY INTRAMUSCULAR INJECTION
- Adult: 20 micrograms for 1 dose, then 20 micrograms after 7 days for 1 dose, followed by 20 micrograms after 14 days for 1 dose, followed by 20 micrograms for 1 dose, to be given 12 months after the first dose, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (in renal insufficiency, including haemodialysis patients)
▶ BY INTRAMUSCULAR INJECTION
- Child 1 month-15 years: 10 micrograms every month for 2 doses, followed by 10 micrograms after 5 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16-17 years: 40 micrograms every month for 3 doses, followed by 40 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 40 micrograms every month for 3 doses, followed by 40 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (in renal insufficiency, including haemodialysis patients (accelerated schedule))
▶ BY INTRAMUSCULAR INJECTION
- Child 1 month-15 years: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)

FENDRIX®
Immunisation against hepatitis B infection in renal insufficiency (including pre-haemodialysis and haemodialysis patients)
▶ BY INTRAMUSCULAR INJECTION
- Child 15-17 years: 20 micrograms every month for 3 doses, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 20 micrograms every month for 3 doses, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection
▶ BY INTRAMUSCULAR INJECTION
- Neonate: 5 micrograms for 1 dose, followed by 5 micrograms after 1 month for 1 dose, then 5 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), dose not to be used for neonate born to hepatitis B surface antigen positive mother.
- Child 1 month-15 years: 5 micrograms for 1 dose, followed by 5 micrograms after 1 month for 1 dose, then 5 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16-17 years: 10 micrograms for 1 dose, followed by 10 micrograms after 1 month for 1 dose, followed by 10 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 10 micrograms for 1 dose, followed by 10 micrograms after 1 month for 1 dose, followed by 10 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule)
▶ BY INTRAMUSCULAR INJECTION
- Neonate: 5 micrograms every month for 3 doses, followed by 5 micrograms after 10 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), dose not to be used for neonate born to hepatitis B surface antigen positive mother.
- Child 1 month-15 years: 5 micrograms every month for 3 doses, followed by 5 micrograms after 10 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16-17 years: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 10 micrograms every month for 3 doses, followed by 10 micrograms after 10 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in older children; not to be injected into the buttock (vaccine efficacy reduced)
muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

**Neonate born to hepatitis B surface antigen-positive mother**
- **BY INTRAMUSCULAR INJECTION**
- Neonate: 5 micrograms every month for 3 doses, first dose given at birth with hepatitis B immunoglobulin injection (separate site), followed by 5 micrograms after 10 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced).

**Chronic haemodialysis patients**
- **BY INTRAMUSCULAR INJECTION**
- Child 16-17 years: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection in older children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 40 micrograms every month for 2 doses, followed by 40 micrograms after 5 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

**SIDE-EFFECTS**
- Common or very common: Drowsiness, gastrointestinal disorder
- Uncommon: Influenza-like illness
- Rare or very rare: Sensation abnormal
- Frequency not known: Angioedema, anaemia, arthritis, encephalitis, encephalopathy, hypotension, meningitis, multiple sclerosis, muscle weakness, nerve disorders, paralysis, seizure, thrombocytopenia, vasculitis

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
**EXCIPIENTS:** May contain Thiomersal
- **Engerix® B** (GSKSmithKline UK Ltd)
- **Fendrix** (GlaxoSmithKline UK Ltd)
- **HBVAXPRO** (Merck Sharp & Dohme Ltd)

**Hepatitis B virus surface antigen 20 microgram per 1 ml**
- **Engerix® B** 10 micrograms/0.5 ml vaccine suspension for injection pre-filled syringes | 1 pre-filled disposable injection [Prescribing Information] £12.97 + £9.67
- **Engerix® B** 20 micrograms/1 ml vaccine suspension for injection pre-filled syringes | 1 pre-filled disposable injection [Prescribing Information] £12.97 + £9.67
- **Fendrix** (GlaxoSmithKline UK Ltd)
- **HBVAXPRO** Smicromgros/0.5 ml vaccine suspension for injection pre-filled syringes | 1 pre-filled disposable injection [Prescribing Information] £8.95

**Hepatitis B virus surface antigen 10 microgram per 1 ml**
- HBVAXPRO Smicromgros/0.5 ml vaccine suspension for injection pre-filled syringes | 1 vial [Prescribing Information] £27.60 + £27.60

**Human papillomavirus vaccines**

**INDICATIONS AND DOSE**

**CERVARIX®**
Prevention of premalignant genital lesions and cervical cancer
- **BY INTRAMUSCULAR INJECTION**
- Child 9-14 years (female): 0.5 ml for 1 dose, followed by 0.5 ml after 5–7 months for 1 dose, if second dose administered earlier than 5 months after the first, a third dose should be administered, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose if or if the girl is then aged 15 years or more.
- Child 15-17 years (female): 0.5 ml for 1 dose, followed by 0.5 ml after 1–2.5 months for 1 dose, then 0.5 ml after 5–12 months from the first dose for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
- Adult (female): 0.5 ml for 1 dose, followed by 0.5 ml after 1–2.5 months for 1 dose, then 0.5 ml after 5–12 months from the first dose for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**GARDASIL®**
Prevention of premalignant genital (cervical, vulvar and vaginal) and anal lesions, cervical and anal cancers, and genital warts
- **BY INTRAMUSCULAR INJECTION**
- Child 9-14 years (female): 0.5 ml for 1 dose, followed by 0.5 ml after 6 months for 1 dose, if the second dose is administered earlier than 6 months after the first dose, a third dose should be administered, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
- Adult (female): 0.5 ml for 1 dose, followed by 0.5 ml after 6 months for 1 dose, then 0.5 ml after 5–12 months from the first dose for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**DT = £**

**Prevention of premalignant genital (cervical, vulvar, and vaginal) and anal lesions, cervical and anal cancers, and genital warts (alternative schedule)**
- **BY INTRAMUSCULAR INJECTION**
- Child 9-14 years (female): 0.5 ml for 1 dose, followed by 0.5 ml for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 ml for 1 dose, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.
- Adult (female): 0.5 ml for 1 dose, followed by 0.5 ml for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 ml for 1 dose, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**www.getintopharma.com**
1322 Vaccination

**UNLICENSED USE**
- *GARDASIL®* Two dose schedule not licensed for use in girls aged 14 years.

**SIDE-EFFECTS**
- **Common or very common** Pain in extremity
- **Rare or very rare** Bronchospasm
- **Frequency not known** Acute disseminated encephalomyelitis - asthenia - chills - Guillain–Barre syndrome - immune thrombocytopenic purpura - syncope

**PREGNANCY** Not known to be harmful, but vaccination should be postponed until completion of pregnancy.

**PRESCRIBING AND DISPENSING INFORMATION** To avoid confusion, prescribers should specify the brand to be dispensed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- *Cervarix* (GlaxoSmithKline UK Ltd) Cervarix vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PSM) £80.50
- *Gardasil* (Merck Sharp & Dohme Ltd) Gardasil vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PSM) £86.50

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**Influenza vaccine**

**INDICATIONS AND DOSE**

**Annual immunisation against seasonal influenza**
- **BY INTRAMUSCULAR INJECTION**
  - Child 6 months–17 years: 0.5 mL for 1 dose
  - Adult: 0.5 mL for 1 dose
- **BY INTRADERMAL INJECTION**
  - Adult 18–59 years: 9 micrograms for 1 dose, dose to be injected into deltoid region
  - Adult 60 years and over: 15 micrograms for 1 dose, dose to be injected into deltoid region
- **BY INTRANASAL ADMINISTRATION**
  - Child 2–17 years: 0.1 mL for 1 dose, dose to be administered into each nostril

**Annual immunisation against seasonal influenza (for children in clinical risk groups who have not received seasonal influenza vaccine previously)**
- **BY INTRAMUSCULAR INJECTION**
  - Child 6 months–8 years: 0.5 mL for 1 dose, followed by 0.5 mL for 1 dose, after at least 4 weeks
- **BY INTRANASAL ADMINISTRATION**
  - Child 2–8 years: 0.1 mL for 1 dose, followed by 0.1 mL for 1 dose, after at least 4 weeks. 0.1 mL dose to be administered to each nostril

**UNLICENSED USE** The Joint Committee on Vaccination and Immunisation advises offering a second dose of vaccine for annual immunisation against seasonal influenza to children in clinical risk groups only.

**CONTRA-INDICATIONS** Preparations marketed by Pfizer, or CSL. Biotherapies in child under 5 years—increased risk of febrile convulsions

**FLUENZ TETRA** Active wheezing - comitant use with antiviral therapy for influenza - severe asthma

**CONTRA-INDICATIONS, FURTHER INFORMATION**
- Comitant use with antiviral therapy for influenza. Avoid influenza antiviral agents for at least 2 weeks after immunisation; avoid immunisation for at least 48 hours after stopping the influenza antiviral agent.

**CAUTIONS** Increased risk of fever in child 5–9 years with preparations marketed by Pfizer or CSL. Biotherapies—use alternative influenza vaccine if available

**INTERACTIONS** → Appendix 1: live vaccines

**SIDE-EFFECTS**
- **Common or very common**
  - With intradermal use: Chills - local reactions - pain
  - With intramuscular use: Chills (uncommon in elderly) - hyperhidrosis - induration - local reactions - pain (uncommon in elderly)
  - With intranasal use: Nasal complaints
- **Uncommon**
  - With intradermal use: Hyperhidrosis
  - With intramuscular use: Cough (in adults)
  - With intranasal use: Epistaxis - face oedema
- **Rare or very rare**
  - With intradermal use: Nerve disorders - paraesthesia
  - With intramuscular use: Vasodilation (in adults)
- **Frequency not known**
  - With intradermal use: Angioedema - encephalomyelitis - febrile seizure - nervous system disorder - shock - thrombocytopenia - vasculitis
  - With intranasal use: Guillain–Barre syndrome

**ALLERGY AND CROSS-SENSITIVITY** Individuals with a history of egg allergy can be immunised with either an egg free influenza vaccine, if available, or an influenza vaccine with an ovalbumin content less than 120 nanograms/mL. (facilities should be available to treat anaphylaxis). Vaccines with an ovalbumin content more than 120 nanograms/mL or where content is not stated should not be used in individuals with egg allergy. If an influenza vaccine containing ovalbumin is being considered in those with a history of anaphylaxis to egg or egg allergy with uncontrolled asthma, these individuals should be referred to a specialist in hospital.

**PREGNANCY** Inactivated vaccines not known to be harmful.

**FLUENZ TETRA®** Avoid in pregnancy.

**BREAST FEEDING** Inactivated vaccines not known to be harmful.

**FLUENZ TETRA®** Avoid in breast-feeding.

**PRESCRIBING AND DISPENSING INFORMATION** The available preparations are not licensed for use in all age-groups—further information can be found in the product literature for the individual vaccines.

**FLUARIX TETRA®** Ovalbumin content less than 100 nanograms/mL.

**PATIENT AND CARER ADVICE**

**FLUENZ TETRA®** Avoid close contact with severely immunocompromised patients for 1–2 weeks after vaccination.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Spray**
- EXCIPIENTS: May contain Gelatin, gentamicin
  - **Fluenz Tetra** (AstraZeneca UK Ltd) Fluenz Tetra vaccine nasal suspension 0.2ml unit dose | 10 unit dose (PSM) £180.00

**Suspension for injection**
- EXCIPIENTS: May contain Gentamicin, kanamycin, neomycin, polymyxin b
  - **Influenza vaccine (non-proprietary)** ▼
    - Trivalent influenza vaccine (split virion, inactivated) High Dose suspension for injection 0.5ml pre-filled syringes | 5 pre-filled disposable injection (PSM) £20.00
    - Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes | 10 pre-filled disposable injection (PSM) £65.90

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www.getintopharma.com
Quadrivalent influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £3.00 | 10 pre-filled disposable injection £30.00
Influenza MVLV vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £8.00 | 10 pre-filled disposable injection £80.00
Influenza MVL vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £8.00 | 10 pre-filled disposable injection £80.00
Fluad (Seqirus Vaccines Ltd) Fluad vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £9.79 | 10 pre-filled disposable injection £97.90
Fluarix Tetra GlaxoSmithKline UK Ltd ▼ Fluvarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £9.94 | 10 pre-filled disposable injection £99.40
Flucelvax Tetra (Seqirus Vaccines Ltd) ▼ Flucelvax Tetra vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £9.94 | 10 pre-filled disposable injection £99.40
Imuvac (Mylan) Imuvac vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £6.59 | 10 pre-filled disposable injection £65.90
Imuvac Sub-unit (Mylan) ▼ Influvac-sub-unit vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £5.22 | 10 pre-filled disposable injection £52.20
Influvac Sub-unit (Mylan) ▼ Influvac-sub-unit Tetra vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection £9.94 | 10 pre-filled disposable injection £99.40

Japanese encephalitis vaccine

**INDICATIONS AND DOSE**

**Immunisation against Japanese encephalitis**
- **BY INTRAMUSCULAR INJECTION**
  - **Child 2–35 months:** 0.25 ml every 28 days for 2 doses, alternatively 0.25 ml every 7 days for 2 doses, anterolateral thigh may be used as the injection site in infants; deltoid muscle is preferred site in older children, immunisation should be completed at least 1 week before potential exposure
  - **Child 3–17 years:** 0.5 ml every 28 days for 2 doses, alternatively 0.5 ml every 7 days for 2 doses, deltoid muscle is preferred site in older children, immunisation should be completed at least 1 week before potential exposure
  - **Adult:** 0.5 ml every 28 days for 2 doses, alternatively 0.5 ml every 7 days for 2 doses, deltoid muscle is preferred site in older children, immunisation should be completed at least 1 week before potential exposure

**First booster**
- **BY INTRAMUSCULAR INJECTION**
  - **Adult:** 0.5 ml after 1–2 years, deltoid muscle is preferred site of injection, for those at continued risk, the booster dose should be given 1 year after completing the primary course
  - **Elderly:** 0.5 ml after 1 year, for those at continued risk, deltoid muscle is preferred site of injection

**Second booster**
- **BY INTRAMUSCULAR INJECTION**
  - **Adult:** 0.5 ml after 10 years, for those at continued risk, deltoid muscle is preferred site of injection

**UNLICENSED USE**
- When used for immunisation against Japanese encephalitis The rapid schedule administered at days 0 and 7 is not licensed in children or the elderly.

**SIDE-EFFECTS**
- **Common or very common** Influenza like illness (frequency not known in children)
- **Uncommon** Abdominal pain (frequency not known in children) - asthenia (in adults) - chills (in adults) - hyperhidrosis (in adults) - migraine (in adults) - musculoskeletal stiffness (in adults) - vertigo (in adults)
- **Rare or very rare** Dyspnoea (in adults) - eyelid oedema (in adults) - neuritis (in adults) - pain in extremity (in adults) - palpitations (in adults) - paraesthesia (in adults) - peripheral oedema (in adults) - tachycardia (in adults) - taste altered (in adults) - thrombocytopenia (in adults)
- **Frequency not known** Cough (in children)

**PREGNANCY** Although manufacturer advises avoid because of limited information, miscarriage has been associated with Japanese encephalitis virus infection acquired during the first 2 trimesters of pregnancy.

**MEDICAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Japanese encephalitis vaccine (Non-proprietary)** Japanese encephalitis GCVC vaccine solution for injection 1 ml vial | 1 vial
- **Japanese encephalitis GCVC vaccine solution for injection 20 ml vials | 1 vial**
- **Japanese encephalitis GCVC vaccine solution for injection 10 ml vials | 1 vial**

**Suspension for injection**
- **Ixaro (Valneva UK Ltd)** Ixaro vaccine suspension for injection 0.5 ml vial | 1 pre-filled disposable injection £9.79

**Measles, mumps and rubella vaccine, live**

**INDICATIONS AND DOSE**

**Primary immunisation against measles, mumps, and rubella (first dose)**
- **BY INTRAMUSCULAR INJECTION, OR BY DEEP SUBCUTANEOUS INJECTION**
  - **Child 12–13 months:** 0.5 ml for 1 dose

**Primary immunisation against measles, mumps, and rubella (second dose)**
- **BY INTRAMUSCULAR INJECTION, OR BY DEEP SUBCUTANEOUS INJECTION**
  - **Child 40 months–5 years:** 0.5 ml for 1 dose

**Rubella immunisation (in seronegative women, susceptible to rubella and in unimmunised, seronegative women, post-partum)**
- **BY INTRAMUSCULAR INJECTION, OR BY DEEP SUBCUTANEOUS INJECTION**
  - **Females of childbearing potential:** (consult product literature or local protocols)

**Children presenting for pre-school booster, who have not received the primary immunisation (first dose)**
- Immunisation for patients at school-leaving age or at entry into further education, who have not completed the primary immunisation course | Control of measles outbreak | Immunisation for patients travelling to areas where measles is endemic or epidemic, who have not completed the primary immunisation
- **BY INTRAMUSCULAR INJECTION, OR BY DEEP SUBCUTANEOUS INJECTION**
  - **Child 6 months–17 years:** (consult product literature or local protocols)
  - **Adult:** (consult product literature or local protocols)

**UNLICENSED USE**
- In children Not licensed for use in children under 9 months.

**IMPORTANT SAFETY INFORMATION**

**MMR VACCINATION AND BOWEL DISEASE OR AUTISM**

Reviews undertaken on behalf of the CSM, the Medical Research Council, and the Cochrane Collaboration, have not found any evidence of a link between MMR...
vaccination and bowel disease or autism. The Chief Medical Officers have advised that the MMR vaccine is the safest and best way to protect children against measles, mumps, and rubella. Information (including fact sheets and a list of references) may be obtained from www.dh.gov.uk/immunisation.

**CAUTIONS** Antibody response to measles component may be reduced after immunoglobulin administration or blood transfusion—leave an interval of at least 3 months before MMR immunisation.

**CAUTIONS, FURTHER INFORMATION**
- Administration with other vaccines: MMR vaccine should not be administered on the same day as yellow fever vaccine; there should be a 4-week minimum interval between the vaccines. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of MMR may be considered.
- MMR and varicella-zoster vaccine can be given on the same day or separated by a 4-week minimum interval. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of the vaccine given second may be considered.
- **INTERACTIONS** → Appendix 1: live vaccines
- **SIDE-EFFECTS**
  - Uncommon: Increased risk of infection - rhinorrhea

**SIDE-EFFECTS, FURTHER INFORMATION** Malaise, fever, or a rash can occur after the first dose of MMR vaccine—most commonly about a week after vaccination and lasting about 2 to 3 days.

Febrile seizures occur rarely 6 to 11 days after MMR vaccination (the incidence is lower than that following measles infection).

**Idiopathic thrombocytopenic purpura** Idiopathic thrombocytopenic purpura has occurred rarely following MMR vaccination, usually within 6 weeks of the first dose. The risk of idiopathic thrombocytopenic purpura after MMR vaccine is much less than the risk after infection with wild measles or rubella virus. Children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR should undergo serological testing before the second dose is due; if the results suggest incomplete immunity against measles, mumps or rubella then a second dose of MMR is recommended. Samples should be sent to the Virus Reference Laboratory of the Health Protection Agency.

**Frequency of side effects** Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first.

**ALLERGY AND CROSS-SENSITIVITY** MMR vaccine can be given safely even when the child has had an anaphylactic reaction to food containing egg. Dislike of eggs, refusal to eat egg, or confirmed anaphylactic reactions to egg-containing food is not a contra-indication to MMR vaccination. Children with a confirmed anaphylactic reaction to the MMR vaccine should be assessed by a specialist.

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before immunisation. Avoid pregnancy for at least 1 month after vaccination.

**PRESCRIBING AND DISPENSING INFORMATION** Available as part of childhood immunisation schedule from health organisations or ImmForm www.immform.dh.gov.uk.

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**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**

<table>
<thead>
<tr>
<th>EXCIPIENTS:</th>
<th>May contain Gelatin, neomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-M-RVAXPRO (Merck Sharp &amp; Dohme Ltd)</td>
<td>M-M-RVAXPRO vaccine powder and solvent for suspension for injection 0.5ml pre-filled syringes</td>
</tr>
</tbody>
</table>

**Powder and solvent for solution for injection**

<table>
<thead>
<tr>
<th>EXCIPIENTS:</th>
<th>May contain Neomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priorix (GlaxoSmithKline UK Ltd)</td>
<td>Priorix vaccine powder and solvent for solution for injection 0.5ml pre-filled syringes</td>
</tr>
</tbody>
</table>

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**Rabies vaccine**

**INDICATIONS AND DOSE**

**Pre-exposure prophylaxis**

- **BY INTRAMUSCULAR INJECTION**
  - Child: 1 mL for 2 doses (on days 0 and 7), followed by 1 mL for 1 dose (on day 28), to be administered in deltoid region or anterolateral thigh in infants, for those at continuous risk, measure plasma-concentration of antirabies antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL, final dose may be given from day 21, if insufficient time before travel
  - Adult: 1 mL for 2 doses (on days 0 and 7), followed by 1 mL for 1 dose (on day 28), to be administered in deltoid region, for those at continuous risk, measure plasma-concentration of antirabies antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL, final dose may be given from day 21, if insufficient time before travel

**Pre-exposure prophylaxis booster dose (for patients at frequent risk of exposure)**

- **BY INTRAMUSCULAR INJECTION**
  - Child: 1 mL after 1 year for 1 dose, to be given 1 year after primary course is completed, then 1 mL every 3–5 years, to be administered in deltoid region or anterolateral thigh in infants, the frequency of booster doses may alternatively be determined according to plasma-concentration of antirabies antibodies
  - Adult: 1 mL for 1 dose, to be given 1 year after primary course is completed, then 1 mL every 3–5 years, to be administered in deltoid region, the frequency of booster doses may alternatively be determined according to plasma-concentration of antirabies antibodies

**Pre-exposure prophylaxis booster dose (for patients at infrequent risk of exposure)**

- **BY INTRAMUSCULAR INJECTION**
  - Child: 1 mL for 1 dose, to be given 10 years after primary course is completed, administered in deltoid region or anterolateral thigh in infants
  - Adult: 1 mL for 1 dose, to be given 10 years after primary course is completed, administered in deltoid region

**Post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine)**

- **BY INTRAMUSCULAR INJECTION**
  - Child (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region or anterolateral thigh in infants, rabies immunoglobulin is not necessary
  - Adult (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region, rabies immunoglobulin is not necessary
Rotavirus vaccine

**DRUG ACTION** Rotavirus vaccine is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection.

**INDICATIONS AND DOSE**

**Immunisation against gastro-enteritis caused by rotavirus**

**BY MOUTH**

- Child 6–23 weeks: 1.5 mL for 2 doses separated by an interval of at least 4 weeks, first dose must be given between 6–14 weeks of age; course should be completed before 24 weeks of age (preferably before 16 weeks)

**SIDE-EFFECTS**

- Rare or very rare: abdominal pain, vomiting (postpone vaccination), diarrhea (postpone vaccination), diaphoresis

**CONTRA-INDICATIONS**

- History of intussusception - predisposition to intussusception - severe combined immunosuppression

**ADDITIONAL INFORMATION**

- Public Health England advises that immunisation with live vaccines should be delayed until 6 months of age in children born to mothers who received immunosuppressive biological therapy during pregnancy. In practice, this means that children born to mothers who were on immunosuppressive biological therapy during pregnancy will not be eligible to receive rotavirus vaccine.

**EXCIPIENTS:** May contain Neomycin

Rabies vaccine (Non-proprietary)

Powder and solvent for suspension for injection

- 1 vial £40.84

**Powder and solvent for solution for injection**

- Rabipur (GlaxoSmithKline UK Ltd)

  Rabipur vaccine powder and solvent for solution for injection 1mL vials

  - 1 vial £34.56

  Rabipur vaccine powder and solvent for solution for injection 1mL pre-filled syringes

  - 1 pre-filled disposable injection £34.56
Vaccines

1326 Vaccination

Varicella-zoster vaccine

- **INDICATIONS AND DOSE**

**VARILRIX ®**

- Prevention of varicella infection (chickenpox)
  - **BY SUBCUTANEOUS INJECTION**
  - Child 1–7 years: 0.5 mL every 4–6 weeks for 2 doses, to be administered into the deltoid region or anterolateral thigh
  - Adult: 0.5 mL every 4–6 weeks for 2 doses, to be administered into the deltoid region or anterolateral thigh

**VARIVAX ®**

- Prevention of varicella infection (chickenpox)
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Child 1–12 years: 0.5 mL for 2 doses, interval of at least 4 weeks between each dose, to be administered into the deltoid region (or higher anterolateral thigh in young children)
  - Child 13–17 years: 0.5 mL for 2 doses, interval of 4–8 weeks between each dose, to be administered preferably into the deltoid region
  - Adult: 0.5 mL for 2 doses, interval of 4–8 weeks between each dose, to be administered preferably into the deltoid region

- Prevention of varicella infection (chickenpox) in children with asymptomatic HIV infection
  - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION**
  - Child 1–12 years: 0.5 mL for 2 doses, interval of 12 weeks between each dose, to be administered into the deltoid region (or higher anterolateral thigh in young children)

**ZOSTAVAX ®**

- Prevention of herpes zoster (shingles)
  - **BY SUBCUTANEOUS INJECTION**
  - Adult 70–79 years: 0.65 mL for 1 dose, to be administered preferably into the deltoid region

- **CAUTIONS**

  - Post-vaccination close contact with susceptible individuals
  - Exceptional: children with severe immune deficiency or those receiving immunosuppressive therapy.

  - Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the lesions and be allowed to continue working unless in contact with patients at high risk of severe varicella.

  - Administration with MMR vaccine Varicella–zoster and MMR vaccines can be given on the same day or separated by a 4-week minimum interval. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of the vaccine given second may be considered.

- **INTERACTIONS** → Appendix 1: live vaccines

- **SIDE-EFFECTS**

  - Common or very common Restlessness (in children) • Sleep disorder (in children)
  - Rare or very rare Asthenia • Autoimmune disorder (in adults) • Chills (uncommon in children) • Demyelination (in adults) • Drowsiness (in adults) • Dyspnoea • Eye pain • Gait abnormality • Gastrointestinal discomfort (uncommon in children) • Hyperhidrosis • Increased risk of infection • Influenza-like illness • Joint swelling (in adults) • Meningism • Meningitis aseptic (in adults) • Motor dysfunction • Musculoskeletal stiffness • Nerve disorders • Oedema • Pain • Seizures • Sensory disorder • Tachycardia (in adults) • Tinnitus • Vertigo • Vision disorders

- **ALLERGY AND CROSS-SENSITIVITY** Individuals with evidence of previous anaphylactic reaction to egg should not be given tick-borne encephalitis vaccine.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **EXCIPIENTS:** May contain Gentamicin, neomycin

  - **TicoVac** (Pfizer Ltd)
    - TicoVac junior vaccine suspension for injection 0.25mL pre-filled syringes | 1 pre-filled disposable injection £28.00
    - TicoVac vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £32.00

- **SIDE-EFFECTS**

  - Common Cough • Drowsiness
  - Uncommon Cough • Drowsiness • Increased risk of infection
  - Rare or very rare Abdominal pain • Conjunctivitis • Kawasaki disease • Seizure • Stroke • Thrombocytopenia • Vasculitis
**CONCEPTION AND CONTRACEPTION** Avoid pregnancy for 3 months after vaccination.

**PRESCRIBING AND DISPENSING INFORMATION**

**ZOSTAVAX** Advice in the BNF may differ from that in product literature.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**

**EXCIPIENTS:** May contain Gelatin, neomycin

- Varilrix (Merck Sharp & Dohme Ltd) Varilrix vaccine powder and solvent for suspension for injection 0.5ml vials | 1 vial (POD) £30.28
- Zostavax (Merck Sharp & Dohme Ltd) Zostavax vaccine powder and solvent for suspension for injection 0.505ml pre-filled syringes | 1 pre-filled disposable injection (POD) £99.96 DT + £99.96

**Powder and solvent for solution for injection**

**EXCIPIENTS:** May contain Neomycin

- Varilrix (GlaxoSmithKline UK Ltd) Varilrix vaccine powder and solvent for solution for injection 0.5ml vials | 1 vial (POD) £27.31

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**VACCINATION**

**INDICATIONS AND DOSE**

**Immunisation against yellow fever**

- **BY DEEP SUBCUTANEOUS INJECTION**
  - Child 6-8 months (administered on expert advice): Infants under 9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (consult product literature or local protocols)
  - Child 9 months-17 years: 0.5 mL for 1 dose
  - Adult: 0.5 mL for 1 dose

**IMPORTANT SAFETY INFORMATION**

**MHRA/CHM ADVICE:** YELLOW FEVER VACCINE (STAMARIL®) AND FATAL ADVERSE REACTIONS: EXTREME CAUTION NEEDED IN PEOPLE WHO MAY BE IMMUNOSUPPRESSED AND THOSE 60 YEARS AND OLDER (APRIL 2019)

The yellow fever vaccine (Stamaril®) has been associated with an increased risk of life-threatening reactions and must not be given to patients with a history of thymus dysfunction (including myasthenia gravis and thymoma), to patients that are immunosuppressed, or that have had a thymectomy. Vaccination in patients aged 60 years and older should be administered with extreme caution, following a careful risk assessment. Prior to administering yellow fever vaccines, healthcare professionals are advised to familiarise themselves with any contra-indications and special precautions, and to defer vaccination if it is suspected that a patient is immunosuppressed, until specialist advice can be sought. Healthcare professionals administering vaccines should consult information in the YF Vaccine Centre code of practice and strengthen protocols and checklists to avoid inappropriate administration.

**CONTRA-INDICATIONS** Children under 6 months - history of thymus dysfunction

**CAUTIONS** Individuals over 60 years—greater risk of vaccine-associated adverse effects

**SIDE-EFFECTS, FURTHER INFORMATION**

- Common or very common Asthenia - crying (in children) - drowsiness (in children)
- Uncommon Abdominal pain
- Rare or very rare Rhinitis - yellow fever vaccine-associated neurotropic disease - yellow fever vaccine-associated viscerotropic disease
- Frequency not known Angioedema - influenza like illness - paraesthesia

**SIDE-EFFECTS**

- Fever
- Headache
- Chills
- Myalgia
- Fatigue
- Nausea
- Vomiting
- Abdominal pain
- Dizziness
- Asthenia
- Rhinitis
- Crying

**PREGNANCY** Live yellow fever vaccine should not be given during pregnancy because there is a theoretical risk of fetal infection. Pregnant women should be advised not to travel to areas at high risk of yellow fever. If exposure cannot be avoided during pregnancy, then the vaccine should be given if the risk from disease in the mother outweighs the risk to the fetus from vaccination.

**BREAST FEEDING** Avoid; seek specialist advice if exposure to virus cannot be avoided.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**

- Stamaril (Sanofi Pasteur) Stamaril vaccine powder and solvent for suspension for injection 0.5ml vials | 1 vial (POD) £30.72

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**REFERENCES**

- Code of practice
- Strengthen protocols and checklists
- YF Vaccine Centre
- BNF 78

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Chapter 15
Anaesthesia

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General anaesthesia

Anaesthesia (general)

Overview

Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug; anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics, usually short-acting opioids, are also used. The use of neuromuscular blocking drugs necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists can be used to reverse central and respiratory depression caused by some drugs used in surgery. A local topical anaesthetic can be used to reduce pain at the injection site.

Individual requirements vary considerably and the recommended doses are only a guide. Smaller doses are indicated in ill, shocked, or debilitated patients and in significant hepatic impairment, while robust individuals may require larger doses. The required dose of induction agent may be less if the patient has been premedicated with a sedative agent or if an opioid analgesic has been used.

Intravenous anaesthetics

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effects in one arm-brain circulation time. Extreme care is required in surgery of the mouth, pharynx, or larynx where the airway may be difficult to maintain (e.g. in the presence of a tumour in the pharynx or larynx).

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug or a short-acting opioid.

The doses of all intravenous anaesthetic drugs should be titrated to effect (except when using ‘rapid sequence induction’); lower doses may be required in premedicated patients.

Total intravenous anaesthesia

This is a technique in which major surgery is carried out with all drugs given intravenously. Respiration can be spontaneous, or controlled with oxygen-enriched air. Neuromuscular blocking drugs can be used to provide relaxation and prevent reflex muscle movements. The main problem to be overcome is the assessment of depth of anaesthesia. Target Controlled Infusion (TCI) systems can be used to titrate intravenous anaesthetic infusions to predicted plasma-drug concentrations in ventilated adult patients.

Drugs used for intravenous anaesthesia

Propofol p. 1330, the most widely used intravenous anaesthetic, can be used for induction or maintenance of anaesthesia in adults and children, but it is not commonly used in neonates. Propofol is associated with rapid recovery and less hangover effect than other intravenous anaesthetics. Propofol can also be used for sedation during diagnostic procedures and sedation in adults in intensive care.

Thiopental sodium p. 338 is a barbiturate that is used for induction of anaesthesia, but has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiovascular and respiratory depression can occur. Awakening from a moderate dose of thiopental sodium is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect and recovery is much slower.

Etomidate p. 1330 is an intravenous agent associated with rapid recovery without a hangover effect. Etomidate causes less hypotension than thiopental sodium and propofol during induction. It produces a high incidence of extraneous muscle movements, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

Ketamine p. 1345 is used rarely. Ketamine causes less hypotension than thiopental sodium and propofol during induction. It is used mainly for paediatric anaesthesia, particularly when repeated administration is required (such as for serial burns dressings); recovery is relatively slow and there is a high incidence of extraneous muscle movements. The main disadvantage of ketamine is the high incidence of hallucinations, nightmares, and other transient psychotic effects; these can be reduced by a benzodiazepine such as diazepam p. 343 or midazolam p. 340.

Inhalational anaesthetics

Inhalational anaesthetics include gases and volatile liquids. Gaseous anaesthetics require suitable equipment for storage and administration. Volatile liquid anaesthetics are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anaesthesia when nitrous oxide p. 1332 is being administered.
Volatile liquid anaesthetics

Volatile liquid anaesthetics can be used for induction and maintenance of anaesthesia, and following induction with an intravenous anaesthetic.

Isoflurane p. 1332 is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart rate can rise, particularly in younger patients. Systemic arterial pressure and cardiac output can fall, owing to a decrease in systemic vascular resistance. Muscle relaxation occurs and the effects of muscle relaxant drugs are potentiated. Isoflurane is the preferred inhalational anaesthetic for use in obstetrics.

Desflurane p. 1332 is a rapid acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritant to the upper respiratory tract.

Sevoflurane p. 1333 is a rapid acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid, but slower than desflurane. Sevoflurane is non-irritant and is therefore often used for inhalational induction of anaesthesia; it has little effect on heart rhythm compared with other volatile liquid anaesthetics.

Nitrous oxide

Nitrous oxide is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For anaesthesia, nitrous oxide is commonly used in a concentration of 50 to 66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage.

For anaesthesia (without loss of consciousness), a mixture of nitrous oxide and oxygen containing 50% of each gas (Entonox®, Equanox®) is used. Self-administration using a demand valve is popular in obstetric practice, for changing painful dressings, as an aid to postoperative physiotherapy, and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intraocular gas injection.

Malignant hyperthermia

Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia. It is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. The most common triggers of malignant hyperthermia are the volatile anaesthetics. Suxamethonium chloride p. 1337 has also been implicated, but malignant hyperthermia is more likely if it is given following a volatile anaesthetic. Volatile anaesthetics and suxamethonium chloride should be avoided during anaesthesia in patients at high risk of malignant hyperthermia.

Dantrolene sodium p. 1346 is used in the treatment of malignant hyperthermia.

Sedation, anaesthesia, and resuscitation in dental practice

Overview

Sedation for dental procedures should be limited to conscious sedation. Diazepam p. 343 and temazepam p. 488 are effective anxiolytics for dental treatment in adults.

For details of sedation, anaesthesia, and resuscitation in dental practice see A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care; report by a group chaired by the Chief Medical Officer and Chief Dental Officer, July 2000 and associated documents. Further details can also be found in Standards for Conscious Sedation in the Provision of Dental Care; report of an Intercollegiate Advisory Committee for Sedation in Dentistry, 2015 www.rcseng.ac.uk/~/media/files/rcs-library-and-publications/non-journal-publications/dental-sedation-report.pdf.

Surgery and long-term medication

Overview

The risk of losing disease control on stopping long-term medication before surgery is often greater than the risk posed by continuing it during surgery. It is vital that the anaesthetist knows about all drugs that a patient is (or has been) taking.

Patients with adrenal atrophy resulting from long-term corticosteroid use may suffer a precipitous fall in blood pressure unless corticosteroid cover is provided during anaesthesia and in the immediate postoperative period.

Anaesthetists must therefore know whether a patient is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).

Other drugs that should normally not be stopped before surgery include antiepileptics, antiparkinsonian drugs, antipsychotics, anxiolytics, bronchodilators, cardiovascular drugs (but see potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor antagonists), glaucoma drugs, immunosuppressants, drugs of dependence, and thyroid or antithyroid drugs. Expert advice is required for patients receiving antivirals for HIV infection. See general advice on surgery in diabetic patients in Diabetes, surgery and medical illness p. 689.

Patients taking antifibrinolytic or an oral anticoagulant present an increased risk for surgery. In these circumstances, the anaesthetist and surgeon should assess the relative risks and decide jointly whether the antifibrinolytic or the anticoagulant drug should be stopped or replaced with heparin (unfractionated) p. 133 or low molecular weight heparin therapy. In patients with stable angina, perioperative aspirin p. 121 should be only continued where there is a high thrombotic risk (e.g. patients with a recent acute coronary syndrome, coronary artery stents, or an ischaemic stroke).

Drugs that should not be stopped before surgery include combined oral contraceptives, see Contraceptives, hormonal p. 791; for advice on hormone replacement therapy, see Sex hormones p. 750. MAOIs can have important interactions with some drugs used during surgery, such as pethidine hydrochloride p. 470. Tricyclic antidepressants need not be stopped, but there may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs); therefore, the anaesthetist should be informed if they are not stopped. Lithium should be stopped 24 hours before major surgery but the normal dose can be continued for minor surgery (with careful monitoring of fluids and electrolytes). Potassium-sparing diuretics may need to be withheld on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or
if there is tissue damage. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists can be associated with severe hypotension after induction of anaesthesia; these drugs may need to be discontinued 24 hours before surgery. Herbal medicines may be associated with adverse effects when given with anaesthetic drugs and consideration should be given to stopping them before surgery.

**ANAESTHETICS, GENERAL**: Intravenous anaesthetics

### Etomidate

**Indications and dose**

**Induction of anaesthesia**

- **By slow intravenous injection**
- Adult: 150–300 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous)
- Elderly: 150–200 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous)

#### Important safety information

Etomidate should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

#### Caution

- Acute circulatory failure (shock) - adrenal insufficiency. Avoid in Acute porphyrias.
- Cardiovascular disease - elderly - fixed cardiac output - hypovolaemia

**Further information**

- Adrenal insufficiency. Etomidate suppresses adrenocortical function, particularly during continuous administration, and it should not be used for maintenance of anaesthesia. It should be used with caution in patients with underlying adrenal insufficiency, for example, those with sepsis.

#### Interactions

- Appendix 1: etomidate

#### Side-effects

- Common or very common: Apnoea, hypotension, movement disorders, nausea, respiratory disorders, skin reactions, vascular pain, vomiting
- Uncommon: Arrhythmias, cough, hiccup, hyperventilation, hypertension, muscle rigidity, neuromuscular dysfunction, nystagmus, procedural complications
- Frequency not known: Adrenal insufficiency, atrioventricular block, cardiac arrest, embolism and thrombosis, seizures, shock, Stevens-Johnson syndrome, trismus

**Pain on injection**

Can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction.

**Extraneous muscle movements**

Extraneous muscle movements can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

#### Pregnancy

May depress neonatal respiration if used during delivery.

#### Breastfeeding

Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

#### Hepatic impairment

Dose adjustments: Manufacturer advises reduce dose in liver cirrhosis.

#### Dose adjustments for administration

To be administered over 30–60 seconds (60 seconds in patients in whom hypotension might be hazardous).

### Propofol

**Indications and dose**

**Induction of anaesthesia using 0.5% or 1% injection**

- **By slow intravenous injection, or by intravenous infusion**
- Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over
- Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

**Induction of anaesthesia using 2% injection**

- **By intravenous infusion**
- Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over
- Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

**Maintenance of anaesthesia using 1% injection**

- **Initially by intravenous infusion**
- Adult: Usual dose 4–12 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response, for debilitated patients use dose for elderly
- Elderly: Usual dose 3–6 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response

**Maintenance of anaesthesia using 2% injection**

- **By intravenous infusion**
- Adult: Usual dose 4–12 mg/kg/hour, for debilitated patients use dose for elderly
- Elderly: Usual dose 3–6 mg/kg/hour

**Sedation of ventilated patients in intensive care using 1% or 2% injection**

- **By continuous intravenous infusion**
- Adult: Usual dose 0.3–4 mg/kg/hour, adjusted according to response

**Induction of sedation for surgical and diagnostic procedures using 0.5% or 1% injection**

- **By slow intravenous injection**
- Adult: Initially 0.5–1 mg/kg, to be administered over 1–5 minutes, dose and rate of administration adjusted according to desired level of sedation and response

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

EXCIPIENTS: May contain Propylene glycol

- **Hypnomidate** (Piramal Critical Care Ltd)
- **Etomidate 2 mg per 1 ml** Hypnomidate 20mg/10ml solution for injection ampoules | 5 ampoule (£6.90)

**Emulsion for injection**

- **Etomidate-Lipuro** (B.Braun Medical Ltd)
- **Etomidate 2 mg per 1 ml** Etomidate-Lipuro 20mg/10ml emulsion for injection ampoules | 10 ampoule (£16.09)

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Maintenance of sedation for surgical and diagnostic procedures using 0.5% injection
- INITIALLY BY INTRAVENOUS INFUSION
- Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow intravenous injection) 10–20 mg, (if rapid increase in sedation required), patients over 55 years or debilitated may require lower initial dose and rate of administration

Maintenance of sedation for surgical and diagnostic procedures using 1% injection
- INITIALLY BY INTRAVENOUS INFUSION
- Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow intravenous injection) 10–20 mg, (if rapid increase in sedation required), patients over 55 years or debilitated may require lower initial dose and rate of administration

Maintenance of sedation for surgical and diagnostic procedures using 2% injection
- INITIALLY BY INTRAVENOUS INFUSION
- Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow intravenous injection) 10–20 mg, using 0.5% or 1% injection (if rapid increase in sedation required), patients over 55 years or debilitated may require lower initial dose and rate of administration

IMPORTANT SAFETY INFORMATION
Propofol should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- CAUTIONS Acute circulatory failure (shock), cardiac impairment, cardiovascular disease, elderly, epilepsy, fixed cardiac output, hypotension, hypovolaemia, raised intracranial pressure, respiratory impairment
- INTERACTIONS ➔ Appendix 1: propofol
- SIDE-EFFECTS
  - Common or very common Apnoea, arrhythmias, headache, hypotension, localised pain, nausea, vomiting
  - Uncommon Thrombosis
  - Rare or very rare Epileptiform seizure (may be delayed), pancreatitis, post procedural complications, pulmonary oedema, sexual disinhibition, soft tissue necrosis, urine discoloration
  - Frequency not known Drug use disorders, dyskinesia, euphoric mood, heart failure, hepatomegaly, hyperkalaemia, hyperlipidaemia, metabolic acidosis, renal failure, respiratory depression, rhabdomyolysis

SIDE-EFFECTS, FURTHER INFORMATION
Bradycardia
Bradycardia may be profound and may be treated with intravenous administration of an antimuscarinic drug.

Pain on injection Pain on injection can be reduced by intravenous lidocaine.

Propofol infusion syndrome Prolonged infusion of propofol doses exceeding 4mg/kg/hour may result in potentially fatal effects, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure.

PREGNANCY May depress neonatal respiration if used during delivery.

Dose adjustments Max. dose for maintenance of anaesthesia 6 mg/kg/hour.

- BREAST FEEDING Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.
- HEPATIC IMPAIRMENT Manufacturer advises caution.
- RENAL IMPAIRMENT Use with caution.
- MONITORING REQUIREMENTS Monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days.
- DIRECTIONS FOR ADMINISTRATION Shake before use; microbiological filter not recommended; may be administered via a Y-piece close to injection site co-administered with Glucose 5% or Sodium chloride 0.9%, 0.5% emulsion for injection or intermittent infusion; may be administered undiluted, or diluted with Glucose 5% or Sodium chloride 0.9%; dilute to a concentration not less than 1 mg/ml. 1% emulsion for injection or infusion; may be administered undiluted, or diluted with Glucose 5% (Diprivan®) or (Propofol-Lipuro®) or Sodium chloride 0.9% (Propofol-Lipuro®) only; dilute to a concentration not less than 2 mg/ml; use within 6 hours of preparation. 2% emulsion for infusion; do not dilute.

- PATIENT AND CARER ADVICE
  - Driving and skilled tasks Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Emulsion for infusion
- Propofol (Non-proprietary)
  - Propofol 10 mg per 1 ml Propofol 500mg/50ml emulsion for infusion vials | 1 vial (POM) £15.00 (Hospital only)
  - Propofol-Lipuro® 1% emulsion for infusion 50ml vials | 10 vial (POM) £97.56 (Hospital only)
  - Propofol 1g/100ml emulsion for infusion vials | 1 vial (POM) £15.00 (Hospital only)
  - Propofol-Lipuro® 1% emulsion for infusion 100ml vials | 10 vial (POM) £186.66 (Hospital only)
  - Propofol 20 mg per 1 ml Propofol 1g/50ml emulsion for infusion vials | 1 vial (POM) £15.00 (Hospital only)
  - Propofol-Lipuro® 2% emulsion for infusion 50ml vials | 10 vial (POM) £186.64 (Hospital only)
  - Diprivan (Aspen Pharma Trading Ltd)
    - Propofol 10 mg per 1 ml Diprivan 1% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection (POM) £10.68
    - Propofol 20 mg per 1 ml Diprivan 2% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection (POM) £15.16
  - Propoven (Fresenius Kabi Ltd)
    - Propofol 10 mg per 1 ml Propoven 1% emulsion for infusion 50ml vials | 10 vial (POM) £120.60 (Hospital only)
    - Propoven 1% emulsion for infusion 100ml vials | 10 vial (POM) £241.50 (Hospital only)
    - Propofol 20 mg per 1 ml Propoven 2% emulsion for infusion 50ml vials | 10 vial (POM) £241.50 (Hospital only)

Emulsion for injection
- Propofol (Non-proprietary)
  - Propofol 10 mg per 1 ml Propofol 200mg/20ml emulsion for injection vials | 5 vial (POM) £20.00 (Hospital only)
  - Propofol-Lipuro® 1% emulsion for injection 20ml ampoules | 5 ampoule (POM) £20.16 (Hospital only)
  - Diprivan (Aspen Pharma Trading Ltd)
    - Propofol 10 mg per 1 ml Diprivan 1% emulsion for injection 20ml ampoules | 5 ampoule (POM) £15.36 (Hospital only)
  - Propofol-Lipuro® (B. Braun Melsungen AG)
    - Propofol 5 mg per 1 ml Propofol-Lipuro 0.5% emulsion for injection 20ml ampoules | 5 ampoule (POM) £15.15
  - Propoven (Fresenius Kabi Ltd)
    - Propofol 10 mg per 1 ml Propoven 1% emulsion for injection 20ml ampoules | 5 ampoule (POM) £23.90 (Hospital only)

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Volatile halogenated anaesthetics

**IMPORTANT SAFETY INFORMATION**

- **CONTRA-INDICATIONS** Susceptibility to malignant hyperthermia
- **CAUTIONS** Can trigger malignant hyperthermia - raised intracranial pressure (can increase cerebrospinal pressure)
- **SIDE-EFFECTS**
  - Common or very common: Agitation, apnoea, arrhythmias, chills, cough, dizziness, headache, hypersalivation, hypotension, hypotension, nausea, respiratory disorders, vomiting
  - Uncommon: Hypoxia
  - Frequency not known: Breath holding, cardiac arrest, haemorrhage, hepatic disorders, hyperkalaemia, malignant hyperthermia, QT interval prolongation, rhabdomyolysis, seizure
- **ALLERGY AND CROSS-SENSITIVITY** Can cause hepatotoxicity in those sensitised to halogenated anaesthetics.
- **DIRECTIONS FOR ADMINISTRATION** Volatile liquid anaesthetics are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times.
- **PATIENT AND CARER ADVICE**
  - Driving and skilled tasks: Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of driving or undertaking skilled tasks afterwards. For a short general anaesthetic, the risk extends **to at least 24 hours** after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**Desflurane**

- **INDICATIONS AND DOSE**
  - Induction of anaesthesia (but not recommended)
    - **BY INHALATION**
      - Adult: 4–11%, to be inhaled through specifically calibrated vaporiser
  - Maintenance of anaesthesia (in nitrous oxide–oxygen)
    - **BY INHALATION**
      - Adult: 2–6%, to be inhaled through a specifically calibrated vaporiser
    - Maintenance of anaesthesia (in oxygen or oxygen-enriched air)
      - **BY INHALATION**
        - Adult: 2.5–8.5%, to be inhaled through a specifically calibrated vaporiser
  - **INTERACTIONS** → Appendix 1: volatile halogenated anaesthetics
  - **SIDE-EFFECTS**
    - Common or very common: Coagulation disorder, conjunctivitis

**Isoflurane**

- **INDICATIONS AND DOSE**
  - Induction of anaesthesia (in oxygen or nitrous oxide–oxygen)
    - **BY INHALATION**
      - Adult: Initially 0.5%, increased to 3%, adjusted according to response, administered using specifically calibrated vaporiser
  - Maintenance of anaesthesia (in nitrous oxide–oxygen)
    - **BY INHALATION**
      - Adult: 1–2.5%, to be administered using specifically calibrated vaporiser; an additional 0.5–1% may be required when given with oxygen alone
  - Maintenance of anaesthesia in caesarean section (in nitrous oxide–oxygen)
    - **BY INHALATION**
      - Adult: 0.5–0.75%, to be administered using specifically calibrated vaporiser
  - **INTERACTIONS** → Appendix 1: volatile halogenated anaesthetics
  - **SIDE-EFFECTS**
    - Carboxyhaemoglobinemia, chest discomfort, cognitive impairment, delirium, dyspnoea, ileus, mood altered (that can last several days), myoglobinuria, skin reactions
  - **PREGNANCY** May depress neonatal respiration if used during delivery.
  - **BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**Nitrous oxide**

- **INDICATIONS AND DOSE**
  - Maintenance of anaesthesia in conjunction with other anaesthetic agents
    - **BY INHALATION**
      - Adult: 50–66%, to be administered using suitable anaesthetic apparatus in oxygen

**Anaesthesia**

- **ANAESTHETICS**
  - Common or very common: Myalgia, myocardial infarction, myocardial ischaemia, vasodilation
  - Frequency not known: Abdominal pain, asthenia, heart failure, hypokalaemia, malaise, metabolic acidosis, pancreatitis acute, shock, skin reactions, ventricular dysfunction, visual acuity decreased
  - **PREGNANCY** May depress neonatal respiration if used during delivery.
  - **BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Inhalation vapour**
    - **Desflurane (Non-proprietary)**
      - Desflurane 1 ml per 1 ml Desflurane volatile liquid | 240 ml (£35.29) (Hospital only)

- **Isoflurane**
  - **Inhalation vapour**
    - **Isoflurane (Non-proprietary)**
      - Isoflurane 1 ml per 1 ml Isoflurane inhalation vapour | 250 ml (£35.29) (Hospital only)
    - **AErrane (Baxter Healthcare Ltd)**
      - Isoflurane 1 ml per 1 ml AErrane volatile liquid | 250 ml (£35.29) (Hospital only)

- **Nitrous oxide**
  - **Maintenance of anaesthesia**
    - **BY INHALATION**
      - Adult: 50–66%, to be administered using suitable anaesthetic apparatus in oxygen

**BNF**

- **1332 General anaesthesia**
  - **Voluntary halogenated anaesthetics**
Anaesthesia adjuvants

Sevoflurane

- **INDICATIONS AND DOSE**

  Induction of anaesthesia (in oxygen or nitrous oxide–oxygen)
  - **BY INHALATION**
    - Adult: Initially 0.5–1.0%, then increased to up to 8.0%, increased gradually, according to response, to be administered using specifically calibrated vaporiser

- **CAUTIONS**

  Susceptibility to QT-interval prolongation

- **INTERACTIONS**
  - ➔ Appendix 1: volatile halogenated anaesthetics

- **SIDE-EFFECTS**

  - Common or very common: Drowsiness, fever, hypothermia

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

### Inhalation vapour

- **Sevoflurane (Non-proprietary)**

  Sevoflurane 1 ml per 1 ml Sevoflurane volatile liquid | 250 ml [P38] £123.00 (Hospital only)

1 Anaesthesia adjuvants

### Pre-medication and peri-operative drugs

#### Drugs that affect gastric pH

Regurgitation and aspiration of gastric contents (Mendelson’s syndrome) can be an important complication of general anaesthesia, particularly in obstetrics and during emergency surgery, and requires prophylaxis against acid aspiration. Prophylaxis is also needed in those with gastro-oesophageal reflux disease and in circumstances where gastric emptying may be delayed.

A H₂-receptor antagonist can be used before surgery to increase the pH and reduce the volume of gastric fluid. It does not affect the pH of fluid already in the stomach and this limits its value in emergency procedures; an oral H₂-receptor antagonist can be given 1–2 hours before the procedure. Antacids are frequently used to neutralise the acidity of the fluid already in the stomach; ‘clear’ (non-particulate) antacids such as sodium citrate p.789 are preferred.

#### Antimuscarinic drugs

Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, upper airway surgery, or some...
Anaesthesia

Inhalational anaesthetics. They are also used before or with
neostigmine p. 1125 to prevent bradycardia, excessive
salivation, and other muscarinic actions of neostigmine.
They also prevent bradycardia and hypotension associated
with drugs such as propofol p. 1330 and suxamethonium
chloride p. 1337.

Atropine sulfate p. 1334 is now rarely used for
premedication but still has an emergency role in the
treatment of vagotonic side-effects. Atropine sulfate may
have a role in acute arrhythmias after myocardial infarction.

Hyoscine hydrobromide p. 439 reduces secretions and also
provides a degree of amnesia, sedation, and anti-emesis.
Unlike atropine sulfate it may produce bradycardia rather
than tachycardia.

Glycopyrronium bromide p. 1335 reduces salivary
secretions. When given intravenously it produces less
tachycardia than atropine sulfate. It is widely used with
neostigmine for reversal of non-depolarising neuromuscular
blocking drugs.

Phenothiazines do not effectively reduce secretions when
used alone.

Sedative drugs

Fear and anxiety before a procedure (including the night
before) can be minimised by using a sedative drug, usually a
benzodiazepine. Premedication may also augment the
action of anaesthetics and provide some degree of pre-
operative amnesia. The choice of drug depends on the
individual, the nature of the procedure, the anaesthetic to be
used, and other prevailing circumstances such as
outpatients, obstetrics, and availability of recovery facilities.
The choice also varies between elective and emergency
procedures.

Premedics can be given the night before major surgery;
a further, smaller dose may be required before surgery.
Alternatively, the first dose may be given on the day of the
procedure.

Benzodiazepines

Benzodiazepines possess useful properties for premedication
including relief of anxiety, sedation, and amnesia; short-
acting benzodiazepines taken by mouth are the most
common premedicants. Benzodiazepines are also used in
intensive care units for sedation, particularly in those
receiving assisted ventilation. Flumazenil p. 1368 is used to
antagonise the effects of benzodiazepines.

Diazepam p. 343 is used to produce mild sedation with
amnesia. It is a long-acting drug with active metabolites and
a second period of drowsiness can occur several hours after
its administration. Peri-operative use of diazepam in
children is not recommended; its effect and timing of
response are unreliable and paradoxical effects may occur.

Diazepam is relatively insoluble in water and preparations
formulated in organic solvents are painful on intravenous
injection and give rise to a high incidence of venous
thrombosis (which may not be noticed for several days after
the injection). Intramuscular injection of diazepam is painful and
absorption is erratic. An emulsion formulated for
intravenous injection is less irritant and reduces the risk of
venous thrombosis; it is not suitable for intramuscular
injection.

Temazepam p. 488 is given by mouth for premedication
and has a shorter duration of action and a more rapid onset
than oral diazepam; anxiolytic and sedative effects last
about 90 minutes although there may be residual
drowsiness.

Lorazepam p. 339 produces more prolonged sedation than
temazepam and it has marked amnestic effects.

Midazolam p. 340 is a water-soluble benzodiazepine that is
often used in preference to intravenous diazepam; recovery
is faster than from diazepam, but may be significantly longer
in the elderly, in patients with a low cardiac output, or after
repeated dosing. Midazolam is associated with profound
sedation when high doses are given intravenously or when it
is used with certain other drugs.

Other drugs for sedation

Dexmedetomidine p. 1346 and clonidine hydrochloride
p. 145 are alpha-agonists with sedative
properties. Dexmedetomidine is licensed for the sedation of
patients receiving intensive care who need to remain
responsive to verbal stimulation. Clonidine hydrochloride
[unlicensed indication] can be used by mouth or by
intravenous injection as a sedative agent when adequate
sedation cannot be achieved with standard treatment.

Antagonists for central and respiratory depression

Respiratory depression is a major concern with opioid
analgesics and it may be treated by artificial ventilation or be
reversed by naloxone hydrochloride p. 1369. Naloxone
hydrochloride will immediately reverse opioid-induced
respiratory depression but the dose may have to be repeated
because of the short duration of action of naloxone
hydrochloride; however, naloxone hydrochloride will also
antagonise the analgesic effect.

Flumazenil is a benzodiazepine antagonist for the reversal
of the central sedative effects of benzodiazepines after
anaesthetic and similar procedures. Flumazenil has a shorter
half-life and duration of action than diazepam or midazolam
so patients may become resedated.

Doxapram hydrochloride p. 299 is a central and respiratory
stimulant but is of limited value in anaesthesia.

ANTIMUSCARINICS

Atropine sulfate

- **INDICATIONS AND DOSE**
  - **Bradydysrhythmia due to acute massive overdosage of beta-
    blockers**
    - **BY INTRAVENOUS INJECTION**
      - Child: 40 micrograms/kg (max. per dose 3 mg)
      - Adult: 3 mg
  - **Treatment of poisoning by organophosphorus insecticide
    or nerve agent (in combination with pralidoxime chloride)**
    - **BY INTRAVENOUS INJECTION**
      - Child: 20 micrograms/kg every 5–10 minutes (max. per
dose 2 mg) until the skin becomes flushed and dry, the
pupils dilate, and bradycardia is abolished, frequency
of administration dependent on the severity of
poisoning
      - Adult: 2 mg every 5–10 minutes until the skin becomes
flushed and dry, the pupils dilate, and bradycardia is
abolished, frequency of administration dependent on
the severity of poisoning
  - **Symptomatic relief of gastro-intestinal disorders
    characterised by smooth muscle spasm**
    - **BY MOUTH**
      - Adult: 0.6–1.2 mg daily, dose to be taken at night
  - **Premedication**
    - **BY INTRAVENOUS INJECTION**
      - Child 12-17 years: 300–600 micrograms, to be
administered immediately before induction of
anaesthesia
      - Adult: 300–600 micrograms, to be administered
immediately before induction of anaesthesia
    - **BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR
      INJECTION**
      - Child 12-17 years: 300–600 micrograms, to be
administered 30–60 minutes before induction of
anaesthesia
      - Adult: 300–600 micrograms, to be administered
30–60 minutes before induction of anaesthesia
Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block

- By Intravenous injection
  - Child 12-17 years: 0.6–1.2 mg
  - Adult: 0.6–1.2 mg

Excessive bradycardia associated with beta-blocker use

- By Intravenous injection
  - Adult: 0.6–2.4 mg in divided doses (max. per dose 600 micrograms)

Bradycardia following myocardial infarction (particularly if complicated by hypotension)

- By Intravenous injection
  - Adult: 500 micrograms every 3–5 minutes; maximum 3 mg per course

**IMPORTANT SAFETY INFORMATION**

Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

- **INTERACTIONS** → Appendix 1: atropine
- **SIDE-EFFECTS**
  - Common or very common
  - Uncommon
    - With intravenous use: Psychotic disorder
  - Rare or very rare
    - With intravenous use: Angina pectoris - hypertensive crisis - seizure
  - Frequency not known
    - With intravenous use: Insomnia
  - With oral use: Angle closure glaucoma - arrhythmias - bronchial secretion altered - chest pain - dysphagia - fever - gastrointestinal disorders - mydriasis - staggering - thirst
  - **PREGNANCY** Not known to be harmful; manufacturer advises caution.
  - **BREAST FEEDING** May suppress lactation; small amount present in milk—manufacturer advises caution.

**MONITORING REQUIREMENTS**

- Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block. Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary.
- **LESS SUITABLE FOR PRESCRIBING** Atropine tablets less suitable for prescribing. Any clinical benefit as a gastrointestinal antispasmodic is outweighed by atropinic side-effects.
- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection, solution for infusion

**Tablet**

- Atropine sulfate (Non-proprietary) Atropine sulfate 600 microgram Atropine 600microgram tablets
  - 28 tablet (PCT) £52.92 DT = £52.92

**Solution for injection**

- **Atropine sulfate (Non-proprietary)**
  - Atropine sulfate 100 microgram per 1 ml Atropine 500micrograms/5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PCT) £11.00 | 10 pre-filled disposable injection (PCT) £130.00
  - Atropine sulfate 200 microgram per 1 ml Atropine 1mg/5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PCT) £7.29–£13.00 | 10 pre-filled disposable injection (PCT) £130.00
  - Atropine sulfate 300 microgram per 1 ml Atropine 3mg/10ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PCT) £7.29–£11.00 DT = £7.29 | 10 pre-filled disposable injection (PCT) £130.00
  - Atropine sulfate 400 microgram per 1 ml Atropine 400micrograms/1ml solution for injection ampoules | 10 ampoule (PCT) £102.26 DT = £102.26
  - Atropine sulfate 600 microgram per 1 ml Atropine 600micrograms/1ml solution for injection ampoules | 10 ampoule (PCT) £117.71 DT = £117.71
  - Atropine 600micrograms/1ml solution for injection ampoules | 1 pre-filled disposable injection (PCT) £7.29
  - Atropine sulfate 1 mg per 1 ml Atropine 1mg/1ml solution for injection ampoules | 10 ampoule (PCT) £94.68 DT = £94.68

**Glycopyrronium bromide**

(Glycopyrrolate)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication at induction</td>
</tr>
<tr>
<td>→ By Intramuscular injection, or by Intravenous injection</td>
</tr>
<tr>
<td>→ Adult: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)</td>
</tr>
</tbody>
</table>

**Intra-operative bradycardia**

- **By Intravenous injection**
  - Adult: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary

**Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block**

- **By Intravenous injection**
  - Adult: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary

**Bowel colic in palliative care / Excessive respiratory secretions in palliative care**

- **By Subcutaneous injection**
  - Adult: 20 micrograms every 4 hours and when required, hourly use is occasionally necessary, particularly in excessive respiratory secretions

- **By Subcutaneous Infusion**
  - Adult: 0.6–1.2 mg/24 hours

**IMPORTANT SAFETY INFORMATION**

Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

- **INTERACTIONS** → Appendix 1: glycopyrronium
- **SIDE-EFFECTS** Anhidrosis - bronchial secretion decreased - mydriasis

**PRESCRIBING AND DISPENSING INFORMATION**

Palliative care For further information on the use of glycopyrronium bromide in palliative care, see www.medicinescomplete.com/#/content/palliative/glycopyrronium.
Neuromuscular blockade

Neuromuscular blocking drugs

Neuromuscular blocking drugs used in anaesthesia are also known as muscle relaxants. By specific blockade of the neuromuscular junction they enable light anaesthesia to be used with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs from the muscle relaxants used in musculoskeletal disorders that act on the spinal cord or brain.

Patients who have received a neuromuscular blocking drug should always have their respiration assiated or controlled until the drug has been inactivated or antagonised. They should also receive sufficient concomitant inhalational or intravenous anaesthetic or sedative drugs to prevent awareness.

Non-depolarising neuromuscular blocking drugs

Non-depolarising neuromuscular blocking drugs (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases such as neostigmine p. 1125. Non-depolarising neuromuscular blocking drugs can be divided into the aminosteroid group, comprising pancuronium bromide p. 1339, rocuronium bromide p. 1339, and vecuronium bromide, and the benzylisoquinolinium group, comprising atracurium besilate p. 1337, cisatracurium p. 1338, and mivacurium p. 1338.

Non-depolarising neuromuscular blocking drugs have a slower onset of action than suxamethonium chloride p. 1337. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–60 minutes), and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium besilate and vecuronium bromide, are more widely used than those with a longer duration of action, such as pancuronium bromide.

Non-depolarising neuromuscular blocking drugs have no sedative or analgesic effects and are not considered to trigger malignant hyperthermia.

For patients receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising neuromuscular blocking drug is chosen according to its onset of effect, duration of action, and side-effects. Rocuronium bromide, with a rapid onset of effect, may facilitate intubation. Atracurium besilate or cisatracurium may be suitable for long-term neuromuscular blockade since their duration of action is not dependent on elimination by the liver or the kidneys.

Atracurium besilate, a mixture of 10 isomers, is a benzylisoquinolinium neuromuscular blocking drug with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release; histamine release can be minimised by administering slowly or in divided doses over at least 1 minute.

Cisatracurium is a single isomer of atracurium besilate. It is more potent and has a slightly longer duration of action than atracurium besilate and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects.

Mivacurium, a benzylisoquinolinium neuromuscular blocking drug, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release can occur, particularly with rapid injection.

Pancuronium bromide, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

Rocuronium bromide exerts an effect within 2 minutes and has the most rapid onset of any of the non-depolarising neuromuscular blocking drugs. It is an aminosteroid neuromuscular blocking drug with an intermediate duration of action. It is reported to have minimal cardiovascular effects; high doses produce mild vagolytic activity.

Vecuronium bromide, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects.

Depolarising neuromuscular blocking drugs

Suxamethonium chloride has the most rapid onset of action of any of the neuromuscular blocking drugs and is ideal if fast onset and brief duration of action are required, e.g. with tracheal intubation. Unlike the non-depolarising neuromuscular blocking drugs, its action cannot be reversed and recovery is spontaneous; anticholinesterases such as neostigmine potentiate the neuromuscular block.

Suxamethonium chloride should be given after anaesthetic induction because paralysis is usually preceded by painful muscle fasciculations. While tachycardia occurs with single use, bradycardia may occur with repeated doses in adults and with the first dose in children. Premedication with atropine reduces bradycardia as well as the excessive salivation associated with suxamethonium chloride use.

Prolonged paralysis may occur in dual block, which occurs with high or repeated doses of suxamethonium chloride and is caused by the development of a non-depolarising block following the initial depolarising block. Individuals with myasthenia gravis are resistant to suxamethonium chloride but can develop dual block resulting in delayed recovery. Prolonged paralysis may also occur in those with low or atypical plasma cholinesterase. Assisted ventilation should be continued until muscle function is restored.
Neuromuscular blockade

**NEUROMUSCULAR BLOCKING DRUGS**

**DEPOLARISING**

<table>
<thead>
<tr>
<th>Suxamethonium chloride</th>
<th>(Succinylcholine chloride)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG ACTION</strong></td>
<td>Suxamethonium acts by mimicking acetylcholine at the neuromuscular junction but hydrolysis is much slower than for acetylcholine; depolarisation is therefore prolonged, resulting in neuromuscular blockade.</td>
</tr>
<tr>
<td><strong>INDICATIONS AND DOSE</strong></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blockade (short duration) during surgery and intubation</td>
<td></td>
</tr>
<tr>
<td>BY INTRAVENOUS INJECTION</td>
<td></td>
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<tr>
<td>Adult: 1–1.5 mg/kg</td>
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</tr>
<tr>
<td><strong>UNLICENSED USE</strong></td>
<td>Doses of suxamethonium in BNF may differ from those in product literature.</td>
</tr>
<tr>
<td><strong>CONTRA-INDICATIONS</strong></td>
<td>Duchenne muscular dystrophy; family history of malignant hyperthermia; hyperkalaemia; low plasma-cholinesterase activity (including severe liver disease); major trauma; neurological disease involving acute wasting of major muscle; personal or family history of congenital myotonic disease; prolonged immobilisation (risk of hyperkalaemia); severe burns</td>
</tr>
<tr>
<td><strong>CAUTIONS</strong></td>
<td>Cardiac disease; neuromuscular disease; raised intra-ocular pressure (avoid in penetrating eye injury); respiratory disease; severe sepsis (risk of hyperkalaemia)</td>
</tr>
<tr>
<td><strong>INTERACTIONS</strong></td>
<td>Appendix 1: suxamethonium</td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS</strong></td>
<td></td>
</tr>
<tr>
<td>Common or very common</td>
<td>Apnoea, cardiac arrest, hypotension, muscle weakness, myopathy, respiratory disorders, trismus</td>
</tr>
<tr>
<td>Rare or very rare</td>
<td>Apnoea, cardiac arrest, hypersensitivity, malignant hyperthermia, respiratory disorders, trismus</td>
</tr>
<tr>
<td><strong>ALLERGY AND CROSS-SENSITIVITY</strong></td>
<td>Allergic cross-reactivity between neuromuscular blocking drugs has been reported; caution advised in cases of hypersensitivity to these drugs.</td>
</tr>
<tr>
<td><strong>PREGNANCY</strong></td>
<td>Non-depolarising neuromuscular blocking drugs are highly ionised at physiological pH and are therefore unlikely to cross the placenta in significant amounts.</td>
</tr>
<tr>
<td><strong>BREAST FEEDING</strong></td>
<td>Non-depolarising neuromuscular blocking drugs are ionised at physiological pH and are unlikely to be present in milk in significant amounts.</td>
</tr>
<tr>
<td><strong>CAUTIONS</strong></td>
<td>Burns (resistance can develop, increased doses may be required); cardiovascular disease (reduce rate of administration); electrolyte disturbances (response unpredictable); fluid disturbances (response unpredictable); hypothermia (activity prolonged, lower doses required); myasthenia gravis (activity prolonged, lower doses required); neuromuscular disorders (response unpredictable)</td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS</strong></td>
<td></td>
</tr>
<tr>
<td>Common or very common</td>
<td>Flushing, hypotension</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Bronchospasms, hypersensitivity, skin reactions</td>
</tr>
<tr>
<td>Rare or very rare</td>
<td>Muscle weakness, myopathy (after prolonged use in intensive care)</td>
</tr>
<tr>
<td><strong>ALLERGY AND CROSS-SENSITIVITY</strong></td>
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<td><strong>INDICATIONS AND DOSE</strong></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blockade (short to intermediate duration) for surgery and intubation</td>
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<tr>
<td>INITIALLY BY INTRAVENOUS INJECTION</td>
<td></td>
</tr>
<tr>
<td>Adult: Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous infusion) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour</td>
<td></td>
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<tr>
<td><strong>DOSES AT EXTREMES OF BODY-WEIGHT</strong></td>
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<tr>
<td>To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.</td>
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<tr>
<td><strong>INTERACTIONS</strong></td>
<td>Appendix 1: neuromuscular blocking drugs, non-depolarising</td>
</tr>
</tbody>
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**Atracurium besilate**

(Tracurium besilate)

**INDICATIONS AND DOSE**

Neuromuscular blockade (short to intermediate duration) for surgery and intubation

INITIALLY BY INTRAVENOUS INJECTION

Adult: Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous infusion) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour

**DOSES AT EXTREMES OF BODY-WEIGHT**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.
Atracurium besilate (Non-proprietary)

Atracurium injection/infusion, Genus), give continuously in Glucose 5% or Sodium Chloride 0.9%; stability varies with diluent; dilute requisite dose with infusion fluid to a concentration of 0.1–5 mg/mL.

For surgery and intubation
Neuromuscular blockade (intermediate duration) during surgery and intubation

Dose adjustments
Adult: Initially 150 micrograms/kg, then (by intravenous injection) maintenance 30 micrograms/kg every 20 minutes, alternatively (by intravenous infusion) initially 180 micrograms/kg/hour, then (by intravenous infusion) maintenance 60–120 micrograms/kg/hour, maintenance dose administered after stabilisation

Neuromuscular blockade (intermediate duration) during intensive care
Adult: Initially 150 micrograms/kg, Initial dose is optional, then (by intravenous infusion) 180 micrograms/kg/hour, adjusted according to response; (by intravenous infusion) usual dose 30–600 micrograms/kg/hour

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

Interactions
Appendix 1: neuromuscular blocking drugs, non-depolarising

Side-effects
Common or very common Bradycardia

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Nimbex®, Nimbex Forte®), give continuously in Glucose 5% or Sodium Chloride 0.9%; solutions of 2 mg/mL and 5 mg/mL may be infused undiluted; alternatively dilute with infusion fluid to a concentration of 0.1–2 mg/mL.

Mivacurium

Indications and dose
Neuromuscular blockade (short duration) during surgery and intubation

Initially by intravenous injection
Adult: 70–250 micrograms/kg; (by intravenous injection) maintenance 100 micrograms/kg every 15 minutes, alternatively (by intravenous infusion) maintenance 8–10 micrograms/kg/minute, (by intravenous infusion) adjusted in steps of 1 microgram/kg/minute every 3 minutes if required; (by intravenous infusion) usual dose 6–7 micrograms/kg/minute

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

Caution
Burns (low plasma cholinesterase activity; dose titration required) - elderly

Interactions
Appendix 1: neuromuscular blocking drugs, non-depolarising

Side-effects
Unlikely Tachycardia

Hepatic impairment
Dose adjustments Reduce dose in severe impairment.

Renal impairment
Dose adjustments Clinical effect prolonged in renal failure—reduce dose according to response.

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute to a concentration of 500 micrograms/ml; may also be given undiluted. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In asthma, cardiovascular disease or in those sensitive to reduced arterial blood pressure, give over 60 seconds.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
Mivacurium (Aspen Pharma Trading Ltd) Mivacuron 10mg/5ml solution for injection ampoules | 5 ampoule (PO) £13.95 Mivacuron 20mg/10ml solution for injection ampoules | 5 ampoule (PO) £22.57
**Pancuronium bromide**

**INDICATIONS AND DOSE**
- **Neuromuscular blockade (long duration) during surgery and intubation**
  - **BY INTRAVENOUS INJECTION**
  - **Adult:** Initially 100 micrograms/kg, then 20 micrograms/kg as required

**Neuromuscular blockade (long duration) during intensive care**
- **BY INTRAVENOUS INJECTION**
- **Adult:** Initially 100 micrograms/kg, initial dose is optional, then 60 micrograms/kg every 60–90 minutes

**DOSES AT EXTREMES OF BODY-WEIGHT**
- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**INTERACTIONS** → Appendix 1: neuromuscular blocking drugs, non-depolarising

**SIDE-EFFECTS** Apnoea, arrhythmia, hypersalivation, increased cardiac output, miosis

**SIDE-EFFECTS, FURTHER INFORMATION** Pancuronium lacks histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia.

**HEPATIC IMPAIRMENT** Possibly slower onset, higher dose requirement, and prolonged recovery time.

**RENAL IMPAIRMENT** Use with caution; prolonged duration of block.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Pancuronium bromide (Non-proprietary)**
  - Pancuronium bromide 2 mg per 1 ml
  - Pancuronium bromide 4 mg/2 ml solution for injection ampoules | 10 ampoule £0.40
  - Pancuronium bromide 100 mg/5 ml solution for injection vials | 10 vial £28.00–£36.50 | 10 vial £57.00–£73.00

**Rocuronium bromide**

**INDICATIONS AND DOSE**
- **Neuromuscular blockade (intermediate duration) during surgery and intubation**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - **Adult:** Initially 600 micrograms/kg; (by intravenous injection) maintenance 150 micrograms/kg, alternatively (by intravenous infusion) maintenance 300–600 micrograms/kg/hour, adjusted according to response

**Neuromuscular blockade (intermediate duration) during intensive care**
- **INITIALLY BY INTRAVENOUS INJECTION**
- **Adult:** Initially 600 micrograms/kg, initial dose is optional; (by intravenous infusion) maintenance 300–600 micrograms/kg/hour for first hour, then (by intravenous infusion), adjusted according to response

**DOSES AT EXTREMES OF BODY-WEIGHT**
- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**INTERACTIONS** → Appendix 1: neuromuscular blocking drugs, non-depolarising

**SIDE-EFFECTS** Procedural complications - tachycardia

**HEPATIC IMPAIRMENT**
- **Dose adjustments** Reduce dose.

**RENAL IMPAIRMENT**
- **Dose adjustments** Reduce maintenance dose; prolonged paralysis.

**DIRECTIONS FOR ADMINISTRATION** For continuous intravenous infusion or via drip tubing, may be diluted with Glucose 5% or Sodium Chloride 0.9%.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Rocuronium bromide (Non-proprietary)**
  - Rocuronium bromide 10 mg per 1 ml
  - Rocuronium bromide 50 mg/5 ml solution for injection ampoules | 10 ampoule £24.00
  - Rocuronium bromide 50 mg/5 ml solution for injection vials | 10 vial £28.00–£36.50 | 10 vial £57.00–£73.00

**Rocuronium bromide 10 mg per 1 ml**
- **Esmeron (Merck Sharp & Dohme Ltd)**
  - Rocuronium bromide 10 mg per 1 ml
  - Rocuronium bromide 50 mg/5 ml solution for injection vials | 10 vial £28.92 (Hospital only)

### 1.2 Neuromuscular blockade reversal

**Neuromuscular blockade reversal**

**Neuromuscular blockade reversal**

**Anticholinesterases**

Anticholinesterases reverse the effects of the non-depolarising (competitive) neuromuscular blocking drugs such as pancuronium bromide but they prolong the action of the depolarising neuromuscular blocking drug suxamethonium chloride.

Neostigmine is used specifically for reversal of non-depolarising (competitive) blockade. It acts within one minute of intravenous injection and its effects last for 20 to 30 minutes; a second dose may then be necessary. Glycopyrrolate bromide p. 1335 or alternatively atropine sulphate p. 1334, given before or with neostigmine, prevent bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

**Other drugs for reversal of neuromuscular blockade**

Sugammadex p. 1340 is a modified gamma cyclodextrin that can be used for rapid reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide. In practice, sugammadex is used mainly for rapid reversal of neuromuscular blockade in an emergency.

**ANTICHOLINESTERASES**

**Neostigmine with glycopyrrolate bromide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, neostigmine p. 1125, glycopyrrolate bromide p. 1335.

**INDICATIONS AND DOSE**

**Reversal of non-depolarising neuromuscular blockade**
- **BY INTRAVENOUS INJECTION**
- **Adult:** 1–2 mL, repeated if necessary, alternatively 0.02 mL/kg/m², repeated if necessary; maximum 2 mL per course
1340 Anaesthesia adjuvants

1.3 Peri-operative analgesia

Peri-operative analgesia

Non-opioid analgesics

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastro-intestinal motility, and do not cause dependence, they may be useful alternatives or adjuncts to opioids for the relief of postoperative pain. NSAIDs may be inadequate for the relief of severe pain. Diclofenac sodium p. 1135, diclofenac potassium p. 1135, flurbiprofen p. 1140, ibuprofen p. 1141, ketoprofen p. 1144, paracetamol p. 444, parecoxib p. 1342, and ketorolac trometamol p. 1342 are licensed for postoperative use. Diclofenac and paracetamol can be given by injection as well as by mouth. Diclofenac sodium can be given by intravenous infusion for the treatment or prevention of postoperative pain. Intramuscular injections of diclofenac sodium and ketoprofen are rarely used; they are given deep into the gluteal muscle to minimise pain and tissue damage. Ketorolac trometamol is less irritant on intramuscular injection but pain has been reported; it can also be given by intravenous injection.

Suppositories of diclofenac sodium and ketoprofen may be effective alternatives to the parenteral use of these drugs.

Opioid analgesics

Opioid analgesics are now rarely used as premedicants; they are more likely to be administered at induction. Preoperative use of opioid analgesics is generally limited to those patients who require control of existing pain. See general notes on opioid analgesics and their use in postoperative pain.

See the management of opioid-induced respiratory depression in Pre-medication and peri-operative drugs p. 1333.

Intra-operative analgesia

Opioid analgesics given in small doses before or with induction reduce the dose requirement of some drugs used during anaesthesia.

Alfentanil p. 1343, fentanyl p. 458, and remifentanil p. 1344 are particularly useful because they act within 1–2 minutes and have short durations of action. The initial doses of alfentanil or fentanyl are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect. Repeated intra-operative doses of alfentanil or fentanyl should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive. Alfentanil, fentanyl, and remifentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by nonspecific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression. Remifentanil should not be given by intravenous injection intraoperatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.
Esketamine

**DRUG ACTION** Esketamine is an isomer of ketamine that blocks N-methyl-D-aspartate (NMDA) receptors and interrupts the association pathways of the brain, resulting in dissociative anaesthesia and analgesia.

**INDICATIONS AND DOSE**

**Induction and maintenance of anaesthesia (specialist use only)**
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 0.5–1 mg/kg, then maintenance 0.25–0.5 mg/kg every 10–15 minutes, adjusted according to response
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 2–4 mg/kg, then maintenance 1–2 mg/kg every 10–15 minutes, adjusted according to response
- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: 0.5–3 mg/kg/hour, adjusted according to response

**Analgesic supplementation of regional and local anaesthesia (specialist use only)**
- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: 0.125–0.25 mg/kg/hour, adjusted according to response

**Analgesia in emergency medicine (specialist use only)**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 0.25–0.5 mg/kg, adjusted according to response
- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 0.125–0.25 mg/kg, adjusted according to response

**MEDICINAL FORMS**

- **Solution for injection**
  - Vesierra (Pfizer Ltd)
    - Esketamine (as Esketamine hydrochloride) 5 mg per 1 ml Vesierra 25 mg/ml solution for injection ampoules | 10 ampoules [POS] £18.98 (Hospital only) [C2]
    - Esketamine (as Esketamine hydrochloride) 25 mg per 1 ml Vesierra 50 mg/ml solution for injection ampoules | 10 ampoules [POS] £26.31 (Hospital only) [C2]

**ANAESTHETICS, LOCAL**

Bupivacaine with fentanyl

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupivacaine hydrochloride p. 1349, fentanyl p. 458.

**INDICATIONS AND DOSE**

**During labour (once epidural block established)**
- **BY CONTINUOUS LUMBAR EPIDURAL INFUSION**
  - Adult: 10–18.75 mg/hour, dose of bupivacaine to be administered, maximum 400 mg bupivacaine in 24 hours and 16–30 micrograms/hour, dose of fentanyl to be administered, maximum 720 micrograms fentanyl in 24 hours

**Postoperative pain (once epidural block established)**
- **BY CONTINUOUS EPIDURAL INFUSION**
  - Adult: 4–18.75 mg/hour, dose of bupivacaine to be administered, maximum 400 mg bupivacaine in 24 hours and 8–30 micrograms/hour, dose of fentanyl to be administered, maximum 720 micrograms fentanyl in 24 hours, to be administered by thoracic, upper abdominal or lower abdominal epidural infusion

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Solution for infusion**
- **Bufyl (Advanz Pharma)**
  - Fentanyl 2 microgram per 1 ml, Bupivacaine hydrochloride 1 mg per 1 ml Bufyl 1 mg/ml and 2 micrograms/ml 250 ml infusion bags | 20 bag [POS] £170.00 (Hospital only) [C2]
  - Bufyl 1 mg/ml and 2 micrograms/ml 500 ml infusion bags | 10 bag [POS] £32.00 (Hospital only) [C2]
  - Fentanyl (as Fentanyl citrate) 2 microgram per 1 ml, Bupivacaine hydrochloride 1.25 mg per 1 ml Bufyl 1.25 mg/ml and
**Ketorolac trometamol**

**INDICATIONS AND DOSE**

**Short-term management of moderate to severe acute postoperative pain only**

- BY INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION
  - Adult (body-weight up to 50 kg): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day
  - Adult (body-weight 50 kg and above): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 90 mg per day
  - Elderly: Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day

**CONTRA-INDICATIONS**
Active or history of gastrointestinal bleeding - active or history of gastrointestinal ulceration - coagulation disorders - complete or partial syndrome of nasal polyps - confirmed or suspected cerebrovascular bleeding - dehydration - following operations with high risk of haemorrhage or incomplete haemostasis - haemorrhagic diatheses - history of gastrointestinal perforation - hypovolaemia - severe heart failure

**CAUTIONS**
- Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

**INTERACTIONS**
- Appendix 1: NSAIDs

**SIDE-EFFECTS**

abnormal - thirst - thrombocytopenia - tinnitus - ulcer - urinary disorders - vertigo - visual impairment - vomiting - weight increased - wound haemorrhage

**SID-EFFECTS, FURTHER INFORMATION**
- For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- **ALLERGY AND CROSS-SENSITIVITY**
  - Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION**
  - Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**
  - Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING**
  - Amount too small to be harmful.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution—may increase risk of renal impairment; avoid in hepatic failure.

- **RENAL IMPAIRMENT**
  - Avoid if possible or use with caution. Avoid if serum creatinine greater than 160 micromol/litre.

- **Dose adjustments**
  - The lowest effective dose should be used for the shortest possible duration. Max. 60 mg daily by intramuscular injection or intravenous injection. Monitoring In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous injection, give over at least 15 seconds.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Ketorolac trometamol (Non-proprietary)**
  - Ketorolac trometamol 30 mg per 1 ml
  - Ketorolac 30mg/1ml solution for injection ampoules | 5 ampoule [POM] £15.60–£20.00 DT + £5.36 (Hospital only)

- **Toradol (Atnahs Pharma UK Ltd)**
  - Ketorolac trometamol 30 mg per 1 ml
  - Toradol 30mg/1ml solution for injection ampoules | 5 ampoule [POM] £5.36 DT + £5.36 (Hospital only)

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**Parecoxib**

**DRUG ACTION**

Parecoxib is a selective inhibitor of cyclooxygenase-2.

**INDICATIONS AND DOSE**

**Short-term management of acute postoperative pain**

- BY DEEP INTRAMUSCULAR INJECTION, OR BY INTRAVENOUS INJECTION
  - Adult: Initially 40 mg, then 20–40 mg every 6–12 hours as required for up to 3 days; maximum 80 mg per day
  - Elderly (body-weight up to 50 kg): Initially 20 mg; maximum 40 mg per day

**CONTRA-INDICATIONS**
Active gastro-intestinal bleeding - active gastro-intestinal ulceration - cerebrovascular disease - inflammatory bowel disease - ischaemic heart disease - mild to severe heart failure - peripheral arterial disease

**CAUTIONS**
- Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - dehydration - elderly (risk of serious side effects and fatalities) - following coronary artery bypass graft surgery - history of cardiac failure - hypertension - left
ventricular dysfunction · oedema · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated)

- **INTERACTIONS** → Appendix 1: NSAIDs

- **SIDE-EFFECTS**
  - Common or very common: Agitation · back pain · constipation · dizziness · gastrointestinal discomfort · gastrointestinal disorders · hyperhidrosis · hypertension · hypokalaemia · hypotension · increased risk of infection · insomnia · nausea · numbness · peripheral oedema · post procedural complications · renal impairment · respiratory disorders · skin reactions · vomiting
  - Uncommon: Appetite decreased · arthralgia · arthrosis · asthma · cerebrovascular insufficiency · dry mouth · ear pain · embolism and thrombosis · hypergammaglobulinemia · myocardial infarction · thrombocytopenia
  - Rare or very rare: Hypersensitivity · pancreatitis · perioral swelling
  - Frequency not known

**SIDE-EFFECTS, FURTHER INFORMATION** For information about cardiovascular and gastrointestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs. p. 1130

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID. Contra-indicated in patients with a history of allergic drug reactions including sulfonamide hypersensitivity.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Avoid—present in milk.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment (risk of increased exposure); avoid in severe impairment (no information available).

**Dose adjustments** Manufacturer advises dose reduction to half the usual recommended dose in moderate impairment; maximum 40 mg daily.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution.

**Dose adjustments** The lowest effective dose should be used for the shortest possible duration.

**Monitoring** In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) decisions**

  The **Scottish Medicines Consortium** has advised (January 2003) that parecoxib is **not** recommended for use within NHS Scotland.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Powder and solvent for solution for injection**

  - **Dynastat** (Pfizer Ltd)
    - Parecoxib (as Parecoxib sodium) 40 mg
  
  **Powder for solution for injection**

  - **Dynastat** (Pfizer Ltd)
    - Parecoxib (as Parecoxib sodium) 40 mg

**DOSAGES AT EXTREMES OF BODY-WEIGHT**

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- **CAUTIONS, FURTHER INFORMATION**

  - Repeated intra-operative doses. Repeated intra-operative doses of alfentanil should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive.

- **INTERACTIONS** → Appendix 1: opioids

- **SIDE-EFFECTS**
  - Common or very common: Apnoea · chills · fatigue · hypertension · movement disorders · muscle rigidity · procedural complications
  - Uncommon: Coma · hiccups · hypercapnia · pain · post procedural complications · respiratory disorders
  - Rare or very rare: Agitation · crying · epistaxis · vascular pain
  - Frequency not known: Cardiac arrest · cough · fever · loss of consciousness · seizure

**SIDE-EFFECTS, FURTHER INFORMATION** Alfentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

- **BREAST FEEDING** Present in milk— withhold breast-feeding for 24 hours.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution. Dose adjustments Manufacturer advises dose reduction and cautious titration.

- **RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.
1344 Anaesthesia adjuvants

- **DIRECTIONS FOR ADMINISTRATION** 5 mg/mL injection to be diluted before use. For continuous or intermittent intravenous infusion dilute in Glucose 5% or Sodium Chloride 0.9%.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection.

  **Solution for injection**
  - Alfentanil (Non-proprietary)
    - Alfentanil (as Alfentanil hydrochloride) 500 microgram per 1 ml Alfentanil 1mg/2ml solution for injection ampoules | 10 ampoule (POM) £7.95 DT + £6.34 (C07)
    - Alfentanil 25mg/50ml solution for injection vials | 1 vial (POM) £14.90 (C07)
    - Alfentanil 5mg/10ml solution for injection ampoules | 10 ampoule (POM) £2.78 (C07)
  - Papaveretum (as Papaveretum hydrochloride) 5 mg per 1 ml Papaveretum hydrochloride solution for injection ampoules | 10 ampoule (POM) £21.95 DT + £23.19 (C07)
  - Rapifen (as Rapifen hydrobromide) 500 microgram per 1 ml Rapifen 5mg/10ml solution for injection ampoules | 5 ampoule (POM) £14.50 (C07)
  - Rapifen 1mg/2ml solution for injection ampoules | 10 ampoule (POM) £6.34 DT + £6.34 (C07)
  - Alfentanil (as Alfentanil hydrochloride) 5 mg per 1 ml Alfentanil 5mg/1ml solution for injection ampoules | 10 ampoule (POM) £23.19 DT + £23.19 (hospital only) (C07)

  **UNLICENSED USE** Remifentanil doses in BNF may differ from those in product literature.

  **CONTRA-INDICATIONS** Analgesia in conscious patients

  **INTERACTIONS** → Appendix 1: hyoscine - opioids

  **LESS SUITABLE FOR PRESCRIBING** Papaveretum with hyoscine hydrobromide is less suitable for prescribing.

  **MEDICINAL FORMS** No licensed medicines listed.

**Papaveretum with hyoscine hydrobromide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, papaveretum p. 469, hyoscine hydrobromide p. 439.

- **INDICATIONS AND DOSE**
  - Premedication
    - BY SUBCUTANEOUS INJECTION, OR BY INTRAMUSCULAR INJECTION
    - Adult: 0.5–1 mL
  - INTERACTIONS → Appendix 1: hyoscine - opioids
  - LESS SUITABLE FOR PRESCRIBING Papaveretum with hyoscine hydrobromide is less suitable for prescribing.

**Remifentanil**

- **INDICATIONS AND DOSE**
  - Analgesia and enhancement of anaesthesia at induction (initial bolus injection)
    - BY INTRAVENOUS INJECTION
    - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, if patient is to be intubated more than 8 minutes after start of intravenous infusion, initial bolus intravenous injection dose is not necessary
  - Analgesia and enhancement of anaesthesia at induction with or without initial bolus dose
    - BY INTRAVENOUS INFUSION
    - Adult: 30–60 micrograms/kg/hour, if patient is to be intubated more than 8 minutes after start of intravenous infusion, initial bolus intravenous injection dose is not necessary

**Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia (initial bolus injection)**

- BY INTRAVENOUS INJECTION
  - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds

**Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia with or without initial bolus dose**

- BY INTRAVENOUS INFUSION
  - Adult: 3–120 micrograms/kg/hour, dose to be administered according to anaesthetic technique and adjusted according to response, in light anaesthesia additional doses can be given by intravenous injection every 2–5 minutes during the intravenous infusion

**Spontaneous respiration: analgesia and enhancement of anaesthesia during maintenance of anaesthesia**

- BY INTRAVENOUS INFUSION
  - Adult: Initially 2.4 micrograms/kg/hour, adjusted according to response; usual dose 1.5–6 micrograms/kg/hour

**Assisted ventilation: analgesia and sedation in intensive-care patients (for max 3 days)**

- BY INTRAVENOUS INFUSION
  - Adult: Initially 6–9 micrograms/kg/hour, then adjusted in steps of 1.5 micrograms/kg/hour, allow at least 5 minutes between dose adjustments; usual dose 0.36–4.44 micrograms/kg/hour, if an infusion rate of 12 micrograms/kg/hour does not produce adequate sedation add another sedative (consult product literature for details)

**Assisted ventilation: additional analgesia during stimulating or painful procedures in intensive-care patients**

- BY INTRAVENOUS INFUSION
  - Adult: Usual dose 15–45 micrograms/kg/hour, maintain infusion rate of at least 6 micrograms/kg/hour for at least 5 minutes before procedure and adjust every 2–5 minutes according to requirements

**Cardiac surgery**

- Adult: (consult product literature)

**DOSES AT EXTREMES OF BODY-WEIGHT**
- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**SIDE-EFFECTS**

- **Common or very common** Apnoea - muscle rigidity - post procedural complications
- **Uncommon** Hypoxia
- **Rare or very rare** Cardiac arrest
- **Frequency not known** Agitation - atrioventricular block - hypertension - seizure

**SIDE-EFFECTS, FURTHER INFORMATION** In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by plasma esterases; it has short duration of action which is independent of dose and duration of infusion.

**Muscle rigidity** Remifentanil can cause muscle rigidity that can be managed by the use of neuromuscular blocking drugs.

**PREGNANCY** No information available.

**BREAST FEEDING** Avoid breast-feeding for 24 hours after administration—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment (limited information available).

www.getintopharma.com
1.4 Peri-operative sedation

Conscious sedation for clinical procedures

Overview
Sedation of patients during diagnostic and therapeutic procedures is used to reduce fear and anxiety, to control pain, and to minimise excessive movement. The choice of sedative drug will depend upon the intended procedure; some procedures are safer and more successful under anaesthesia. The patient should be monitored carefully; monitoring should begin as soon as the sedative is given or when the patient becomes drowsy, and should be continued until the patient wakes up.

Anaesthetics, General > NMDA Receptor Antagonists

Ketamine

- INDICATIONS AND DOSE
  - Induction and maintenance of anaesthesia for short procedures
    - By Intramuscular Injection
      - Adult: Initially 6.5–13 mg/kg, adjusted according to response, a dose of 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia
take patients home. The dangers of taking alcohol should also be emphasised.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including ketamine, see Drugs and driving under Guidance on prescribing p. 1.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, solution for injection, spray

**Solution for injection**

- **Ketamine (Non-proprietary)**
  - Ketamine (as Ketamine hydrochloride) 10 mg per 1 ml Ketamin 10 Curamed 50mg/5ml solution for injection ampoules | 10 ampoule (£0.21 CD)
  - Ketamine (as Ketamine hydrochloride) 50 mg per 1 ml Ketamin 500mg/10ml solution for injection vials | 10 vial (£0.60 CD)
  - Ketamin 100mg/2ml solution for injection ampoules | 10 ampoule (£0.21 CD)
  - Ketoject (Pfizer Ltd)
  - Ketalar (Hospital only)

- **Dexmedetomidine (Non-proprietary)**
  - Dexmedetomidine (as Dexmedetomidine hydrochloride) 100 microgram per 1 ml Dexmedetomidine 1mg/10ml concentrate for solution for infusion vials | 4 vial (£5.60 CD)
  - Dexmedetomidine 400micrograms/4ml concentrate for solution for infusion vials | 4 vial (£12.70 CD)
  - Dexmedetomidine 200micrograms/2ml concentrate for solution for infusion ampoules | 5 ampoule (£78.30 CD)
  - Dexor (Orion Pharma (UK) Ltd)
  - Dexdor (Hospital only)

**HYPNOTICS, SEDATIVES AND ANXIOLYTIKS › NON-BENZODIAZEPINE HYPNOTICS AND SEDATIVES**

**Dexmedetomidine**

- **INDICATIONS AND DOSE**
  - **Maintenance of sedation during intensive care**
    - **BY INTRAVENOUS INJECTION**
      - Adult: 0.7 microgram/kg/hour, adjusted according to response; usual dose 0.2–1.4 micrograms/kg/hour
  - **BY RAPID INTRAVENOUS INJECTION**
    - Adult: 1–2 micrograms/kg
  - **BY INTRAVENOUS INFUSION**
    - Adult: 1–2 micrograms/kg/hour
  - **BY INTRADERMAL INJECTION**
    - Adult: 1 microgram/kg

**INTERACTIONS**

- **Common or very common**
  - Agitation
  - Locomotion
  - Hiccups
  - Delirium
  - Fever
  - Shivering
  - Sweating
  - Hypotension
  - Palpitations
  - Episodic hypertension
  - Dizziness
  - Gastrointestinal symptoms
  - Somnolence
  - Movement disorders

**SIDE-EFFECTS**

- **Gastrointestinal symptoms**
  - Nausea
  - Vomiting

- **Respiratory symptoms**
  - Tachypnoea
  - Dyspnoea
  - Hypoventilation

- **Cardiovascular effects**
  - Bradycardia
  - Hypotension
  - Hypertension

- **Central nervous system effects**
  - Sedation
  - Drowsiness
  - Restlessness
  - Agitation

- **Other effects**
  - Fatigue
  - Dry mouth
  - Thirst

**CONTRA-INDICATIONS**

- Hypersensitivity to dantrolene or any component of the preparation
- Myasthenia gravis
- Severe hypovolaemia
- Refractory ventricular arrhythmias
- Severe hypothermia
- Fever
- Severe hypotension
- Cardiac failure
- Acute cerebrovascular disorders
- Severe anaemia
- Significant dehydration
- During labour
- Adults with lung disease
- Children

**Dose adjustments** Manufacturer advises consider dose reduction.

- **MONITORING REQUIREMENTS**
  - Blood pressure
  - Heart rate
  - Oxygen saturation

**DIRECTIONS FOR ADMINISTRATION** To be diluted before use. For intravenous infusion given continuously in Glucose 5% or Sodium chloride 0.9%, dilute to a concentration of 4 micrograms/ml.

**INTERACTIONS**

- **Common or very common**
  - Propranolol
  - Aminophylline
  - Monoamine oxidase (MAO) inhibitors
  - Calcium channel blockers
  - Thromboxane synthase inhibitors
  - Thromboxane synthase inhibitors

- **SIDE-EFFECTS**
  - Bradycardia
  - Hypotension
  - Hypertension
  - Palpitations
  - Dizziness
  - Gastrointestinal symptoms
  - Somnolence
  - Movement disorders

- **INTERACTIONS**
  - **Common or very common**
    - Locomotion
    - Hypoglycaemia
    - Hyperthermia
    - Respiratory depression
    - Depression
    - Drowsiness
    - Agitation
    - Nausea
    - Vomiting
    - Hypotension
    - Hypertension
    - Palpitations
    - Gastrointestinal symptoms
    - Somnolence
    - Movement disorders
  - **SIDE-EFFECTS**
    - Bradycardia
    - Hypotension
    - Hypertension
    - Palpitations
    - Dizziness
    - Gastrointestinal symptoms
    - Somnolence
    - Movement disorders

**IMPORTANT SAFETY INFORMATION**

Dexametomidine should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management.

**CONTRA-INDICATIONS**

- Acute cerebrovascular disorders - second- or third-degree AV block (unless pacemaker fitted) - uncontrolled hypotension

**CAUTIONS**

- Abrupt withdrawal after prolonged use - bradycardia - ischaemic heart disease - malignant hyperthermia - severe cerebrovascular disease (especially at higher doses) - severe neurological disorders - spinal cord injury

**INTERACTIONS**

- Appendix 1: dexametomidine

**SIDE-EFFECTS**

- **Common or very common**
  - Agitation
  - Arterial hypotension
  - Bradycardia
  - Hypotension
  - Hypertension
  - Palpitations
  - Vomiting

- **Uncommon**
  - Abdominal distension
  - Anopia
  - Atrioventricular block
  - Dyspnoea
  - Hallucination
  - Hypoalbuminaemia
  - Metabolic acidosis
  - Thirst

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution (increased risk of toxicity due to decreased clearance).

**Dose adjustments** Manufacturer advises consider dose reduction.

- **MONITORING REQUIREMENTS**
  - Blood pressure
  - Heart rate
  - Oxygen saturation

**DIRECTIONS FOR ADMINISTRATION** To be diluted before use. For intravenous infusion given continuously in Glucose 5% or Sodium chloride 0.9%, dilute to a concentration of 4 micrograms/ml.

**INTERACTIONS**

- **Common or very common**
  - Propranolol
  - Aminophylline
  - Monoamine oxidase (MAO) inhibitors
  - Calcium channel blockers
  - Thromboxane synthase inhibitors
  - Thromboxane synthase inhibitors

- **SIDE-EFFECTS**
  - Bradycardia
  - Hypotension
  - Hypertension
  - Palpitations
  - Dizziness
  - Gastrointestinal symptoms
  - Somnolence
  - Movement disorders

**INTERACTIONS**

- **Common or very common**
  - Locomotion
  - Hypoglycaemia
  - Hyperthermia
  - Respiratory depression
  - Depression
  - Drowsiness
  - Agitation
  - Nausea
  - Vomiting
  - Hypotension
  - Hypertension
  - Palpitations
  - Gastrointestinal symptoms
  - Somnolence
  - Movement disorders

**IMPORTANT SAFETY INFORMATION**

Should only be administered by, or under the direct supervision of, personnel experienced in the use of dantrolene when used for malignant hyperthermia.

**CONTRA-INDICATIONS**

- With oral use
  - Acute muscle spasm
  - Avoid when spasticity is useful, for example, locomotion

**CAUTIONS**

- With intravenous use
  - Avoid extravasation (risk of tissue necrosis)
- With oral use
  - Females (hepatotoxicity) - history of liver disorders (hepatotoxicity) - doses greater than 400 mg daily (hepatotoxicity) - impaired cardiac function - impaired pulmonary function - patients over 30 years (hepatotoxicity) - therapeutic effect may take a few weeks to develop—discontinue if no response within 6–8 weeks

**INTERACTIONS**

- Appendix 1: dantrolene

**DIRECTIONS FOR ADMINISTRATION**

- **BY MOUTH**
  - Adult: Initially 25 mg daily, then increased to up to 100 mg 4 times a day, dose increased at weekly intervals; usual dose 75 mg 3 times a day

**IMPORTANT SAFETY INFORMATION**

Should only be administered by, or under the direct supervision of, personnel experienced in the use of dantrolene when used for malignant hyperthermia.

**CONTRA-INDICATIONS**

- With oral use
  - Acute muscle spasm
  - Avoid when spasticity is useful, for example, locomotion

**CAUTIONS**

- With intravenous use
  - Avoid extravasation (risk of tissue necrosis)
- With oral use
  - Females (hepatotoxicity) - history of liver disorders (hepatotoxicity) - doses greater than 400 mg daily (hepatotoxicity) - impaired cardiac function - impaired pulmonary function - patients over 30 years (hepatotoxicity) - therapeutic effect may take a few weeks to develop—discontinue if no response within 6–8 weeks

**INTERACTIONS**

- Appendix 1: dantrolene

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  - Adult: Initially 25 mg daily, then increased to up to 100 mg 4 times a day, dose increased at weekly intervals; usual dose 75 mg 3 times a day

**IMPORTANT SAFETY INFORMATION**

Should only be administered by, or under the direct supervision of, personnel experienced in the use of dantrolene when used for malignant hyperthermia.

**CONTRA-INDICATIONS**

- With oral use
  - Acute muscle spasm
  - Avoid when spasticity is useful, for example, locomotion

**CAUTIONS**

- With intravenous use
  - Avoid extravasation (risk of tissue necrosis)
- With oral use
  - Females (hepatotoxicity) - history of liver disorders (hepatotoxicity) - doses greater than 400 mg daily (hepatotoxicity) - impaired cardiac function - impaired pulmonary function - patients over 30 years (hepatotoxicity) - therapeutic effect may take a few weeks to develop—discontinue if no response within 6–8 weeks

**INTERACTIONS**

- Appendix 1: dantrolene
Local anaesthesia

Anaesthesia (local)

Local anaesthetic drugs

The use of local anaesthetics by injection or by application to mucous membranes to produce local anaesthesia is discussed in this section.

Local anaesthetic drugs act by causing a reversible block to conduction along nerve fibres. They vary widely in their potency, toxicity, duration of action, stability, solubility in water, and ability to penetrate mucous membranes. These factors determine their application, e.g. topical (surface), infiltration, peripheral nerve block, intravenous regional anaesthesia (Bier’s block), plexus, epidural (extradural), or spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be used for postoperative pain relief, thereby reducing the need for analgesics such as opioids.

Bupivacaine hydrochloride p. 1349 has a longer duration of action than other local anaesthetics. It has a slow onset of action, taking up to 30 minutes for full effect. It is often used in lumbar epidural blockade and is particularly suitable for continuous epidural analgesia in labour, or for postoperative pain relief. It is the principal drug used for spinal anaesthesia. Hyperbaric solutions containing glucose may be used for spinal block.

Levobupivacaine p. 1351, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine hydrochloride, but is thought to have fewer adverse effects.

Lidocaine hydrochloride p. 130 is effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations up to 10%. Except for surface anaesthesia and dental anaesthesia, solutions should not usually exceed 1% in strength. The duration of the block (with adrenaline/epinephrine p. 1353) is about 90 minutes.

Prilocaine hydrochloride p. 1356 is a local anaesthetic of low toxicity which is similar to lidocaine hydrochloride. A hyperbaric solution of prilocaine hydrochloride (containing glucose) may be used for spinal anaesthesia.

Ropivacaine hydrochloride p. 1357 is an amide-type local anaesthetic agent similar to bupivacaine hydrochloride. It is less cardiotoxic than bupivacaine hydrochloride, but also less potent.

Tetracaine p. 1358, a para-aminobenzoic acid ester, is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia before venepuncture or venous cannulation. It is rapidly absorbed from mucous membranes and should never be applied to inflamed, traumatised, or highly vascular surfaces. It should never be used to provide anaesthesia for bronchoscopy or cystoscopy because lidocaine hydrochloride is a safer alternative.

Administration by injection

The dose of local anaesthetic depends on the injection site and the procedure used. In determining the safe dosage, it is important to take account of the rate of absorption and excretion, and of the potency. The patient’s age, weight, physique, and clinical condition, and the vascularity of the administration site and the duration of administration, must also be considered.

Uptake of local anaesthetics into the systemic circulation determines their duration of action and produces toxicity.

NHS Improvement has advised (September 2016) that, prior to administration, all injectable medicines must be drawn directly from their original ampoule or container into a syringe and should never be decanted into gallipots or open containers. This is to avoid the risk of medicines being confused with other substances, e.g. skin disinfectants, and to reduce the risk of contamination.
Local anaesthetics should not be injected into damaged skin, application to the middle ear (may cause ototoxicity), or into infected tissues; preservatives should not be used for caudal, epidural, or intrathecal injection into damaged skin, or into infected tissues.

Severe local anaesthetic-induced cardiovascular toxicity

Overview

After injection of a bolus of local anaesthetic, toxicity may develop at any time in the following hour. In the event of signs of toxicity during injection, the administration of the local anaesthetic must be stopped immediately. Cardiovascular status must be assessed and cardiopulmonary resuscitation procedures must be followed.

In the event of local anaesthetic-induced cardiac arrest, standard cardiopulmonary resuscitation should be initiated immediately. Lidocaine must not be used as anti-arrhythmic therapy.

If the patient does not respond rapidly to standard procedures, 20% lipid emulsion such as Intralipid® [unlicensed indication] should be given intravenously at an initial bolus dose of 1.5 mL/kg over 1 minute, followed by an infusion of 15 mL/kg/hour. After 5 minutes, if cardiovascular stability has not been restored or circulation deteriorates, give a maximum of two further bolus doses of 1.5 mL/kg over 1 minute, 5 minutes apart, and increase the infusion rate to 30 mL/kg/hour. Continue infusion until cardiovascular stability and adequate circulation are restored or maximum cumulative dose of 12 mL/kg is given.

Standard cardiopulmonary resuscitation must be maintained throughout lipid emulsion treatment.

Propofol is not a suitable alternative to lipid emulsion.

Further advice on ongoing treatment should be obtained from the National Poisons Information Service.

Detailed treatment algorithms and accompanying notes are available at www.toxbase.org or can be found in the Association of Anaesthetists of Great Britain and Ireland safety guidelines, Management of Severe Local Anaesthetic Toxicity and Management of Severe Local Anaesthetic Toxicity - Accompanying notes.

ANAESTHETICS, LOCAL

Adrenaline with articaine hydrochloride

(Carticaine hydrochloride with epinephrine)

28-Mar-2017

- INDICATIONS AND Dose

- infiltration anaesthesia in dentistry
- BY REGIONAL ADMINISTRATION
  - Adult: Consult expert dental sources

DOSES AT EXTREMES OF BODY-WEIGHT

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

IMPORTANT SAFETY INFORMATION

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected.

- CONTRA-INDICATIONS Application to damaged skin - application to the middle ear (may cause ototoxicity) - complete heart block - injection into infected tissues - injection into inflamed tissues - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block)

CONTRA-INDICATIONS, FURTHER INFORMATION

- Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Inadequate absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.
Bupivacaine hydrochloride

**INDICATIONS AND DOSE**

**Surgical anaesthesia, lumbar epidural block**

- **BY REGIONAL ADMINISTRATION**
- Adult: 75–150 mg, dose administered using a 5 mg/mL (0.5%) solution

**Surgical anaesthesia, field block**

- **BY REGIONAL ADMINISTRATION**
- Adult: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, thoracic epidural block**

- **BY THORACIC EPIDURAL**
- Adult: 12.5–50 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, caudal epidural block**

- **BY REGIONAL ADMINISTRATION**
- Adult: 50–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, major nerve block**

- **BY REGIONAL ADMINISTRATION**
- Adult: 50–175 mg, dose administered using 5 mg/mL (0.5%) solution

**Acute pain, intra-articular block**

- **BY INTRA-ARTICULAR INJECTION**
- Adult: Up to 100 mg, dose administered using 2.5 mg/mL (0.25%) solution; when co-administered with bupivacaine by another route, total max. 150 mg

**Acute pain, thoracic epidural block**

- **BY CONTINUOUS EPIDURAL INFUSION**
- Adult: 6.3–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Acute pain, labour**

- **BY CONTINUOUS EPIDURAL INFUSION**
- Adult: 6.25–12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution; maximum 400 mg per day

**Acute pain, lumbar epidural block**

- **INITIALLY BY LUMBAR EPIDURAL**
- Adult: 15–37.5 mg, then (by lumbar epidural) 15–37.5 mg, repeated when required at intervals of at least 30 minutes, dose administered by intermittent injection using a 2.5 mg/mL (0.25%) solution, alternatively (by continuous epidural infusion) 12.5–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Acute pain, field block**

- **BY REGIONAL ADMINISTRATION**
- Adult: Up to 150 mg, dose administered using 2.5 mg/mL (0.25%) solution

**DOSES AT EXTREMES OF BODY-WEIGHT**

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**MARCAINE HEAVY ®**

**Intrathecal anaesthesia for surgery**

- **BY INTRATECHAL INJECTION**
- Adult: 10–20 mg

**IMPORTANT SAFETY INFORMATION**

The licensed doses stated may not be appropriate in some settings and expert advice should be sought.

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**CONTRA-INDICATIONS**

Application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous
Regional anaesthesia (Bier’s block) should not be applied to damaged skin.

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- **CAUTIONS**
  - Cardiovascular disease • cerebral atheroma • debilitated patients (consider dose reduction) • elderly (consider dose reduction) • epilepsy • hypotension • hypovolaemia • impaired cardiac conduction • impaired respiratory function • myasthenia gravis • myocardial depression may be more severe and more resistant to treatment • shock

- **INTERACTIONS** → Appendix 1: anaesthetics, local

- **SIDE-EFFECTS**
  - Common or very common • Arrhythmias • dizziness • hypertension • hypotension • nausea • paraesthesia • urinary retention • vomiting

  - Uncommon • Neurotoxicity

  - Rare or very rare • Arachnoiditis • cardiac arrest • diplopia • nerve disorders • paraplegia • paresis • respiratory depression

**SIDE-EFFECTS, FURTHER INFORMATION**

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems. The onset of toxicity can be unpredictable and delayed. Monitor as per local protocol for at least 30 minutes after administration.

- **ALLERGY AND CROSS-SENSITIVITY**
  - hypersensitivity and cross-sensitivity. Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY**
  - Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block.

- **Dose adjustments**

- **BREAST FEEDING**
  - Amount too small to be harmful.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises use with caution in advanced liver dysfunction.

- **RENAL IMPAIRMENT**
  - Use with caution in severe impairment.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Bupivacaine hydrochloride (Non-proprietary)**
  - Bupivacaine hydrochloride 2.5 mg per 1 ml
  - Bupivacaine 25mg/10ml (0.25%) solution for injection vials | 10 vial [PTD] [NS]
  - Bupivacaine 0.25% solution for injection 10ml Sure-Amp ampoules | 20 ampoule [PTD] £17.50 DT + £17.50
  - Bupivacaine hydrochloride 5 mg per 1 ml
  - Bupivacaine 50mg/10ml (0.5%) solution for injection vials | 10 vial [PTD] [NS]
  - Bupivacaine 100mg/20ml (0.5%) solution for injection vials | 10 vial [PTD] £18.30 DT + £18.30
  - Bupivacaine hydrochloride anhydrous 40 mg per 1 ml
  - Bupivacaine 40mg/ml (4%) solution for injection ampoules | 10 ampoule [PTD] [NS]
  - Bupivacaine hydrochloride 1.25 mg per 1 ml
  - Bupivacaine 312.5mg/250ml (0.125%) infusion bags | 20 bag [PTD] £248.47

**Bupivacaine with adrenaline**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupivacaine hydrochloride p. 1349, adrenaline/epinephrine p. 222.

- **INDICATIONS AND DOSE**

  - **Surgical anaesthesia**
    - BY LUMBAR EPIDURAL, OR BY LOCAL INJECTION, OR BY CAUDAL EPIDURAL
    - Adult: (consult product literature)
  - **Acute pain management**
    - BY LUMBAR EPIDURAL, OR BY LOCAL INJECTION
    - Adult: (consult product literature)

- **IMPORTANT SAFETY INFORMATION**

Adrenaline/epinephrine must be used in a low concentration when administered with a local anesthetic. The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected.

- **CAUTIONS**

  - **CAUTIONS, FURTHER INFORMATION**

  - In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline should be used.

- **INTERACTIONS** → Appendix 1: anaesthetics, local - sympathomimetics, vasoconstrictor

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Bupivacaine with adrenaline (Non-proprietary)**
  - Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml
  - Bupivacaine hydrochloride 2.5 mg per 1 ml
  - Bupivacaine hydrochloride 5 mg per 1 ml
  - Bupivacaine hydrochloride anhydrous 2.5 mg per 1 ml
  - Adrenaline (base) 0.5% / 25mg/5ml (1 in 200,000) solution for injection ampoules | 10 ampoule [PTD] £46.00 DT + £46.00
  - Bupivacaine hydrochloride 5 mg per 1 ml
  - Bupivacaine hydrochloride anhydrous 5 mg per 1 ml
  - Adrenaline (base) 0.25% / 100mg/1ml (1 in 200,000) solution for injection ampoules | 10 ampoule [PTD] £51.75 DT + £51.75
  - Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml
  - Adrenaline (base) 0.5% / 25mg/5ml (1 in 200,000) solution for injection ampoules | 10 ampoule [PTD] £51.75 DT + £51.75
  - Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml
  - Carboestin-adrenaline 0.25% / 100/200 micrograms (100/200,000) solution for injection ampoules | 10 ampoule [PTD] £46.00 DT + £46.00
  - Carboestin-adrenaline 0.25% / 50/100 micrograms (50/100,000) solution for injection ampoules | 10 ampoule [PTD] £51.75 DT + £51.75
  - Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml
  - Carboestin-adrenaline 0.5% / 25mg/5ml (1 in 200,000) solution for injection ampoules | 10 ampoule [PTD] £51.75 DT + £51.75
  - Carboestin-adrenaline 0.5% / 50/100 micrograms (50/100,000) solution for injection ampoules | 10 ampoule [PTD] £51.75 DT + £51.75

www.getintopharma.com
Levobupivacaine

**INDICATIONS AND DOSE**

**Acute postoperative pain**
- **BY CONTINUOUS EPIDURAL INFUSION**
  - Adult: 12.5–18.75 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Acute labour pain**
- **BY LUMBAR EPIDURAL**
  - Adult: 15–25 mg, repeated at intervals of at least 15 minutes, dose administered using a 2.5 mg/mL (0.25%) solution; maximum 400 mg per day
- **BY CONTINUOUS EPIDURAL INFUSION**
  - Adult: 5–12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution; maximum 400 mg per day

**Surgical anaesthesia, peripheral nerve block**
- **BY REGIONAL ADMINISTRATION**
  - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, peribulbar nerve block**
- **BY REGIONAL ADMINISTRATION**
  - Adult: 37.5–112.5 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia for caesarean section**
- **BY LUMBAR EPIDURAL**
  - Adult: 75–150 mg, to be given over 15–20 minutes, dose administered using a 5 mg/mL (0.5%) solution

**Surgical anaesthesia**
- **BY LUMBAR EPIDURAL**
  - Adult: 50–150 mg, to be given over 5 minutes, dose administered using a 5 mg/mL (0.5%) or 7.5 mg/mL (0.75%) solution
- **BY INTRATHECAL INJECTION**
  - Adult: 15 mg, dose administered using a 5 mg/mL (0.5%) solution
- **BY LOCAL INFILTRATION**
  - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

**DOSES AT EXTREMES OF BODY-WEIGHT**
- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

**IMPORTANT SAFETY INFORMATION**

The licensed doses stated may not be appropriate in some settings and expert advice should be sought.

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**CONTRA-INDICATIONS**

Application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - should not be applied to damaged skin

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood maximises the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**CAUTIONS**

Cardiovascular disease - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock

**INTERACTIONS**

- **Appendix 1: anaesthetics, local**

**SIDE-EFFECTS**

- **Common or very common** Anaeimia - back pain - dizziness - fever - headache - hypotension - nausea - procedural pain - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION** The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems. Systemic toxicity may occur due to inadvertent intravascular injection. The onset of toxicity can be unpredictable and delayed. Monitor as per local protocol for at least 30 minutes after administration.

**ALLERGY AND CROSS-SENSITIVITY**

- Hypersensitivity and cross-sensitivity. Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

**PREGNANCY**

Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid if possible in the first trimester—toxicity in animal studies. May cause fetal distress syndrome. Do not use for paracervical block in obstetrics. Do not use 7.5 mg/mL strength in obstetrics.

**BREAST FEEDING**

Amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in hepatic impairment or patients with reduced hepatic blood flow (no information available).

**DIRECTIONS FOR ADMINISTRATION**

For 1.25 mg/mL concentration dilute standard solutions with sodium chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION**

Levobupivacaine is an isomer of bupivacaine.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Levobupivacaine (Non-proprietary)**
  - **Levobupivacaine (as Levobupivacaine hydrochloride)** 2.5 mg per 1 ml Levobupivacaine 25mg/10ml solution for injection ampoules £9.00 (Hospital only) 5 ampoule (PO) 10.00 (Hospital only)
  - **Levobupivacaine (as Levobupivacaine hydrochloride)** 5 mg per 1 ml Levobupivacaine 50mg/10ml solution for injection ampoules £10.35 (Hospital only) 5 ampoule (PO) 15.50 (Hospital only)
  - **Levobupivacaine (as Levobupivacaine hydrochloride)** 7.5 mg per 1 ml Levobupivacaine 75mg/10ml solution for injection ampoules £13.45 (Hospital only) 5 ampoule (PO) 20.50 (£24.23 (Hospital only))

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**Infusion**

- **Levobupivacaine (Non-proprietary)**  
  Levobupivacaine (as Levobupivacaine hydrochloride) 6.25 mg per 1 ml Levobupivacaine 62.5 mg/100 ml infusion bags | 5 bag (PN)  
  Levobupivacaine 125 mg/200 ml infusion bags | 5 bag (PN)  
  Levobupivacaine (as Levobupivacaine hydrochloride) 1.25 mg per 1 ml Levobupivacaine 125 mg/100 ml infusion bags | 5 bag (PN)  
  **Chirocaine** (AbbVie Ltd)  
  Levobupivacaine (as Levobupivacaine hydrochloride) 1.25 mg per 1 ml Chirocaine 125 mg/100 ml infusion bags | 24 bag (PN) E174.22  
  Chirocaine 250 mg/200 ml infusion bags | 12 bag (PN)

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**Lidocaine hydrochloride**  
(Lignocaine hydrochloride)

- **INDICATIONS AND DOSE**
  - **Infiltration anaesthesia**
    - **By local infiltration**
      - Adult: Dose to be given according to patient’s weight and nature of procedure; max. 200 mg, maximum dose 500 mg if given in solutions containing adrenaline
  - **Doses at extremes of body-weight**
    - When used by local infiltration. To avoid excessive dosage in obese patients, weight-based doses for non-emergency indications may need to be calculated on the basis of ideal body-weight.
  - **Intravenous regional anaesthesia and nerve block**
    - **By regional administration**
      - Adult: Seek expert advice
  - **Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster, or herpes labialis)**
  - **Lubricant in cystoscopy | lubricant in proctoscopy**
    - **To the skin using ointment**
      - Adult: Apply 1–2 mL as required, avoid long-term use
    - **Sore nipples from breast-feeding**
      - **To the skin using ointment**
        - Adult: Apply using gauze and wash off immediately before next feed
    - **LMX 4®**
  - **Anaesthesia before venous cannulation or venepuncture**
    - **To the skin**
      - Child 1–2 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 60 minutes, remove cream with gauze and perform procedure after approximately 5 minutes
      - Child 3–11 months: Apply up to 1 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 4 hours, remove cream with gauze and perform procedure after approximately 5 minutes
      - Child 1–17 years: Apply 1–2.5 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours, remove cream with gauze and perform procedure after approximately 5 minutes
      - Adult: Apply 1–2.5 g, apply thick layer to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours, remove cream with gauze and perform procedure after approximately 5 minutes

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**Versatis®**

**Postherpetic neuralgia**

- **To the skin**
  - Adult: Apply once daily for up to 12 hours, followed by a 12-hour plaster-free period; discontinue if no response after 4 weeks, to be applied to intact, dry, non-hairy, non-irritated skin, up to 3 plasters may be used to cover large areas; plasters may be cut

**Xylocaine®**

**During delivery in obstetrics**

- **To the skin**
  - Adult: Up to 20 doses

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**Important safety information**

- **When used by local infiltration**
  - The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

- **CONTRA-INDICATIONS**
  - **When used by regional administration** All grades of atrioventricular block - application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - severe myocardial depression - should not be applied to damaged skin - sino-atrial disorders
  - **CONTRA-INDICATIONS, FURTHER INFORMATION**
    - **When used by regional administration** Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- **CAUTIONS**
  - **When used by regional administration** Acute porphyrias p.1058 (consider infusion with glucose for its anti-porphyrinogenic effects) - children (consider dose reduction) - congestive cardiac failure (consider lower dose) - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - post cardiac surgery (consider lower dose) - shock

- **INTERACTIONS**
  - Appendix: antiarrhythmics

- **SIDE-EFFECTS**
  - With parenteral use: Anxiety - arrhythmias - atrioventricular block - cardiac arrest - circulatory collapse - confusion - dizziness - drowsiness - euphoric mood - headache - hypotension (may lead to cardiac arrest) - loss of consciousness - methaemoglobinemia - muscle twitching - myocardial contractility decreased - nausea - neurological effects - nystagmus - pain - psychosis - respiratory disorders - seizure - sensation abnormal - temperature sensation altered - tinnitus - tremor - vision blurred - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Toxic effects**

The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

**Methaemoglobinemia**

Methylthioninium chloride is licensed for the acute symptomatic treatment of drug-induced methaemoglobinemia.

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**Local anaesthesia 1353**

**Lidocaine with adrenaline**

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 103, adrenaline/epinephrine p. 222.

- **Indications and dose**
  - **Local anaesthesia**
    - **By local infiltration**
    - **Adult:** Dosed according to the type of nerve block required (consult product literature)

**Important safety information**

Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected.

**Interactions**
- Appendix 1: antiarrhythmics, sympathomimetics, vasodilator

**Profession specific information**

**Dental information**

A variety of lidocaine injections with adrenaline is available in dental cartridges. Consult expert dental sources for specific advice in relation to dose of lidocaine for dental anaesthesia.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, liquid, ointment.

**Solution for injection**

- **Lidocaine hydrochloride (Non-proprietary)**
  - **Lidocaine hydrochloride 5 mg per 1 ml** Lidocaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule (Pﬁzer) £1.00
  - **Lidocaine hydrochloride 10 mg per 1 ml** Lidocaine 100mg/10ml (1%) solution for injection Mini-Plasco ampoules | 20 ampoule (Pﬁzer) £1.15–£1.21

  - **Lidocaine 100mg/10ml** 10% solution for injection ampoules | 10 ampoule (Pﬁzer) £4.00–£5.00 DT + £4.40
  - **Lidocaine 200mg/20ml** (1%) solution for injection via | 10 vial (Pﬁzer) £11.00–£12.00 DT + £22.00
  - **Lidocaine 200mg/20ml** (1%) solution for injection ampoules | 10 ampoule (Pﬁzer) £7.00–£8.00 DT + £22.00
  - **Lidocaine 50mg/5ml** (1%) solution for injection ampoules | 10 ampoule (Pﬁzer) £2.50–£3.00 DT + £2.50
  - **Lidocaine 200mg/20ml** (1%) solution for injection Mini-Plasco ampoules | 20 ampoule (Pﬁzer) £6.50
  - **Lidocaine 50mg/5ml** (1%) solution for injection ampoules | 10 ampoule (Pﬁzer) £2.00 DT + £2.20
  - **Lidocaine 50mg/5ml** (1%) solution for injection Mini-Plasco ampoules | 20 ampoule (Pﬁzer) £7.00
  - **Lidocaine 100mg/5ml** (2%) solution for injection Sure-Amp ampoules | 10 ampoule (Pﬁzer) £6.60
  - **Lidocaine 200mg/20ml** (2%) solution for injection ampoules | 10 ampoule (Pﬁzer) £12.00 DT + £2.70

  - **Lidocaine 400mg/20ml** (2%) solution for injection vials | 10 vial (Pﬁzer) £19.50–£23.00 DT + £23.00
  - **Lidocaine 200mg/20ml** (2%) solution for injection Mini-Plasco ampoules | 20 ampoule (Pﬁzer) £14.95
  - **Lidocaine 400mg/20ml** (2%) solution for injection Mini-Plasco ampoules | 20 ampoule (Pﬁzer) £22.00 DT + £2.37

  - **Lidocaine 100mg/5ml** (2%) solution for injection ampoules | 10 ampoule (Pﬁzer) £8.00–£11.40 DT + £11.40

**Medicated plaster**

**Excipients:** May contain Hydroxybenzoates (parabens), propylene glycol

- **Ralvo (Grunenthal Ltd)**
  - **Lidocaine 50 mg per 1 gram** Ralvo 700mg medicated plasters | 30 plaster (Pﬁzer) £61.54 DT + £72.40

- **Versatis (Grunenthal Ltd)**
  - **Lidocaine 50 mg per 1 gram** Versatis 700mg medicated plasters | 30 plaster (Pﬁzer) £72.40 DT + £72.40

**Cream**

**Excipients:** May contain Benzyl alcohol, propylene glycol

- **L MX 4 (Ferndale Pharmaceuticals Ltd)**
  - **Lidocaine 40 mg per 1 gram** L MX 4 cream | 5 gram (Pﬁzer) £2.98 DT + £2.98 | 30 gram (Pﬁzer) £14.90 DT + £14.90

- **Vagisil medicated (Combe International Ltd)**
  - **Lidocaine 20 mg per 1 gram** Vagisil 2% medicated cream | 30 gram (Pﬁzer) £2.99 DT + £2.99

**Ointment**

- **Lidocaine hydrochloride (Non-proprietary)**
  - **Lidocaine hydrochloride 50 mg per 1 gram** Lidocaine 9% ointment | 15 gram (Pﬁzer) £9.00 DT + £6.18

**Lidocaine hydrochloride 10 mg per 1 gram**

**Lidocaine hydrochloride 20 mg per 1 gram**

**Lidocaine hydrochloride 50 mg per 1 gram**

**Lidocaine 100 mg per 1 gram**

**Lidocaine 200 mg per 1 gram**

**Adrenaline (as Adrenaline acid tartrate) 12.5 microgram per 1 ml**

**Lignospan Special 2% injection 2.2ml cartridges** | 50 cartridge (Pﬁzer) £21.95

**Lignospan Special 2% injection 1.6ml cartridges** | 50 cartridge (Pﬁzer) £21.95

**Rexocaine (Henry Schein Ltd)**

**Adrenaline (as Adrenaline acid tartrate) 12.5 microgram per 1 ml**

**Lignospan Special 18mg per 1 ml**

**Lignospan Special 60mg per 1 ml**
Lidocaine with prilocaine

25-Apr-2019

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 103, prilocaine hydrochloride p. 1356.

- **INDICATIONS AND DOSE**

  **Anaesthesia before minor skin procedures including venepuncture**
  - **To the skin**
    - Child 1-2 months: Apply up to 1 g for maximum 1 hour before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 1 dose per day
    - Child 3-11 months: Apply up to 2 g for maximum 1 hour before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
    - Child 1-11 years: Apply 1–5 hours before procedure, a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
    - Child 12-17 years: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca)
  - Adult: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing

  **Anaesthesia on genital skin before injection of local anaesthetics**
  - **To the skin**
    - Adult: Apply under occlusive dressing for 15 minutes (males) or 60 minutes (females) before procedure

  **Anaesthesia before surgical treatment of lesions on genital mucosa**
  - **To the skin**
    - Adult: Apply up to 10 g, to be applied 5–10 minutes before procedure

  **Anaesthesia before cervical curettage**
  - **To the skin**
    - Adult: Apply 10 g in lateral vaginal fornices for 10 minutes

  **Anaesthesia before mechanical cleansing or debridement of leg ulcer**
  - **To the skin**
    - Adult: Apply up to 10 g for 30–60 minutes, to be applied under occlusive dressing

  **Fortacin**

  **Primary premature ejaculation**
  - **To the skin**
    - Adult: 3 sprays every 4 hours as required, to be applied to cover the glans penis (excess spray should be removed after 5 minutes and before intercourse); maximum 9 sprays per day

  **Dose equivalence and conversion**
  - For Fortacin®: Each dose of 3 sprays is equivalent to lidocaine 22.5 mg and prilocaine 7.5 mg.

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**Lidocaine with cetrimide**

27-Apr-2018

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 103, cetrimide hydrochloride p. 1354.

- **INDICATIONS AND DOSE**

  **Anaesthesia and disinfection in dental practice**
  - **To mucus membranes using oromucosal spray**
    - Adult: 10–20 mg, no more than 30 mg should be applied to the same quadrant of the buccal cavity—consult product literature, dose expressed as lidocaine

  **Anaesthesia in dental practice**
  - **To mucus membranes using dental gel**
    - Adult: Apply 100–500 mg, use cotton pellet for application to dried mucosa, dose expressed as weight of gel

  **DOSE EQUIVALENCE AND CONVERSION**
  - 1 metered dose of Xylonor® spray is equivalent to 10 mg of lidocaine.
  - 2 millimetres of Xylonor® gel is approximately equivalent to 100 mg of gel (approximately equivalent to 5 mg of lidocaine).

- **CAUTIONS**
  - Sepsis (risk of rapid systemic absorption) - traumatised mucosa (risk of rapid systemic absorption)

- **INTERACTIONS**
  - Appendix 1: antiarrhythmics

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - Oromucosal gel
      - Xylonor (Septodont Ltd)
      - Cetrimide 1.5 mg per 1 gram, Lidocaine 50 mg per 1 gram: Xylonor 5% gel sugar-free | 15 gram [POD] £4.00
        - Spray
          - Xylonor (Septodont Ltd)
          - Cetrimide 100 microgram per 1 gram, Lidocaine 10 mg per 1 gram: Xylonor 10% spray sugar-free | 36 gram [POD] £20.15

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**Lidocaine with phenylephrine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 103, phenylephrine hydrochloride p. 189.

- **INDICATIONS AND DOSE**

  **Anaesthesia before nasal surgery, endoscopy, laryngoscopy, or removal of foreign bodies from the nose**
  - **By intranasal administration**
    - Adult: Up to 8 sprays

- **INTERACTIONS**
  - Appendix 1: antiarrhythmics - sympathomimetics, vasoconstrictor

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - Spray
      - Lidocaine with phenylephrine (Non-proprietary)
        - Phenylephrine hydrochloride 5 mg per 1 ml, Lidocaine hydrochloride 50 mg per 1 ml: Lidocaine 5% / Phenylephrine 0.5% nasal spray | 2.5 ml [POD] £12.90 DT + £12.00

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Adrenaline 100 micrograms/20 ml (1 in 200,000) solution for injection vials | 5 vial [POD] £8.85 DT + £8.85

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DOSES AT EXTREMES OF BODY-WEIGHT
- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

IMPORTANT SAFETY INFORMATION
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

CONTRA-INDICATIONS
- Application to the middle ear (can cause ototoxicity).
- Avoid injection into inflamed or infected tissues.
- Avoid injection into inflamed tissues - complete heart block.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

CONTRA-INDICATIONS
- Type II diabetes: increased risk of toxic plasma concentrations in severe diabetes.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

CONTRA-INDICATIONS
- Application to the middle ear (can cause ototoxicity).
- Avoid injection into inflamed tissues.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

CONTRA-INDICATIONS
- Application to the middle ear (can cause ototoxicity).
- Avoid injection into inflamed tissues.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

CONTRA-INDICATIONS
- Application to the middle ear (can cause ototoxicity).
- Avoid injection into inflamed tissues.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

CONTRA-INDICATIONS
- Application to the middle ear (can cause ototoxicity).
- Avoid injection into inflamed tissues.

INTERACTIONS
- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.

SIDE-EFFECTS
- Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin.
Mepivacaine with adrenaline

The properties listed below are those particular to the combination only. For the properties of the components please consider, mepivacaine hydrochloride p. 1355, adrenaline/epinephrine p. 222.

- **INDICATIONS AND DOSE**
  - **Infiltration anaesthesia and nerve block in dentistry**
    - **BY LOCAL INFILTRATION**
    - Adult: (consult product literature)

- **INTERACTIONS**
  - **Appendix 1: anaesthetics, local - sympathomimetics, vasoconstrictor**

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **EXCIPIENTS:** May contain Sulfites
  - **Scandonest special** (Septodont Ltd)

- **Adrenaline 10 microgram per 1 ml, Mepivacaine hydrochloride 20 mg per 1 ml Scandonest special 2% solution for injection 2.2ml cartridges | 50 cartridge £21.95**

Prilocaine hydrochloride

- **INDICATIONS AND DOSE**
  - **DOSES AT EXTREMES OF BODY-WEIGHT**
  - To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.
  - **CITANEST 1%**

- **Infiltration anaesthesia | Nerve block**
  - **BY REGIONAL ADMINISTRATION**
  - Adult: 100–200 mg/minute, alternatively may be given in incremental doses; dose adjusted according to site of administration and response, and in elderly and debilitated patients (smaller doses may be required); maximum 400 mg per course

- **PRILOTEKAL**

- **Spinal anaesthesia**
  - **BY INTRATHECAL INJECTION**
  - Adult: Usual dose 40–60 mg (max. per dose 80 mg), dose may need to be reduced in elderly or debilitated patients, or in late pregnancy

- **INTERACTIONS**
  - **Appendix 1: anaesthetics, local - sympathomimetics, vasoconstrictor**

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Solution for injection**
  - **EXCIPIENTS:** May contain Sulfites
  - **Scandonest special** (Septodont Ltd)

- **Adrenaline 10 microgram per 1 ml, Mepivacaine hydrochloride 20 mg per 1 ml Scandonest special 2% solution for injection 2.2ml cartridges | 50 cartridge £21.95**

**IMPORTANT SAFETY INFORMATION**

- **CONTRA-INDICATIONS, FURTHER INFORMATION**
  - Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.
  - **CAUTIONS**
    - Cardiovascular disease - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - severe or untreated hypertension - shock

- **INTERACTIONS**
  - **Appendix 1: anaesthetics, local - sympathomimetics, vasoconstrictor**

- **SIDE-EFFECTS**
  - **Common or very common** Arrhythmias - dizziness - hypotension - nausea - paraesthesia - vomiting
  - **Uncommon** Neurotoxicity
  - **Rare or very rare** Bradycardia after epidural block. Avoid paracervical or intrathecal anaesthesia. 

- **FURTHER INFORMATION**
  - **TOXIC EFFECTS**
    - Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems. The onset of toxicity can be unpredictable and delayed. Monitor as per local protocol for at least 30 minutes after administration.

**Methaemoglobinemia**

- Methaemoglobinemia can be treated with an intravenous injection of methyleneblue.

- **ALLERGY AND CROSS-SENSITIVITY**
  - Hypersensitivity and cross-sensitivity Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY**
  - Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid paracervical or pudendal block in obstetrics (neonatal methaemoglobinemia reported).

- **Dose adjustments**
  - Use lower doses for intrathecal use during late pregnancy.

- **BREAST FEEDING**
  - Present in milk but not known to be harmful.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution.

- **Dose adjustments**
  - With intrathecal use Manufacturer advises consider dose reduction.

- **RENAL IMPAIRMENT**
  - Use with caution.

- **Dose adjustments**
  - Lower doses may be required for intrathecal anaesthesia.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **PRILOTEKAL**

- **Scottish Medicines Consortium (SMC) decisions**
  - With intrathecal use The Scottish Medicines Consortium has advised (December 2010) that prilocaine 2% hyperbaric solution for injection (Prilotekal®) is accepted for restricted use within NHS Scotland for use in spinal anaesthesia in ambulatory surgery settings.
**Prilocaine with felypressin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, prilocaine hydrochloride p. 1356.

- **INDICATIONS AND DOSE**
  - Dental anaesthesia
    - By regional administration
      - Adult: Consult expert dental sources for specific advice
  - Interactions
    - Appendix 1: anaesthetics, local
  - **SIDE-EFFECTS**
    - Bradycardia, cardiac arrest, dizziness, drowsiness, hypotension, loss of consciousness, methaemoglobinemia, myocardial contractility decreased, nervousness, respiratory arrest, seizure, tremor, vision blurred

**Solution for injection**
- Prilocaine hydrochloride 10 mg per 1 ml Citanest 1% solution for injection 5ml vials | 1 vial £0.96
- Prilotekal (Sintetica Ltd)
  - Prilocaine hydrochloride 20 mg per 1 ml Prilotekal 100mg/5ml solution for injection ampoules | 10 ampoule (PO) £78.80

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Citanest with Octapressin (Dentsply Ltd)
  - Prilocaine hydrochloride 30 mg per 1 ml, Felypressin 0.3 unit per 1 ml Citanest 3% with Octapressin Dental 0.066units/2.2ml solution for injection self aspirating cartridges | 50 cartridge

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**Ropivacaine hydrochloride**

- **INDICATIONS AND DOSE**
  - Acute pain, peripheral nerve block
    - By regional administration
      - Adult: 10–20 mg/hour, dose administered as a continuous infusion or by intermittent injection using a 2 mg/mL (0.2%) solution
  - Acute pain, field block
    - By regional administration
      - Adult: 2–200 mg, dose administered using a 2 mg/mL (0.2%) solution
  - Acute pain, lumbar epidural block
    - By lumbar epidural
      - Adult: 20–40 mg, followed by 20–30 mg at least every 30 minutes, dose administered using a 2 mg/mL (0.2%) solution
  - Acute labour pain
    - By continuous epidural infusion
      - Adult: 12–20 mg/hour, dose administered using a 2 mg/mL (0.2%) solution
  - Acute postoperative pain
    - By continuous epidural infusion
      - Adult: Up to 28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution
  - Postoperative pain, thoracic epidural block
    - By continuous epidural infusion
      - Adult: 12–28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution
  - Surgical anaesthesia, field block
    - By regional administration
      - Adult: 7.5–225 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, major nerve block (brachial plexus block)**
- By regional administration
  - Adult: 225–300 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, thoracic epidural block (to establish block for postoperative pain)**
- By thoracic epidural
  - Adult: 38–113 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia for caesarean section**
- By lumbar epidural
  - Adult: 113–150 mg, to be administered in incremental doses using a 7.5 mg/mL (0.75%) solution

**DOSES AT EXTREMES OF BODY-WEIGHT**
- To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal bodyweight.

**IMPORTANT SAFETY INFORMATION**

- Only should be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**CONTRA-INDICATIONS**

- Application to the middle ear (can cause ototoxicity), avoid injection into infected tissues, avoid injection into inflamed tissues, complete heart block, preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block). Should not be applied to damaged skin.

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- Injection site: Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**CAUTIONS**

- Acute porphyrias p. 1058, cardiovascular disease, debilitated patients (consider dose reduction), elderly (consider dose reduction), epilepsy, hypovolaemia, impaired cardiac conduction, impaired respiratory function, myasthenia gravis, shock.

**INTERACTIONS**

- Appendix 1: anaesthetics, local

**SIDE-EFFECTS**

- Common or very common
  - Arrhythmias, back pain, chills, dizziness, headache, hypotension, nausea, sensation abnormal, urinary retention, vomiting
- Uncommon
  - Anxiety, dyspnoea, hypothermia, neurotoxicity, syncope
- Rare or very rare
  - Cardiac arrest
- Frequency not known
  - Dyskinesia

**SIDE-EFFECTS, FURTHER INFORMATION**

- Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems. The onset of toxicity can be unpredictable and delayed. Monitor as per local protocol for at least 30 minutes after administration.

**ALLERGY AND CROSS-SENSITIVITY**

- Hypersensitivity and cross-sensitivity. Hypersensitivity reactions occur mainly with the ester-type local anaesthetics. There can be variation in the licensing of different medicines containing the same drug.
anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Not known to be harmful. Do not use for paracervical block in obstetrics.
- **BREAST FEEDING** Not known to be harmful.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment.

### Dose adjustments
Manufacturer advises consider dose reduction for repeat doses in severe impairment.

### RENAL IMPAIRMENT
Caution in severe impairment. Increased risk of systemic toxicity in chronic renal failure.

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**ELECTROLYTES**: May contain Sodium
- Ropivacaine hydrochloride (Non-proprietary) Tetracaine gel for local anaesthesia: Tetracaine 40 mg per 1 gram | 1.5 gram | £1.08
- Naropin (Aspen Pharma Trading Ltd) Tetracaine 40 mg per 1 gram | 1.5 gram | £1.08

**Infusion**

**ELECTROLYTES**: May contain Sodium
- Ropivacaine hydrochloride (Non-proprietary) Tetracaine gel for local anaesthesia: Tetracaine 40 mg per 1 gram | 1.5 gram | £1.08

**Gel**

**EXCIPIENTS**: May contain Hydroxybenzoates (parabens)
- Ametop (Forum Health Products Ltd) Tetracaine 40 mg per 1 gram | 1.5 gram | £1.08

**Tetracaine (Amethocaine)**

#### INDICATIONS AND DOSE

**Anaesthesia before venepuncture or venous cannulation**
- TO THE SKIN
  - Child 1 month–4 years: Apply contents of up to 1 tube (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation
  - Child 5–17 years: Apply contents of up to 5 tubes (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation
  - Adult: Apply contents of up to 5 tubes (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

#### CONTRA-INDICATIONS
Should not be applied to damaged skin

#### SIDE-EFFECTS, FURTHER INFORMATION
The systemic toxicity of local anaesthetics mainly involves the central nervous system; systemic side effects unlikely as minimal absorption following topical application.

#### ALLERGY AND CROSS-SENSITIVITY
- Hypersensitivity and cross-sensitivity
  - Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

#### BREAST FEEDING
Not known to be harmful.

#### PATIENT AND CARER ADVICE
Medicines for Children leaflet: Tetracaine gel for local anaesthesia www.medicinesforchildren.org.uk/tetracaine-gel-local-anaesthesia

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Chapter 16
Emergency treatment of poisoning

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Poisoning, emergency treatment

Overview
These notes provide only an overview of the treatment of poisoning, and it is strongly recommended that either TOXBASE or the UK National Poisons Information Service be consulted when there is doubt about the degree of risk or about management.

Hospital admission
Patients who have features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed action should also be admitted, even if they appear well. Delayed-action poisons include aspirin p. 121, iron, paracetamol p. 444, tricyclic antidepressants, and co-phenetropine p. 66 (diphenoxylate with atropine, Lomotil®); the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

Further information
TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the internet to registered users at www.toxbase.org (a backup site is available at www.toxbasebackup.org if the main site cannot be accessed). It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the UK National Poisons Information Service on the following number: Tel: 0344 892 0111.

Advice on laboratory analytical services can be obtained from TOXBASE or from the National Poisons Information Service. Help with identifying capsules or tablets may be available from a regional medicines information centre or from the National Poisons Information Service (out of hours).

General care
It is often impossible to establish with certainty the identity of the poison and the size of the dose. This is not usually important because only a few poisons (such as opioids, paracetamol, and iron) have specific antidotes; few patients require active removal of the poison. In most patients, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned individual and from carers or parents. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses and patients should be assessed carefully. Accidents may involve domestic and industrial products (the contents of which are not generally known). The National Poisons Information Service should be consulted when there is doubt about any aspect of suspected poisoning.

Respiration
Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be used if the main site cannot be accessed. A bag-valve-mask device may be needed. Oxygen is not a substitute for adequate ventilation; such patients should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is often given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

Blood pressure
Hypotension is common in severe poisoning with central nervous system depressants. A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by raising the foot of the bed and administration of an infusion of either sodium chloride p. 1040 or a colloid. Vasoconstrictor sympathomimetics are rarely required and their use may be discussed with the National Poisons Information Service. Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnea.

Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs such as amphetamines, phencyclidine, and cocaine.

Heart
Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis,
Emergency treatment of poisoning

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or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypotension require treatment. If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the patient reaches hospital.

Body temperature

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hypothermia should be managed by prevention of further heat loss and appropriate re-warming as clinically indicated.

Hyperthermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome.

Both hypothermia and hyperthermia require urgent hospitalisation for assessment and supportive treatment.

Convulsions during poisoning

Single short-lived convulsions (lasting less than 5 minutes) do not require treatment. If convulsions are protracted or recur frequently, lorazepam p. 339 or diazepam p. 343 (preferably as emulsion) should be given by slow intravenous injection into a large vein. Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, midazolam oromucosal solution p. 340 [unlicensed use in adults and children under 3 months] can be given by the buccal route or diazepam can be administered as a rectal solution.

Methaemoglobinaemia

Drug- or chemical-induced methaemoglobinaemia should be treated with methylthioninium chloride p. 1371 if the methaemoglobin concentration is 30% or higher, or if symptoms of tissue hypoxia are present despite oxygen therapy. Methylthioninium chloride reduces the ferric iron of methaemoglobin back to the ferrous iron of haemoglobin; therapy. Methylthioninium chloride reduces the ferric iron symptoms of tissue hypoxia are present despite oxygen absorption. The

is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is particularly useful for the prevention of absorption of poisons that are toxic in small amounts, such as antidepressants.

Active elimination techniques

Repeated doses of charcoal, activated by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

- Carbamazepine
- Dapsone
- Phentoobarbital
- Quinine
- Theophylline

If vomiting occurs after dosing it should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be reduced and the frequency increased but this may compromise efficacy.

Charcoal, activated should not be used for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, cyanides and metal salts including iron and lithium salts.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate;
- alkalisation of the urine for salicylates.

Removal from the gastro-intestinal tract

Gastric lavage is rarely required; for substances that cannot be removed effectively by other means (e.g. iron), it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Gastric lavage is contra-indicated if a corrosive substance or a petroleum distillate has been ingested, but it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal, such as iron or lithium. Induction of emesis (e.g. with ipecacuanha) is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration.

Whole bowel irrigation (by means of a bowel cleansing preparation) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with iron and lithium salts, and if illicit drugs are carried in the gastro-intestinal tract ("body-packing"). However, it is not clear that the procedure improves outcome and advice should be sought from the National Poisons Information Service.

Alcohol, acute intoxication

Acute intoxication with alcohol (ethanol) is common in adults but also occurs in children. The features include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Aspiration of vomit is a special hazard and hypoglycaemia may occur in children and some adults. Patients are managed supportively, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

Aspirin poisoning

The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital, where plasma salicylate, pH, and electrolytes can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in the young and the elderly, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is less below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre), unless there is evidence of metabolic acidosis. Activated charcoal can be given within 1 hour of ingesting more than 125 mg/kg of aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5).
Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis.

**Opioid poisoning**

Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone hydrochloride p. 1369 is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone.

Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Naloxone reverses the opioid effects of dextropropoxyphene. The long duration of action of dextropropoxyphene calls for prolonged monitoring and further doses of naloxone may be required.

Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with sodium bicarbonate p. 1038 or magnesium sulfate p. 1051, or both. Arrhythmias may occur for up to 12 hours.

**Paracetamol poisoning**

In cases of intravenous paracetamol poisoning contact the National Poisons Information Service for advice on risk assessment and management.

Toxic doses of paracetamol p. 444 may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after paracetamol overdose and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Therefore, despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

To avoid underestimating the potentially toxic paracetamol dose ingested by obese patients who weigh more than 110 kg, use a body-weight of 110 kg (rather than their actual body-weight) when calculating the total dose of paracetamol ingested (in mg/kg).

Acetylcysteine p. 1370 protects the liver if infused up to, and possibly beyond, 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after which effectiveness declines. Very rarely, giving acetylcysteine p. 1370 by mouth [unlicensed route] is an alternative if intravenous access is not possible—contact the National Poisons Information Service for advice.
Emergency treatment of poisoning

Neonates less than 45 weeks corrected gestational age may be more susceptible to paracetamol-induced liver toxicity, therefore, treatment with acetylcysteine should be considered in all paracetamol p. 444 overdoses, and advice should be sought from the National Poisons Information Service.

**Acute overdose**

Hepatotoxicity may occur after a single ingestion of more than 150 mg/kg of paracetamol taken in less than 1 hour. Rarely, hepatotoxicity may develop with single ingestions as low as 75 mg/kg of paracetamol taken in less than 1 hour. Patients who have ingested 75 mg/kg or more of paracetamol in less than 1 hour should be referred to hospital. Administration of charcoal, activated p. 1366 should be considered if paracetamol in excess of 150 mg/kg is thought to have been ingested within the previous hour.

Patients at risk of liver damage and, therefore, requiring acetylcysteine, can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line (‘treatment line’) joining plots of 100 mg/litre (0.66 mmol/litre) at 4 hours and 3.13 mg/litre (0.02 mmol/litre) at 24 hours. Acetylcysteine treatment should commence immediately in patients:

- whose plasma-paracetamol concentration falls on or above the treatment line on the paracetamol treatment graph;
- who present 8–24 hours after taking an acute overdose of more than 150 mg/kg of paracetamol, even if the plasma-paracetamol concentration is not yet available; acetylcysteine can be discontinued if the plasma-paracetamol concentration is later reported to be below the treatment line on the paracetamol treatment graph, provided that the patient is asymptomatic and liver function tests, serum creatinine and INR are normal.

The prognostic accuracy of a plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration on or above the treatment line on the paracetamol treatment graph should be regarded as carrying a serious risk of liver damage. If more than 15 hours have elapsed since ingestion, or there is doubt about appropriate management, advice should be sought from the National Poisons Information Service.

**‘Staggered’ overdose, uncertain time of overdose, or therapeutic excess**

A ‘staggered’ overdose involves ingestion of a potentially toxic dose of paracetamol over more than one hour, with the possible intention of causing self-harm. Therapeutic excess is the inadvertent ingestion of a potentially toxic dose of paracetamol during its clinical use. The paracetamol treatment graph is unreliable if a ‘staggered’ overdose is taken, if there is uncertainty about the time of the overdose, or if there is therapeutic excess. In these cases, patients who have taken more than 150 mg/kg of paracetamol in any 24-hour period are at risk of toxicity and should be commenced on acetylcysteine immediately, unless it is more than 24 hours since the last ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal.

Rarely, toxicity can occur with paracetamol doses between 75–150 mg/kg in any 24-hour period; clinical judgement of the individual case is necessary to determine whether to treat those who have ingested this amount of paracetamol. For small adults, this may be within the licensed dose, but ingestion of a licensed dose of paracetamol is not considered an overdose.

Although there is some evidence suggesting that factors such as the use of liver enzyme-inducing drugs (e.g. carbamazepine p. 311, efavirenz p. 644, nevirapine p. 645, phenobarbital p. 335, phenytoin p. 323, primidone p. 336, rifabutin p. 575, rifampicin p. 582, St John’s wort), chronic alcoholism, and starvation may increase the risk of hepatotoxicity, the CHM has advised that these should no longer be used in the assessment of paracetamol toxicity.

Significant toxicity is unlikely if, 24 hours or longer after the last paracetamol ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal. Patients with clinical features of hepatic injury such as jaundice or hepatic tenderness should be treated urgently with acetylcysteine. If there is uncertainty about a patient’s risk of toxicity after paracetamol overdose, treatment with acetylcysteine should be commenced. Advice should be sought from the National Poisons Information Service whenever necessary.

**Acetylcysteine dose and administration**

For paracetamol overdosage, acetylcysteine is given in a total dose that is divided into 3 consecutive intravenous infusions over a total of 21 hours. The tables below include the dose of acetylcysteine, for adults and children of body-weight 40 kg and over, in terms of the volume of acetylcysteine Concentrate for Intravenous Infusion required for each of the 3 infusions. The requisite dose of acetylcysteine is added to glucose Intravenous Infusion 5% p. 1041.

**First infusion**

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare first infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>34 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>42 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>49 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>57 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>64 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>72 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>79 mL</td>
</tr>
<tr>
<td>&gt;110 kg</td>
<td>83 mL (max. dose)</td>
</tr>
</tbody>
</table>

**First infusion** (based on an acetylcysteine dose of approx. 150 mg/kg)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 200 mL Glucose Intravenous Infusion 5%; infuse over 1 hour.

**Second infusion**

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare second infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>12 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>14 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>17 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>19 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>22 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>24 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>27 mL</td>
</tr>
<tr>
<td>&gt;110 kg</td>
<td>28 mL (max. dose)</td>
</tr>
</tbody>
</table>

**Second infusion** (based on an acetylcysteine dose of approx. 50 mg/kg; start immediately after completion of first infusion)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 500 mL Glucose Intravenous Infusion 5%; infuse over 4 hours.
Emergency treatment of poisoning

<table>
<thead>
<tr>
<th>Third infusion</th>
<th>Volume of Acetylcysteine Concentrate for intravenous infusion 200 mg/mL required to prepare third infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>23 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>28 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>33 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>38 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>43 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>48 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>53 mL</td>
</tr>
<tr>
<td>&gt;110 kg</td>
<td>55 mL (max. dose)</td>
</tr>
</tbody>
</table>

Third infusion (based on an acetylcysteine dose of approx. 100 mg/kg; start immediately after completion of second infusion)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 1 litre Glucose Intravenous Infusion 5%; infuse over 16 hours.

**Antidepressant poisoning**

Tricyclic and related antidepressants

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hypreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Assessment in hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

Selective serotonin re-uptake inhibitors (SSRIs)

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

Management of SSRI poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or midazolam oromucosal solution [unlicensed use in adults and children under 3 months] (see Convulsions). Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

Antimalarial poisoning

Overdose with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

**Antipsychotic poisoning**

Phenothiazines and related drugs

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine hydrochloride p. 411 or diazepam p. 343 (emulsion preferred).

Second-generation antipsychotic drugs

Features of poisoning by second-generation antipsychotic drugs include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Charcoal, activated p. 1366 can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected. Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil p. 1368 [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine–dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert advice only and not as a diagnostic test in patients with a reduced level of consciousness.

**Beta blockers poisoning**

Therapeutic overdoses with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (some of the torsade de pointes type). The effects of massive overdose can vary from one beta-blocker to another; propranolol overdose in particular may cause coma and convulsions.

**Acute massive overdose**

Acute massive overdose must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine sulfate p. 1334 is required to treat bradycardia. Cardiogenic shock unresponsive to atropine sulfate is probably best treated with an intravenous injection of glucagon p. 724 [unlicensed] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion. If glucagon is not available, intravenous isoprenaline (available from ‘special-order’ manufacturers or specialist importing companies) is an alternative. A cardiac pacemaker can be used to increase the heart rate.
Emergency treatment of poisoning

**Calcium-channel blockers poisoning**

Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Charcoal, activated should be considered if the patient presents within 1 hour of overdose with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved. In patients with significant features of poisoning, calcium chloride p. 1045 or calcium gluconate p. 1045 is given by injection; atropine sulphate is given to correct symptomatic bradycardia. In severe cases, an insulin and glucose infusion may be required in the management of hypotension and myocardial failure. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression—advice should be sought from the National Poisons Information Service.

**Iron salts poisoning**

Iron poisoning in childhood is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension and hepatic cellular necrosis can occur later. Coma, shock, and metabolic acidosis indicate severe poisoning.

Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with desferrioxamine mesilate p. 1028, which chelates iron. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine mesilate given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine mesilate should be given immediately without waiting for the result of the serum-iron measurement.

**Lithium poisoning**

Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug because of a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) owing to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes arising from the patient’s depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic serum–lithium concentrations are within the range of 0.4–1 mmol/litre; concentrations in excess of 2 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage much higher serum–lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. Gastric lavage may be considered if it can be performed within 1 hour of ingesting significant quantities of lithium. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service.

**Stimulant-drug poisoning**

Amphetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by diazepam p. 343 or lorazepam p. 339; advice should be sought from the National Poisons Information Service on the management of hypertension.

Later, tachypnoea, anticonvulsants, and artificial respiration may be needed.

**Cocaine**

Cocaine stimulates the central nervous system, causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hypertension, and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Initial treatment of cocaine poisoning involves intravenous administration of diazepam to control agitation and cooling measures for hyperthermia (see Body temperature); hypertension and cardiac effects require specific treatment and expert advice should be sought.

**Ecstasy**

Ecstasy (methylenedioxymethamphetamine, MDMA) may cause severe reactions even at doses that were previously tolerated. The most serious effects are delirium, coma, convulsions, ventricular arrhythmias, hyperthermia, rhabdomyolysis, acute renal failure, acute hepatitis, disseminated intravascular coagulation, adult respiratory distress syndrome, hyperreflexia, hypotension and intracerebral haemorrhage; hypernatraemia has also been associated with ecstasy poisoning.

Treatment of methylenedioxymethamphetamine poisoning is supportive, with diazepam to control severe agitation or persistent convulsions and close monitoring including ECG.

Self-induced water intoxication should be considered in patients with ecstasy poisoning.

‘Liquid ecstasy’ is a term used for sodium oxybate (gamma-hydroxybutyrate, GHB), which is a sedative.

**Theophylline poisoning**

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repeated doses of activated charcoal can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques). Ondansetron p. 436 may be effective for severe vomiting that is resistant to other antiemetics [unlicensed indication]. Hypokalaemia is corrected by intravenous infusion of potassium chloride p. 1057 and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring). Convulsions should be controlled by intravenous administration of lorazepam or diazepam (see Convulsions). Sedation with diazepam may be necessary in agitated patients.

Provided the patient does not suffer from asthma, a short-acting beta-blocker can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.
Emergency treatment of poisoning

Cyanide poisoning
Oxygen should be administered to patients with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. Dicobalt edetate p. 1367 is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning, but it should not be used as a precautionary measure. Dicobalt edetate itself is toxic, associated with anaphylactoid reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of sodium nitrite p. 1367 followed by sodium thiosulfate p. 1367 is an alternative if dicobalt edetate is not available.

Hydroxocobalamin p. 1026 (Cyanokit®) — no other preparation of hydroxocobalamin is suitable) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

Ethylene glycol and methanol poisoning
Fomepizole (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, ethanol (by mouth or by intravenous infusion) can be used, but with caution. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

Heavy metal poisoning
Heavy metal antidotes include succimer (DMSA) [unlicensed], unithiol (DMPS) [unlicensed], sodium calcium edetate [unlicensed], and dimercaprol. Dimercaprol in the management of heavy metal poisoning has been superseded by other chelating agents. In all cases of heavy metal poisoning, the advice of the National Poisons Information Service should be sought.

Noxious gases poisoning
Carbon monoxide
Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Immediate treatment of carbon monoxide poisoning is essential. The person should be moved to fresh air, the airway cleared, and high-flow oxygen 100% administered through a tight-fitting mask with an inflated face seal. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The patient should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema may occur in severe poisoning and is treated with an intravenous infusion of mannitol p. 229. Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the patient is pregnant or in cases of severe poisoning, such as if the patient is or has been unconscious, or has psychiatric or neurological features other than a headache, or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%.

Sulfur dioxide, chlorine, phosgene, and ammonia
All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Patients are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

CS Spray poisoning
CS spray, which is used for riot control, irritates the eyes (hence ‘tear gas’) and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

Nerve agent poisoning
Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning, but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits (‘NAAS pods’) containing pralidoxime chloride p. 1367 can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

Pesticide poisoning
Organophosphorus insecticides
Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. All are absorbed through the bronchi and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure.

Further absorption of the organophosphorus insecticide should be prevented by moving the patient to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. Atropine sulfate p. 1334 will reverse the muscarinic effects of acetylcholine and is given by intravenous injection until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

Pralidoxime chloride, a cholinesterase reactivator, is used as an adjunct to atropine sulfate in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is continued until the patient has not required atropine sulfate for 12 hours. Pralidoxime chloride can be obtained from designated centres, the names of which are held by the National Poisons Information Service.

Snake bites and animal stings
Snake bites
Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (Vipera berus). The
Active elimination from the gastro-intestinal tract

Other poisons
Consult either the National Poisons Information Service day and night or TOXBASE.
The National Poisons Information Service (Tel: 0344 892 0111) will provide specialist advice on all aspects of poisoning day and night.

1 Active elimination from the gastro-intestinal tract

ANTIDOTES AND CHELATORS > INTESTINAL ADSORBENTS

Charcoal, activated

- INDICATIONS AND DOSE
  - Reduction of absorption of poisons in the gastro-intestinal system
    - BY MOUTH
      - Neonate: 1 g/kg.
      - Child 1 month-11 years: 1 g/kg (max. per dose 50 g)
      - Child 12-17 years: 50 g
      - Adult: 50 g
  - Active elimination of poisons
    - BY MOUTH
      - Neonate: 1 g/kg every 4 hours, dose may be reduced and the frequency increased if not tolerated, reduced dose may compromise efficacy.
      - Child 1 month-11 years: 1 g/kg every 4 hours (max. per dose 50 g), dose may be reduced and the frequency increased if not tolerated, reduced dose may compromise efficacy
      - Child 12-17 years: Initially 50 g, then 50 g every 4 hours, reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, reduced dose may compromise efficacy
      - Adult: Initially 50 g, then 50 g every 4 hours, reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, reduced dose may compromise efficacy

- ACCELERATED ELIMINATION
  - Teriflunomide
    - BY MOUTH USING GRANULES
      - Adult: 50 g every 12 hours for 11 days
    - Accelerated elimination of leflunomide (washout procedure)
      - BY MOUTH USING GRANULES
      - Adult: 50 g 4 times a day for 11 days

- UNLICENSED USE
  - In adults Activated charcoal doses in BNF may differ from those in product literature.
  - Comatose patient (risk of aspiration—ensure airway is protected) drowsy patient (risk of aspiration—ensure airway protected) reduced gastrointestinal motility (risk of obstruction)
  - Bezoar constipation diarrhoea gastrointestinal disorders
  - Suspension or reconstituted powder may be mixed with soft drinks (e.g. caffeine-free diet cola) or fruit juices to mask the taste.
  - There can be variation in the licensing of different medicines containing the same drug.

- Oral suspension
  - Charcodote (Teva UK Ltd)
    - Activated charcoal 200 mg per 1 ml Charcodote 200mg/ml oral suspension sugar-free £11.88

- Oral liquid
  - Charcodote 250 mg oral suspension 250 ml £5.40
  - Charcodote 50 mg oral suspension 250 ml £6.60
  - Charcodote 100 mg oral suspension 250 ml £8.70

- Oral granules
  - Charcodote 500 mg oral granules 250 g £4.30
2 Chemical toxicity

2.1 Cyanide toxicity

**ANTIDOTES AND CHELATORS**

**Dicobalt edetate**

- **INDICATIONS AND DOSE**
  - Severe poisoning with cyanides
    - **BY INTRAVENOUS INJECTION**
    - Child: Consult the National Poisons Information Service
    - Adult: 300 mg, to be given over 1 minute (or 5 minutes if condition less serious), dose to be followed immediately by 50 mL of glucose intravenous infusion 50%; if response inadequate a second dose of both may be given, but risk of cobalt toxicity

- **CAUTIONS** Owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness
- **SIDE-EFFECTS** Reflex tachycardia - vomiting
- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - Dicobalt edetate (Non-proprietary)
      - Dicobalt edetate 15 mg per 1 ml Dicobalt edetate 300mg/20ml solution for injection ampoules | 6 ampoule [POM] £11.72

**Sodium nitrite**

- **INDICATIONS AND DOSE**
  - Poisoning with cyanides
    - **BY INTRAVENOUS INJECTION**
    - Child: Consult the National Poisons Information Service
    - Adult: 12.5 g, to be given over 10 minutes, dose may be repeated in severe cyanide poisoning

- **DOSE EQUIVALENCE AND CONVERSION**
  - 12.5 g equates to 50 mL of a 25% solution or 25 mL of a 50% solution.

- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection
  - **Solution for injection**
    - Sodium thiosulfate (Non-proprietary)
      - Sodium thiosulfate 250 mg per 1 ml Sodium thiosulfate 12.5g/50ml solution for injection vials | 1 vial [POM] £

**2.2 Organophosphorus toxicity**

**Other drugs used for Organophosphorus toxicity** Atropine sulfate, p. 1334

**ANTIDOTES AND CHELATORS**

**Pralidoxime chloride**

- **INDICATIONS AND DOSE**
  - Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent
    - **BY INTRAVENOUS INJECTION**
    - Child: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour; maximum 12 g per day
    - Adult: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour; maximum 12 g per day

- **UNLICENSED USE** Pralidoxime chloride doses may differ from those in product literature.
  - In children Licensed for use in children (age range not specified by manufacturer).
  - **CONTRA-INDICATIONS** Poisoning with carbamates - poisoning with organophosphorus compounds without anticholinesterase activity
  - **CAUTIONS** Myasthenia gravis
  - **SIDE-EFFECTS** Dizziness - drowsiness - headache - hyperventilation - muscle weakness - nausea - tachycardia - visual impairment
  - **RENAI IMPAIRMENT** Use with caution.

- **DIRECTIONS FOR ADMINISTRATION** The loading dose may be administered by intravenous injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an intravenous infusion.
  - In children For intravenous infusion, reconstitute each vial with 20 mL Water for Injections, then dilute to a concentration of 10–20 mg/mL with Sodium Chloride 0.9%.

- **PRESCRIBING AND DISPENSING INFORMATION** Available from designated centres for organophosphorus insecticide poisoning or from the National Blood Service (or Welsh
Emergency treatment of poisoning

3 Drug toxicity
3.1 Benzodiazepine toxicity

ANTIDOTES AND CHELATORS ＞ BENZODIAZEPINE ANTAGONISTS

Flumazenil

INDICATIONS AND DOSE
Reversal of sedative effects of benzodiazepines in anaesthesia and clinical procedures
- **BY INTRAVENOUS INJECTION**
  - Adult: 200 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required; usual dose 300–600 micrograms; maximum 1 mg per course

Reversal of sedative effects of benzodiazepines in intensive care
- **BY INTRAVENOUS INJECTION**
  - Adult: 300 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required; maximum 2 mg per course

Reversal of sedative effects of benzodiazepines in intensive care (if drowsiness recurs after injection)
- **INITIALLY BY INTRAVENOUS INFUSION**
  - Adult: 100–400 micrograms/hour, adjusted according to response, alternatively (by intravenous injection) 300 micrograms, adjusted according to response

IMPORTANT SAFETY INFORMATION
Flumazenil should only be administered by, or under the direct supervision of, personnel experienced in its use.

CONTRA-INDICATIONS
Life-threatening condition (e.g. raised intracranial pressure, status epilepticus) controlled by benzodiazepines

CAUTIONS
Avoid rapid injection following major surgery - avoid rapid injection in high-risk or anxious patients - benzodiazepine dependence (may precipitate withdrawal symptoms) - elderly - ensure neuromuscular blockade cleared before giving - head injury (rapid reversal of benzodiazepine sedation may cause convulsions) - history of panic disorders (risk of recurrence) - prolonged benzodiazepine therapy for epilepsy (risk of convulsions) - short-acting (repeat doses may be necessary - benzodiazepine effects may persist for at least 24 hours)

SIDE-EFFECTS
- Common or very common - Anxiety - diplopia - dry mouth - eye disorders - flushing - headache - hiccups - hyperhidrosis - hyperventilation - hypotension - insomnia - nausea - palpitations - paraesthesia - speech disorder - tremor - vertigo - vomiting
- Uncommon - Abnormal hearing - arrhythmias - chest pain - chills - cough - dyspnoea - nasal congestion - seizure (more common in patients with epilepsy)

- Frequency not known - Withdrawal syndrome
- PREGNANCY - Not known to be harmful.
- BREAST FEEDING - Avoid breast-feeding for 24 hours.
- HEPATIC IMPAIRMENT - Manufacturer advises caution (risk of increased half-life).
- Dose adjustments - Manufacturer advises cautious dose titration.

DIRECTIONS FOR ADMINISTRATION
For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Flumazenil (Non-proprietary)
  - Flumazenil 100 microgram per 1 ml
  - Flumazenil 500 micrograms/5 ml solution for injection ampoules | 5 ampoule £7.46 (Hospital only) | 5 ampoule £65.50– £70.00 | 10 ampoule £140.00

3.2 Digoxin toxicity

ANTIDOTES AND CHELATORS ＞ ANTIBODIES

Digoxin-specific antibody

INDICATIONS AND DOSE
Treatment of known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine and when measures beyond the withdrawal of digoxin and correction of any electrolyte abnormalities are considered necessary
- **BY INTRAVENOUS INFUSION**
  - Child: Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (consult product literature)
  - Adult: Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service (consult product literature)

DIRECTIONS FOR ADMINISTRATION
In adults For intravenous infusion (Digifab®), given intermittently in Sodium chloride 0.9%. Reconstitute with water for injections (4 mL/vial), then dilute with infusion fluid and give over 30 minutes.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
- Digifab (BTG International Ltd)
  - Digoxin-specific antibody fragments 40 mg
  - Digifab 40 mg powder for solution for infusion vials | 1 vial £75.00 (Hospital only)

3.3 Heparin toxicity

ANTIDOTES AND CHELATORS

Protamine sulfate

INDICATIONS AND DOSE
Overdosage with intravenous injection of unfractionated heparin
- **BY INTRAVENOUS INJECTION**
  - Adult: Dose to be administered at a rate not exceeding 5 mg/minute, 1 mg neutralises 60–100 units heparin when given within 15 minutes; if longer than 15 minutes since heparin, less protamine required (consult product literature)

- Frequency not known - Withdrawal syndrome
- PREGNANCY - Not known to be harmful.
- BREAST FEEDING - Avoid breast-feeding for 24 hours.
- HEPATIC IMPAIRMENT - Manufacturer advises caution (risk of increased half-life).
- Dose adjustments - Manufacturer advises cautious dose titration.

DIRECTIONS FOR ADMINISTRATION
For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Flumazenil (Non-proprietary)
  - Flumazenil 100 microgram per 1 ml
  - Flumazenil 500 micrograms/5 ml solution for injection ampoules | 5 ampoule £7.46 (Hospital only) | 5 ampoule £65.50– £70.00 | 10 ampoule £140.00

BNF 78

Ambulance Services for Mid West and South East Wales—see TOXBASE for list of designated centres.

EXCEPTIONS TO LEGAL CATEGORY
Prescription only medicine restriction does not apply where administration is for saving life in emergency.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
- Pralidoxime chloride (imported (United States))
  - Pralidoxime chloride 1 gram
  - Pralidoxime Chloride 1g powder for solution for injection vials | 6 vial £20.46

Exceptions to legal category
Raised intracranial pressure, status epilepticus) controlled by medicine restriction does not apply where administration is for saving life in emergency.

Different medicines containing the same drug.

There can be variation in the licensing of different medicines containing the same drug.

Prescription only
See TOXBASE for list of designated centres.

Ambulance Services for Mid West and South East Wales

BNF 78

1368 Drug toxicity

www.getintopharma.com
literature for details) as heparin rapidly excreted; maximum 50 mg

**Overdosage with intravenous infusion of unfractionated heparin**

- **BY INTRAVENOUS INJECTION**
  - Adult: 25–50 mg, to be administered once heparin infusion stopped at a rate not exceeding 5 mg/minute

**Overdosage with subcutaneous injection of unfractionated heparin**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 25–50 mg, to be administered at a rate not exceeding 5 mg/minute, 1 mg neutralises approx. 100 units heparin, then (by intravenous infusion), any remaining dose to be administered over 8–16 hours; maximum 50 mg per course

**Overdosage with subcutaneous injection of low molecular weight heparin**

- **BY INTRAVENOUS INJECTION, OR BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: Dose to be administered by intermittent intravenous injection at a rate not exceeding 5 mg/minute, 1 mg neutralises approx. 100 units low molecular weight heparin (consult product literature of low molecular weight heparin for details); maximum 50 mg

**CAUTIONS** Excessive doses can have an anticoagulant effect

**SIDE-EFFECTS**

- Rare or very rare Hypertension, pulmonary oedema, non-cardiogenic edema
- Frequency not known Acute pulmonary vasoconstriction, back pain, bradycardia, circulatory collapse, dyspnoea, hypotension, nausea, vomiting, headache, fever

**ALLERGY AND CROSS-SENSITIVITY** Caution if increased risk of allergic reaction to protamine (includes previous treatment with protamine or protamine insulin, allergy to fish, men who are infertile or who have had a vasectomy and who may have antibodies to protamine).

**MONITORING REQUIREMENTS** Monitor activated partial thromboplastin time or other appropriate blood clotting parameters.

**PRESCRIBING AND DISPENSING INFORMATION** The long half-life of low molecular weight heparins should be taken into consideration when determining the dose of protamine sulfate; the effects of low molecular weight heparins can persist for up to 24 hours after administration.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Protamine sulfate (Non-proprietary)
  - Protamine sulfate 10 mg per 1 ml Protamine sulfate 100 mg/10 ml solution for injection ampoules | 5 ampoule (POM) \[\]
  - Protamine sulfate 50 mg/5 ml solution for injection ampoules | 10 ampoule (POM) £4.95

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### 3.4 Opioid toxicity

**OPIOID RECEPTOR ANTAGONISTS**

- **Naloxone hydrochloride**

**INDICATIONS AND DOSE**

**Overdosage with opioids**

- **BY INTRAVENOUS INJECTION**
  - Child 1 month–11 years: Initially 100 micrograms/kg (max. per dose 2 mg), if no response, repeat at intervals of 1 minute to a max. of 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates, doses can be given by subcutaneous or intramuscular routes but only if intravenous route is not feasible; intravenous administration has more rapid onset of action
  - Child 12–17 years: Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response (4 mg dose may be required in seriously poisoned patients), then review diagnosis; further doses may be required if respiratory function deteriorates, doses can be given by subcutaneous or intramuscular routes but only if intravenous route is not feasible; intravenous administration has more rapid onset of action

- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Child: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes
  - Adult: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes

**Overdosage with opioids in a non-medical setting**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 400 micrograms every 2–3 minutes, each dose given in subsequent resuscitation cycles if patient not breathing normally, continue until consciousness regained, breathing normally, medical assistance available, or contents of syringe used up; to be injected into deltoid region or anterolateral thigh

**Reversal of postoperative respiratory depression**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Child 1 month–11 years: 1 microgram/kg, repeated every 2–3 minutes if required
  - Child 12–17 years: Initially 100–200 micrograms, alternatively (by intravenous injection) initially 1.5–3 micrograms/kg, if response inadequate, give subsequent doses, (by intravenous injection) 100 micrograms every 2 minutes, alternatively (by intramuscular injection) 100 micrograms every 1–2 hours

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Emergency treatment of poisoning

**MEDICINAL FORMS**

**With intravenous use in adults**

**PHARMACOKINETICS**

- Naloxone has a short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.

**DIRECTIONS FOR ADMINISTRATION**

**BREAST FEEDING**

- Frequency not known
- Uncommon
- Common or very common

**Titration of dose**

To avoid excessive dosage in obese patients, a ceiling dose for paracetamol overdosage.

**UNLICENSED USE**

Naloxone doses in BNF may differ from those in product literature.

**IMPORTANT SAFETY INFORMATION**

**SAFE PRACTICE**

Doses used in acute opioid overdosage may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use.

**IMPORTANT SAFETY INFORMATION**

**FURTHER INFORMATION**

To avoid excessive dosage in obese patients, a ceiling dose for paracetamol overdosage.

**SIDE-EFFECTS**

- Common or very common: Arrhythmias - dizziness - headache - hypertension - hypotension - nausea - vomiting
- Uncommon: Diarrhoea - dry mouth - hyperhidrosis - hyperventilation - inflammation localised - pain - tremor - vascular irritation
- Rare or very rare: Anxiety - cardiac arrest - erythema multiforme - pulmonary oedema - seizure
- Frequency not known: Analgesia reversed - asthenia - chills - death - dyspnoea - fever - irritability - nasal complaints - piloerection - yawning
- PREGNANCY: Use only if potential benefit outweighs risk.
- BREAST FEEDING: Not orally bioavailable.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children: For continuous intravenous infusion, dilute to a concentration of up to 200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%.
- With intravenous use in adults: For intravenous infusion (Minjet® Naloxone Hydrochloride), give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute to a concentration of up to 200 micrograms/mL and administer via an infusion pump.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Naloxone hydrochloride (Non-proprietary)
  - Naloxone hydrochloride 20 microgram per 1 ml Naloxone 40micrograms/2ml solution for injection ampoules | 10 ampoule | £5.00
  - Naloxone hydrochloride dihydrate 400 microgram per 1 ml Naloxone 400micrograms/1ml solution for injection ampoules | 10 ampoule | £36.00-£53.70 07 = £40.79
- Naloxone hydrochloride 1 mg per 1 ml Naloxone 2mg/2ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £16.80

**3.5 Paracetamol toxicity**

**ANTIDOTES AND CHELATORS**

**Acetylcysteine**

**INDICATIONS AND DOSE**

**Paracetamol overdose**

**BY INTRAVENOUS INFUSION**

- Child (body-weight up to 20 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 3 mL/kg glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 7 mL/kg glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 14 mL/kg glucose 5%
- Child (body-weight 20–39 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 100 mL glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 250 mL glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 500 mL glucose 5%
- Child (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL Glucose Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL Glucose Intravenous Infusion 5%, then 100 mg/kg over 16 hours, to be started immediately after completion of second infusion, dose to be administered in 1 litre Glucose Intravenous Infusion 5%
- Adult (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL Glucose Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL Glucose Intravenous Infusion 5%, then 100 mg/kg over 16 hours, to be started immediately after completion of second infusion, dose to be administered in 1 litre Glucose Intravenous Infusion 5%

**DOSES AT EXTREMES OF BODY WEIGHT**

To avoid excessive dosage in obese patients, a ceiling weight of 110 kg should be used when calculating the dose for paracetamol overdosage.

**IMPORANT SAFETY INFORMATION**

MHRA/CHM ADVICE: INTRAVENOUS ACETYLCYSTEINE FOR PARACETAMOL OVERDOSE: REMINDER OF AUTHORISED DOSE REGIMEN; POSSIBLE NEED FOR CONTINUED TREATMENT (JANUARY 2017)

The authorised dose regimen for acetylcysteine in paracetamol overdose is 3 consecutive intravenous infusions given over a total of 21 hours.

Continued treatment (given at the dose and rate as used in the third infusion) may be necessary depending on the clinical evaluation of the individual patient.

**CAUTIONS**

Asthma (see Side-effects for management of asthma but do not delay acetylcysteine treatment) - atopy - may slightly increase INR - may slightly increase prothrombin time

**SIDE-EFFECTS**


**SIDE-EFFECTS, FURTHER INFORMATION**

Anaphylactoid reactions (with intravenous use) can be managed by suspending treatment and initiating appropriate
management. Treatment may then be restarted at lower rate.

**DIRECTIONS FOR ADMINISTRATION**
- **In children** Glucose 5% is preferred fluid; Sodium Chloride 0.9% is an alternative if Glucose 5% is unsuitable.
- **In adults** For *Intravenous infusion* (Parvolex®), give continuously in Glucose 5% or Sodium chloride 0.9%. Glucose Intravenous Infusion 5% is the preferred fluid; Sodium Chloride Intravenous Infusion 0.9% is an alternative if Glucose Intravenous Infusion 5% is unsuitable.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

- **Acetylcysteine (Non-proprietary)**
- **Acetylcysteine 200 mg per 1 ml** Acetylcysteine 2g/10ml solution for infusion ampoules | 10 ampoule £21.26–£24.99 DT = £21.26
- **Parvolex (Phoenix Labs Ltd)**
- **Acetylcysteine 200 mg per 1 ml** Parvolex 2g/10ml concentrate for solution for infusion ampoules | 10 ampoule £22.50 DT = £21.26

## 4 Methaemoglobinaemia

### ANTIDOTES AND CHELATORS

**Methylthioninium chloride**  
(Methylene blue)

**INDICATIONS AND DOSE**

**Drug- or chemical-induced methaemoglobinaemia**
- **BY SLOW INTRAVENOUS INJECTION**
  - **Child 3 months–17 years:** Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course
  - **Adult:** Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

**Aniline- or dapson-induced methaemoglobinaemia**
- **BY SLOW INTRAVENOUS INJECTION**
  - **Child 3 months–17 years:** Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 4 mg/kg per course
  - **Adult:** Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 4 mg/kg per course

**CAUTIONS** Chlorate poisoning (reduces efficacy of methylthioninium) - G6PD deficiency (seek advice from National Poisons Information Service) - methaemoglobinaemia due to treatment of cyanide poisoning with sodium nitrite (seek advice from National Poisons Information Service) - pulse oximetry may give false estimation of oxygen saturation

**INTERACTIONS** → Appendix 1: methylthioninium chloride

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - anxiety - chest pain - dizziness - headache - hyperhidrosis - nausea - pain in extremity - paraesthesia - skin reactions - taste altered - urine discolouration - vomiting

**SIDE-EFFECTS**

**Frequency not known** Aphasia - arthralgia - confusion - faeces discoloured - fever - haemolytic anaemia - hyperbilirubinaemia (in infants) - hypertension - hypotension - injection site necrosis - mydriasis - tremor

**PREGNANCY** No information available, but risk to fetus of untreated methaemoglobinaemia likely to be significantly higher than risk of treatment.

**BREAST FEEDING** Manufacturer advises avoid breastfeeding for up to 6 days after administration—no information available.

**RENAL IMPAIRMENT**

**Dose adjustments** Use with caution in severe impairment; dose reduction may be required.

**DIRECTIONS FOR ADMINISTRATION**
- **In children** For *intravenous injection*, may be diluted with Glucose 5% to minimise injection-site pain; not compatible with Sodium Chloride 0.9%.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- **Methylthioninium chloride (Non-proprietary)**
- **Methylthioninium chloride 5 mg per 1 ml** Methylthioninium chloride Proverb 50mg/10ml solution for injection ampoules | 5 ampoule £196.89

## 5 Snake bites

### IMMUNE SERA AND IMMUNOGLOBULINS

#### ANTITOXINS

**European viper snake venom antiserum**

**INDICATIONS AND DOSE**

**Systemic envenoming from snake bites** | **Marked local envenoming**

**BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- **Child:** Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service
- **Adult:** Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

**Severe systemic envenoming from snake bites in patients presenting with clinical features**

**BY INTRAVENOUS INJECTION, OR BY INTRAVENOUS INFUSION**
- **Child:** Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service
- **Adult:** Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

**DIRECTIONS FOR ADMINISTRATION** By intravenous injection given over 10–15 minutes or by intravenous infusion over 30 minutes after diluting in sodium chloride 0.9% (use 5 mL diluent/kg body-weight).

**PRESCRIBING AND DISPENSING INFORMATION** To order, email immform@dh.gsi.gov.uk.
MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Viper venom antiserum, European (equine) (Imported (Croatia))
  European viper snake venom antiserum 100 mg per 1 ml Viper venom antiserum, European (equine) 1g/10ml solution for injection vials | 1 vial
## Appendix 1 Interactions

Changes have been made to the interactions content in BNF publications. For more information, see [www.bnf.org/new-bnf-interactions/](http://www.bnf.org/new-bnf-interactions/).

Two or more drugs given at the same time can exert their effects independently or they can interact. Interactions may be beneficial and exploited therapeutically; this type of interaction is not within the scope of this appendix. Many interactions are harmless, and even those that are potentially harmful can often be managed, allowing the drugs to be used safely together. Nevertheless, adverse drug interactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA), through the Yellow Card Scheme (see Adverse reactions to drugs p. 12), as for other adverse drug reactions.

Potentially harmful drug interactions may occur in only a small number of patients, but the true incidence is often hard to establish. Furthermore the severity of a harmful interaction is likely to vary from one patient to another. Patients at increased risk from drug interactions include the elderly and those with impaired renal or hepatic function. Interactions can result in the potentiation or antagonism of one drug by another, or result in another effect, such as renal impairment. Drug interactions may develop either through pharmacokinetic or pharmacodynamic mechanisms.

### Pharmacokinetic interactions

These occur when one drug alters the absorption, distribution, metabolism, or excretion of another, thus increasing or decreasing the amount of drug available to produce its pharmacological effects. Pharmacokinetic interactions occurring with one drug do not necessarily occur uniformly across a group of related drugs. **Affecting absorption** The rate of absorption and the total amount absorbed can both be altered by drug interactions. Delayed absorption is rarely of clinical importance unless a rapid effect is required (e.g. when giving an analgesic). Reduction in the total amount absorbed, however, can result in ineffective therapy.

**Affecting distribution** Due to changes in protein binding: To a variable extent most drugs are loosely bound to plasma proteins. Protein-binding sites are non-specific and one drug can displace another thereby increasing the proportion free to diffuse from plasma to its site of action. This only produces a detectable increase in effect if it is an extensively bound drug (more than 90%) that is not widely distributed throughout the body. Even so displacement rarely produces more than transient potentiation because this increased concentration of free drug will usually be eliminated.

Displacement from protein binding plays a part in the potentiation of warfarin by sulfonamides but these interactions become clinically relevant mainly because warfarin metabolism is also inhibited.

**Induction or inhibition of drug transporter proteins:** Drug transporter proteins, such as P-glycoprotein, actively transport drugs across biological membranes. Transporters can be induced or inhibited, resulting in changes in the concentrations of drugs that are substrates for the transporter. For example, rifampicin induces P-glycoprotein, particularly in the gut wall, resulting in decreased plasma concentrations of digoxin, a P-glycoprotein substrate.

**Affecting metabolism** Many drugs are metabolised in the liver. Drugs are either metabolised by phase I reactions (oxidation, reduction, or hydrolysis) or by phase II reactions (e.g. glucoronidation).

Phase I reactions are mainly carried out by the cytochrome P450 family of isoenzymes, of which CYP3A4 is the most important isoenzyme involved in the metabolism of drugs. Induction of cytochrome P450 isoenzymes by one drug can increase the rate of metabolism of another, resulting in lower plasma concentrations and a reduced effect. On withdrawal of the inducing drug, plasma concentrations increase and toxicity can occur.

Conversely when one drug inhibits cytochrome P450 isoenzymes, it can decrease the metabolism of another, leading to higher plasma concentrations, resulting in an increased effect with a risk of toxicity.

Isoenzymes of the hepatic cytochrome P450 system interact with a wide range of drugs. With knowledge of which isoenzymes are involved in a drug’s metabolism, it is possible to predict whether certain pharmacokinetic interactions will occur. For example, carbamazepine is a potent inducer of CYP3A4, ketoconazole is potent inhibitor of CYP3A4, and midazolam is a substrate of CYP3A4.

Carbamazepine reduces midazolam concentrations, and it is therefore likely that other drugs that are potent inducers of CYP3A4 will interact similarly with midazolam. Ketoconazole, however, increases midazolam concentrations, and it can be predicted that other drugs that are potent inhibitors of CYP3A4 will interact similarly.

**Affecting renal excretion** Drugs are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule. For example, salicylates and some other NSAIDs delay the excretion of methotrexate; serious methotrexate toxicity is possible. Changes in urinary pH can also affect the reabsorption of a small number of drugs, including methenamine.
Relative importance of interactions

Levels of severity: Most interactions have been assigned a severity; this describes the likely effect of an unmanaged interaction on the patient.

- Severe—the result may be a life-threatening event or have a permanent detrimental effect.
- Moderate—the result could cause considerable distress or partially incapacitate a patient; they are unlikely to be life-threatening or result in long-term effects.
- Mild—the result is unlikely to cause concern or incapacitate the majority of patients.
- Unknown—used for those interactions that are predicted, but there is insufficient evidence to hazard a guess at the outcome.
- Levels of evidence: Most interactions have been assigned a rating to indicate the weight of evidence behind the interaction.

Study—for interactions where the information is based on formal study including those for other drugs with same mechanism (e.g. known inducers, inhibitors, or substrates of cytochrome P450 isoenzymes or P-glycoprotein).

Anecdotal—interactions based on either a single case report or a limited number of case reports.

Appendix 1 structure

1. Drugs
   - Drugs are listed alphabetically. If a drug is a member of a drug class, all interactions for that drug will be listed under the drug class entry; in this case the drug entry provides direction to the relevant drug class where its interactions can be found.
   - Within a drug or drug class entry, interactions are listed alphabetically by the interacting drug or drug class. The interactions describe the effect that occurs, and the action to be taken, either based on manufacturer’s advice from the relevant Summary of Product Characteristics or advice from a relevant authority (e.g. MHRA). An action message is only included where the combination is to be avoided, where a dose adjustment is required, or where specific administration requirements (e.g. timing of doses) are recommended. If two drugs have a pharmacodynamic effect in addition to a pharmacokinetic interaction, a cross-reference to the relevant pharmacodynamic effect table is included at the end of the pharmacokinetic message.

2. Drug classes
   - The drugs that are members of a drug class are listed underneath the drug class entry in a blue box. Interactions for the class are then listed alphabetically by the interacting drug or drug class. If the interaction only applies to certain drugs in the class, these drugs will be shown in brackets after the drug class name.

3. Supplementary information
   - If a drug has additional important information to be considered, this is shown in a blue box underneath the drug or drug class entry. This information might be food and lifestyle advice (including smoking and alcohol consumption), relate to the pharmacology of the drug or applicability of interactions to certain routes of administration, or it might be advice about separating administration times.

4. Pharmacodynamic effects
   - Tables at the beginning of Appendix 1 cover pharmacodynamic effects. If a drug is included in one or more of these tables, this will be indicated at the top of the list of interactions for the drug or drug class. In addition to the list of interactions for a drug or drug class, these tables should always be consulted.
   - Each table describes the relevant pharmacodynamic effect and lists those drugs that are commonly associated with the effect. Concurrent use of two or more drugs from the same table is expected to increase the risk of the pharmacodynamic effect occurring. Please note these tables are not exhaustive.

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### Table 1: Drugs that cause hepatotoxicity

The following is a list of some drugs that cause hepatotoxicity (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol (beverage)</td>
<td>dactinomycin</td>
<td>isoniazid</td>
<td>micafungin</td>
<td>streptozocin</td>
</tr>
<tr>
<td>alectinib</td>
<td>dantrolene</td>
<td>itraconazole</td>
<td>minocycline</td>
<td>sulfasalazine</td>
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<tr>
<td>asparaginase</td>
<td>demeclocycline</td>
<td>leflunomide</td>
<td>oxytetracycline</td>
<td>tetracycline</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>didanosine</td>
<td>lenalidomide</td>
<td>paracetamol</td>
<td>tigecycline</td>
</tr>
<tr>
<td>bedaquiline</td>
<td>doxycycline</td>
<td>lomitapide</td>
<td>pegaspargase</td>
<td>trabectedin</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>flucloxacillin</td>
<td>lymecycline</td>
<td>pravastatin</td>
<td>valproate</td>
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<tr>
<td>clavulanic acid</td>
<td>flucloxacinil</td>
<td>mercaptopurine</td>
<td>rosuvastatin</td>
<td>vincristine</td>
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<tr>
<td>crisantaspase</td>
<td>flucnazole</td>
<td>methotrexate</td>
<td>simvastatin</td>
<td>vinorelbine</td>
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<td></td>
<td>fluvastatin</td>
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### Table 2: Drugs that cause nephrotoxicity

The following is a list of some drugs that cause nephrotoxicity (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
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<th>Drug</th>
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<tr>
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<td>cefalotin</td>
<td>diclofenac</td>
<td>methotrexate</td>
<td>tacrolimus</td>
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<td>aciclovir</td>
<td>cefazolin</td>
<td>etodolac</td>
<td>nabumetone</td>
<td>telavancin</td>
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<tr>
<td>adefovir</td>
<td>cefoxorime</td>
<td>etoricoxib</td>
<td>naproxen</td>
<td>tenofovir disoproxil</td>
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<tr>
<td>amikacin</td>
<td>ceftriaxone</td>
<td>foscarnet</td>
<td>neomycin</td>
<td>tenoxicam</td>
</tr>
<tr>
<td>amphotericin</td>
<td>cefuroxime</td>
<td>ganciclovir</td>
<td>oxaliplatin</td>
<td>tiaprofenic acid</td>
</tr>
<tr>
<td>bacitracin</td>
<td>celecoxib</td>
<td>gentamicin</td>
<td>parecoxib</td>
<td>tobramycin</td>
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<tr>
<td>capreomycin</td>
<td>cefixime</td>
<td>ibuprofen</td>
<td>pemetrexed</td>
<td>tolenfamic acid</td>
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<tr>
<td>carboplatin</td>
<td>ceftazolin</td>
<td>ifosfamide</td>
<td>penicillamine</td>
<td>trimethoprim</td>
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<td>celecoxib</td>
<td>ceftazolin</td>
<td>indometacin</td>
<td>pentamidine</td>
<td>valaciclovir</td>
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<tr>
<td>cefaclor</td>
<td>ceftaroline</td>
<td>ketoprofen</td>
<td>piroxidam</td>
<td>valganciclovir</td>
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<td>cefadroxil</td>
<td>cefotaxime</td>
<td>ketorolac</td>
<td>polymyxins</td>
<td>vancomycin</td>
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<tr>
<td>cefalexin</td>
<td>cefpodoxime (particularly</td>
<td>mefenamic acid</td>
<td>streptomyacin</td>
<td>zidovudine</td>
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<tr>
<td>cefotaxime</td>
<td>intravenous)</td>
<td>meloxicam</td>
<td>streptozocin</td>
<td>zoledronic acid</td>
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<td>cefradine</td>
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### Table 3: Drugs with anticoagulant effects

The following is a list of drugs that have anticoagulant effects. Concurrent use of two or more drugs from this list might increase the risk of bleeding; concurrent use of drugs with antiplatelet effects (see table of drugs with antiplatelet effects) might also increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>dabigatran</td>
<td>fondaparinux</td>
<td>rivaroxaban</td>
<td>warfarin</td>
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<tr>
<td>alteplase</td>
<td>dalteparin</td>
<td>heparin (unfractionated)</td>
<td>streptokinase</td>
<td>tenecleptase</td>
</tr>
<tr>
<td>apixaban</td>
<td>danaparoid</td>
<td>nicotinic acid</td>
<td>tenecteplase</td>
<td>tinzaparin</td>
</tr>
<tr>
<td>argatroban</td>
<td>edoxaban</td>
<td>omega-3-acid ethyl esters</td>
<td>urokinase</td>
<td></td>
</tr>
<tr>
<td>bivalirudin</td>
<td>enoxaparin</td>
<td>phenindione</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Drugs with antiplatelet effects

The following is a list of drugs that have antiplatelet effects (note that this list is not exhaustive). Concurrent use of two or more drugs from this list might increase the risk of bleeding; concurrent use of drugs with anticoagulant effects (see table of drugs with anticoagulant effects) might also increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
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<tr>
<td>aceclofenac</td>
<td>dasatinib</td>
<td>etoricoxib</td>
<td>ketorolac</td>
<td>sertraline</td>
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<td>anagrelide</td>
<td>dextubuprofen</td>
<td>fluoxetine</td>
<td>mefenamic acid</td>
<td>sulindac</td>
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<tr>
<td>aspirin</td>
<td>desketoprofen</td>
<td>flurbiprofen</td>
<td>meloxicam</td>
<td>tenoxilam</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>dicyclofen</td>
<td>fluoroxime</td>
<td>nabumetone</td>
<td>tiaprofenic acid</td>
</tr>
<tr>
<td>cangrelor</td>
<td>dipyridamole</td>
<td>fluvaxamine</td>
<td>naproxen</td>
<td>ticagrelor</td>
</tr>
<tr>
<td>celecoxib</td>
<td>duloxetine</td>
<td>ibrutinib</td>
<td>parecoxib</td>
<td>tiroliban</td>
</tr>
<tr>
<td>cilostazol</td>
<td>epoprostenol</td>
<td>ibuprofen</td>
<td>paroxetine</td>
<td>tolenfamic acid</td>
</tr>
<tr>
<td>cilostazol (oral)</td>
<td>epitiabatide</td>
<td>iloprost</td>
<td>piroxidam</td>
<td>trastuzumab emtansine</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>escitalopram</td>
<td>indometacin</td>
<td>prasugrel</td>
<td>vanlafaxine</td>
</tr>
<tr>
<td>daptaxetine</td>
<td>etodolac</td>
<td>inotersen</td>
<td>regorafenib</td>
<td>vortioxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ketoprofen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5: Drugs that cause thromboembolism

The following is a list of some drugs that cause thromboembolism (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>bleomycin</td>
<td>epoetin zeta</td>
<td>pentostatin</td>
<td>toremifene</td>
<td>vinflunine</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>fluoroacil</td>
<td>pomalidomide</td>
<td>tranexamic acid</td>
<td>vinorelbine</td>
</tr>
<tr>
<td>darbepoetin alfa</td>
<td>fulvestrant</td>
<td>roxifene</td>
<td>tretinoin</td>
<td></td>
</tr>
<tr>
<td>doxorubicin</td>
<td>lenalidomide</td>
<td>tamoxifen</td>
<td>vinblastine</td>
<td></td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>methotrexate</td>
<td>thalidomide</td>
<td>vincristine</td>
<td></td>
</tr>
<tr>
<td>epoetin beta</td>
<td>mitomycin</td>
<td>tibolone</td>
<td>vindesine</td>
<td></td>
</tr>
</tbody>
</table>

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### TABLE 6
Drugs that cause bradycardia

The following is a list of drugs that cause bradycardia (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>acebutolol</td>
<td>carvedilol</td>
<td>fentanyl</td>
<td>nadolol</td>
<td>selegiline</td>
<td>sotalol</td>
<td></td>
</tr>
<tr>
<td>alectinib</td>
<td>celirolol</td>
<td>fingolimod</td>
<td>nebivolol</td>
<td>sotolol</td>
<td>sufentanil</td>
<td></td>
</tr>
<tr>
<td>alfentanil</td>
<td>cisatracurium</td>
<td>flecainide</td>
<td>neostigmine</td>
<td>thalidomide</td>
<td>timolol</td>
<td></td>
</tr>
<tr>
<td>amiodarone</td>
<td>clonidine</td>
<td>galantamine</td>
<td>pasireotide</td>
<td>tizanidine</td>
<td>verapamil</td>
<td></td>
</tr>
<tr>
<td>apraclonidine</td>
<td>crizotinib</td>
<td>ivabradine</td>
<td>pindolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atenolol</td>
<td>diltiazem</td>
<td>labetalol</td>
<td>propranolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>betaaxolol</td>
<td>donepezil</td>
<td>levoobunolol</td>
<td>pyridostigmine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bisoprolol</td>
<td>esmolol</td>
<td>methadone</td>
<td>remifentanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brimonidine</td>
<td></td>
<td>methotropin</td>
<td>rivastigmine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 7
Drugs that cause first dose hypotension

The following is a list of some drugs that can cause first-dose hypotension (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfuzosin</td>
<td>eprosartan</td>
<td>losartan</td>
<td>prazosin</td>
<td>trandolapril</td>
<td></td>
</tr>
<tr>
<td>azilsartan</td>
<td>fosinopril</td>
<td>olmesartan</td>
<td>quinapril</td>
<td>valsartan</td>
<td></td>
</tr>
<tr>
<td>candesartan</td>
<td>glyceryl trinitrate</td>
<td>imidapril</td>
<td>ramiplol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>captopril</td>
<td>indapril</td>
<td>isosorbide dinitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxazosin</td>
<td>indoramin</td>
<td>isosorbide mononitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>enalapril</td>
<td>irbesartan</td>
<td>lisinopril</td>
<td>telmisartan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 8
Drugs that cause hypotension

The following is a list of some drugs that cause hypotension (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>acebutolol</td>
<td>chlorothiazide</td>
<td>guanfacine</td>
<td>minoxidil</td>
<td>risperidone</td>
<td></td>
</tr>
<tr>
<td>alcohol (beverage)</td>
<td>chlorpromazine</td>
<td>haloperidol</td>
<td>moxisylyte</td>
<td>ropinirole</td>
<td></td>
</tr>
<tr>
<td>alfuzosin</td>
<td>chordortaldone</td>
<td>hydralazine</td>
<td>moxonidine</td>
<td>rotigotine</td>
<td></td>
</tr>
<tr>
<td>aliskiren</td>
<td>clevidipine</td>
<td>hydrochlorothiazide</td>
<td>neadolol</td>
<td>sacubitril</td>
<td></td>
</tr>
<tr>
<td>alprastadil</td>
<td>clonidine</td>
<td>hydroflumethiazide</td>
<td>nebivolol</td>
<td>sapropterin</td>
<td></td>
</tr>
<tr>
<td>amantadine</td>
<td>clotiazine</td>
<td>imidapril</td>
<td>nicardipine</td>
<td>selegline</td>
<td></td>
</tr>
<tr>
<td>amitriptyline</td>
<td>desflurane</td>
<td>impiramine</td>
<td>nicorandil</td>
<td>sevoflurane</td>
<td></td>
</tr>
<tr>
<td>amlodipine</td>
<td>diazoxide</td>
<td>indapamide</td>
<td>nifedipine</td>
<td>sulindafil</td>
<td></td>
</tr>
<tr>
<td>apomorphine</td>
<td>diltiazem</td>
<td>indoramin</td>
<td>nimodipine</td>
<td>sodium nitroprusside</td>
<td></td>
</tr>
<tr>
<td>apraclonidine</td>
<td>diprydiamole</td>
<td>isosorbide dinitrate</td>
<td>nitrous oxide</td>
<td>sodium oxybate</td>
<td></td>
</tr>
<tr>
<td>aripiprazole</td>
<td>dosulepin</td>
<td>isosorbide mononitrate</td>
<td>nortriptyline</td>
<td>sotalol</td>
<td></td>
</tr>
<tr>
<td>asenapine</td>
<td>doxazosin</td>
<td>ketamine</td>
<td>olanzapine</td>
<td>spironolactone</td>
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</tr>
<tr>
<td>atenolol</td>
<td>doxepin</td>
<td>labetalol</td>
<td>olmesartan</td>
<td>sulpiride</td>
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</tr>
<tr>
<td>avanafil</td>
<td>droperidol</td>
<td>lacidipine</td>
<td>paliperidone</td>
<td>tadalafil</td>
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<tr>
<td>azilsartan</td>
<td>emapragifazon</td>
<td>lercanidipine</td>
<td>pergolide</td>
<td>tamulosin</td>
<td></td>
</tr>
<tr>
<td>baclofen</td>
<td>enalapril</td>
<td>levobunolol</td>
<td>pericyazine</td>
<td>telmisartan</td>
<td></td>
</tr>
<tr>
<td>bendroflumethiazide</td>
<td>eplerenone</td>
<td>levodopa</td>
<td>perindopril</td>
<td>terazosin</td>
<td></td>
</tr>
<tr>
<td>benperidol</td>
<td>eprosartan</td>
<td>levomepromazine</td>
<td>phezonezine</td>
<td>thiopental</td>
<td></td>
</tr>
<tr>
<td>betaxolol</td>
<td>ertugriflazin</td>
<td>lisinopril</td>
<td>pimozeide</td>
<td>timolol</td>
<td></td>
</tr>
<tr>
<td>bortezomib</td>
<td>esketamine</td>
<td>losartan</td>
<td>pindolol</td>
<td>tizanidine</td>
<td></td>
</tr>
<tr>
<td>brimonidine</td>
<td>esmolol</td>
<td>losatan</td>
<td>pramipexole</td>
<td>torasemide</td>
<td></td>
</tr>
<tr>
<td>bromocriptine</td>
<td>etomidade</td>
<td>losatan</td>
<td>prazosin</td>
<td>trandolapril</td>
<td></td>
</tr>
<tr>
<td>bumetanide</td>
<td>felodipine</td>
<td>loxapine</td>
<td>prochlorperazone</td>
<td>tranylcypromine</td>
<td></td>
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<tr>
<td>cabergoline</td>
<td>flupentixol</td>
<td>lurasidone</td>
<td>promazine</td>
<td>trifluoperazone</td>
<td></td>
</tr>
<tr>
<td>canagliflozin</td>
<td>fluphenazine</td>
<td>methylfluorfrone</td>
<td>propranolol</td>
<td>trimipramine</td>
<td></td>
</tr>
<tr>
<td>candesartan</td>
<td>fosinoprol</td>
<td>methyldopa</td>
<td>quetapine</td>
<td>valsartan</td>
<td></td>
</tr>
<tr>
<td>captopril</td>
<td>furosemide</td>
<td>metolazone</td>
<td>quinagolide</td>
<td>vardenafil</td>
<td></td>
</tr>
<tr>
<td>cariprazine</td>
<td>glyceryl trinitrate</td>
<td>methotropin</td>
<td>quinapril</td>
<td>verapamil</td>
<td></td>
</tr>
<tr>
<td>carvedilol</td>
<td>guanethidine</td>
<td>metoprolol</td>
<td>ramipril</td>
<td>xipamid</td>
<td></td>
</tr>
<tr>
<td>celirolol</td>
<td></td>
<td></td>
<td>riocigut</td>
<td>zuclopenthixol</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 9
Drugs that prolong the QT interval

The following is a list of some drugs that prolong the QT-interval (note that this list is not exhaustive). In general, manufacturers advise that the use of two or more drugs that are associated with QT prolongation should be avoided. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation—concurrent use of drugs that reduce serum potassium might further increase this risk (see table of drugs that reduce serum potassium).

Drugs that are not known to prolong the QT interval but are predicted (by the manufacturer) to increase the risk of QT prolongation include: domperidone, fingolimod, graniisetron, ivabradine, metlojquzine, moizostaline, palonosetron, and intravenous pentamidin. Most manufacturers advise avoiding concurrent use with drugs that prolong the QT interval.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>amifampridine</td>
<td>clarithromycin</td>
<td>fluphenazine</td>
<td>panobinostat</td>
</tr>
<tr>
<td>amiodarone</td>
<td>clomipramine</td>
<td>haloperidol</td>
<td>tetrabenazine</td>
</tr>
<tr>
<td>amisulpride</td>
<td>clotrimazol</td>
<td>hydroxyzine</td>
<td>tizanidnin</td>
</tr>
<tr>
<td>anagrelide</td>
<td>cycloclorverine</td>
<td>inotuzumab ozogamicin</td>
<td>tolterodine</td>
</tr>
<tr>
<td>apalutamide</td>
<td>dicycloverine</td>
<td>lapatinib</td>
<td>trifluoperazine</td>
</tr>
<tr>
<td>apomorphine</td>
<td>disopyramide</td>
<td>lenvatinib</td>
<td>trifluoperidyl</td>
</tr>
<tr>
<td>arsenic trioxide</td>
<td>dotremoterone</td>
<td>levomepromazine</td>
<td>trimipramine</td>
</tr>
<tr>
<td>artemetether</td>
<td>droperidol</td>
<td>lithium</td>
<td>tropicamide</td>
</tr>
<tr>
<td>arteminol</td>
<td>efavirenz</td>
<td>lofexidine</td>
<td>trolonol</td>
</tr>
<tr>
<td>bedaquiline</td>
<td>encorafenib</td>
<td>methadone</td>
<td>ubecium</td>
</tr>
<tr>
<td>bosutinib</td>
<td>eribulin</td>
<td>moxifloxacin</td>
<td>umecilidium</td>
</tr>
</tbody>
</table>
| cabozantinib              | erythromycin             | nilotinib                 | |}

TABLE 10
Drugs with antimuscarinic effects

The following is a list of some drugs that have antimuscarinic effects (note that this list is not exhaustive). Concurrent use of two or more drugs from this list might increase the risk of these effects occurring. Drugs with antimuscarinic effects decrease the absorption of levodopa.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>aclidinium</td>
<td>cycloproctolate</td>
<td>haloperidol</td>
<td>orphenadrine</td>
</tr>
<tr>
<td>amantadine</td>
<td>cyproheptadine</td>
<td>homatropine</td>
<td>oxybutynin</td>
</tr>
<tr>
<td>amitryptiline</td>
<td>darifenacine</td>
<td>hydroxyzine</td>
<td>pimozone</td>
</tr>
<tr>
<td>atropine</td>
<td>dicycloverine</td>
<td>hyoscine</td>
<td>prochloperazine</td>
</tr>
<tr>
<td>baclofen</td>
<td>dimenhydrinate</td>
<td>hydroxyzine</td>
<td>procyclidine</td>
</tr>
<tr>
<td>chlorphenamine</td>
<td>disopyramide</td>
<td>hyoscine</td>
<td>promethazone</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>dosulepin</td>
<td>imipramine</td>
<td>propafonene</td>
</tr>
<tr>
<td>clemastine</td>
<td>doxepin</td>
<td>iraprotiapum</td>
<td>propaphionine</td>
</tr>
<tr>
<td>clobazepine</td>
<td>esctalopram</td>
<td>levomepromazine</td>
<td>propiverine</td>
</tr>
<tr>
<td>cyclozepine</td>
<td>flavoxetine</td>
<td>lopexamine</td>
<td>solifenacin</td>
</tr>
<tr>
<td>cyclazine</td>
<td>glycopyrotrium</td>
<td>lofexapine</td>
<td>tioptropium</td>
</tr>
</tbody>
</table>

TABLE 11
Drugs with CNS depressant effects

The following is a list of some drugs with CNS depressant effects (note that this list is not exhaustive). Concurrent use of two or more drugs from this list might increase the risk of CNS depressant effects, such as drowsiness, which might affect the ability to perform skilled tasks (see ‘Drugs and Driving’ in Guidance on Prescribing p. 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>agomelatine</td>
<td>clonazepam</td>
<td>hydromorphone</td>
<td>mirtazapine</td>
</tr>
<tr>
<td>alcohol (beverage)</td>
<td>clonazepam</td>
<td>hydroxyzine</td>
<td>morphine</td>
</tr>
<tr>
<td>alfentanil</td>
<td>clonazepam</td>
<td>iso-flurane</td>
<td>moxonitidine</td>
</tr>
<tr>
<td>alimemazine</td>
<td>clonazepam</td>
<td>ketamine</td>
<td>nabilone</td>
</tr>
<tr>
<td>alprazolam</td>
<td>clonazepam</td>
<td>ketotifen</td>
<td>nitrazepam</td>
</tr>
<tr>
<td>amisulpride</td>
<td>clonazepam</td>
<td>lamotrigine</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>apraclocidine</td>
<td>clonazepam</td>
<td>levetiracetam</td>
<td>olanzapine</td>
</tr>
<tr>
<td>apripiprazole</td>
<td>clonazepam</td>
<td>lepomepromazine</td>
<td>oxazepam</td>
</tr>
<tr>
<td>articaine</td>
<td>clonazepam</td>
<td>lidocaine</td>
<td>oxycodone</td>
</tr>
<tr>
<td>asenapine</td>
<td>clonazepam</td>
<td>lofexidine</td>
<td>paliperidone</td>
</tr>
<tr>
<td>baclofen</td>
<td>clonazepam</td>
<td>loprazolam</td>
<td>papaveretum</td>
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<tr>
<td>benperidol</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>pentazocine</td>
</tr>
<tr>
<td>bromidinide</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>perampanili</td>
</tr>
<tr>
<td>butazolide</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>pericyazine</td>
</tr>
<tr>
<td>canabolinide</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>pethidine</td>
</tr>
<tr>
<td>chloral hydrate</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>phen borelina</td>
</tr>
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<td>chlordiazepoxide</td>
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<td>lorazepam</td>
<td>pimozide</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>pizotifen</td>
</tr>
<tr>
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<td>clonazepam</td>
<td>lorazepam</td>
<td>pregabalin</td>
</tr>
<tr>
<td>clemastine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>prilocaine</td>
</tr>
<tr>
<td>clozapine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>primidone</td>
</tr>
<tr>
<td>codeine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>promazine</td>
</tr>
<tr>
<td>codeine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>promazine</td>
</tr>
<tr>
<td>codeine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>promazine</td>
</tr>
<tr>
<td>codeine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>promazine</td>
</tr>
<tr>
<td>codeine</td>
<td>clonazepam</td>
<td>lorazepam</td>
<td>promazine</td>
</tr>
</tbody>
</table>
Appendix 1: Interactions

### TABLE 12: Drugs that cause peripheral neuropathy

The following is a list of some drugs that cause peripheral neuropathy (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiodarone</td>
<td>didanosine</td>
<td>isoniazid</td>
<td>phenytoin</td>
<td>vindesine</td>
</tr>
<tr>
<td>bortezomib</td>
<td>disulfram</td>
<td>lamivudine</td>
<td>stavudine</td>
<td>vinflunine</td>
</tr>
<tr>
<td>brentuximab vedotin</td>
<td>docetaxel</td>
<td>metronidazole</td>
<td>thalidomide</td>
<td>vinorelbine</td>
</tr>
<tr>
<td>cabazitaxel</td>
<td>eribulin</td>
<td>nitrofurantoin</td>
<td>vinblastine</td>
<td></td>
</tr>
<tr>
<td>cisplatin</td>
<td>fosphenytoin</td>
<td>paclitaxel</td>
<td>vircristine</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 13: Drugs that cause serotonin syndrome

The following is a list of some drugs that cause serotonin syndrome (note that this list is not exhaustive). See 'Serotonin Syndrome' and 'Monoamine-Oxidase Inhibitors' under Antidepressants drugs p. 359 for more information and for specific advice on avoiding monoamine-oxidase inhibitors during and after administration of other serotonergic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>almotriptan</td>
<td>fentanyl</td>
<td>methadone</td>
<td>pethidine</td>
<td>tapentadol</td>
</tr>
<tr>
<td>bupropion</td>
<td>fluoxetine</td>
<td>methylenedioxyinin chloride</td>
<td>phenelzine</td>
<td>tramadol</td>
</tr>
<tr>
<td>citalopram</td>
<td>imipramine</td>
<td>mianserin</td>
<td>procarbazine</td>
<td>tranylcypromine</td>
</tr>
<tr>
<td>clomipramine</td>
<td>isocarboxazid</td>
<td>mirtazapine</td>
<td>rasagiline</td>
<td>trazodone</td>
</tr>
<tr>
<td>dapoxetine</td>
<td>linezolid</td>
<td>moclobemide</td>
<td>rizatriptan</td>
<td>tryptophan</td>
</tr>
<tr>
<td>dexamfetamine</td>
<td>lisdexamfetamine</td>
<td>naratriptan</td>
<td>safinamide</td>
<td>venlafaxine</td>
</tr>
<tr>
<td>duloxetine</td>
<td>lithium</td>
<td>ondansetron</td>
<td>selegiline</td>
<td>vortioxetin</td>
</tr>
<tr>
<td>eletriptan</td>
<td></td>
<td>palonosetron</td>
<td>sertraline</td>
<td>zolmitriptan</td>
</tr>
<tr>
<td>escitalopram</td>
<td></td>
<td>paroxetine</td>
<td>St John's Wort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sumatriptan</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 14: Antidiabetic drugs

The following is a list of antidiabetic drugs (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase the risk of hypoglycaemia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose</td>
<td>empagliflozin</td>
<td>glimepiride</td>
<td>lixisenatide</td>
<td>saxagliptin</td>
</tr>
<tr>
<td>alogliptin</td>
<td>exetibulin</td>
<td>glibizide</td>
<td>metformin</td>
<td>semaglutide</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>glibenclamide</td>
<td>glipizide</td>
<td>nateglinide</td>
<td>sitagliptin</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>gliclazide</td>
<td>insulin</td>
<td>pioglitazone</td>
<td>tobutamide</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>gliclazide</td>
<td>linagliptin</td>
<td>repaglinide</td>
<td>vildagliptin</td>
</tr>
</tbody>
</table>

### TABLE 15: Drugs that cause myelosuppression

The following is a list of some drugs that cause myelosuppression (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>aclacinidin</td>
<td>carmustine</td>
<td>fludarabine</td>
<td>nivolumab</td>
<td>siltuximab</td>
</tr>
<tr>
<td>afibercept</td>
<td>ceritinib</td>
<td>fluorouracil</td>
<td>obinutuzumab</td>
<td>sorafenib</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>cetuximab</td>
<td>ganciclovir</td>
<td>olanzapine</td>
<td>sulfadiazine</td>
</tr>
<tr>
<td>amscarine</td>
<td>chlorambucil</td>
<td>gefitinib</td>
<td>olaparib</td>
<td>sulfamethoxazole</td>
</tr>
<tr>
<td>anakinra</td>
<td>cisplatin</td>
<td>gemcitabine</td>
<td>olsalazine</td>
<td>sulfasalazine</td>
</tr>
<tr>
<td>arsenic trioxide</td>
<td>cladribine</td>
<td>hydroxy carbamide</td>
<td>oxaliplatin</td>
<td>sunitinib</td>
</tr>
<tr>
<td>asparaginase</td>
<td>clofarabine</td>
<td>ibrutinib</td>
<td>paclitaxel</td>
<td>temozolomide</td>
</tr>
<tr>
<td>axitinib</td>
<td>clozapine</td>
<td>idarubicin</td>
<td>panitumumab</td>
<td>thalidomide</td>
</tr>
<tr>
<td>azacitidine</td>
<td>crisantaspase</td>
<td>idelalisib</td>
<td>panobinostat</td>
<td>thiopeta</td>
</tr>
<tr>
<td>azathioprine</td>
<td>crizotinib</td>
<td>ifosfamide</td>
<td>pazopanib</td>
<td>tioguanine</td>
</tr>
<tr>
<td>balsalazide</td>
<td>cyclophosphamide</td>
<td>imatinib</td>
<td>pegylpagase</td>
<td>topotecan</td>
</tr>
<tr>
<td>belimumab</td>
<td>cytarabine</td>
<td>interferon alfa</td>
<td>pegylferon alfa</td>
<td>trabectedin</td>
</tr>
<tr>
<td>bendamustine</td>
<td>dabrafenib</td>
<td>interferon beta</td>
<td>pegylferon beta-ia</td>
<td>trastuzumab emtansine</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>dacarbazine</td>
<td>irinotecan</td>
<td>pentametrexed</td>
<td>treosulfan</td>
</tr>
<tr>
<td>bleomycin</td>
<td>dactinomycin</td>
<td>leflunomide</td>
<td>pentostatin</td>
<td>valganciclovir</td>
</tr>
<tr>
<td>bilinumomab</td>
<td>dasatinib</td>
<td>lenalidomide</td>
<td>pixantrone</td>
<td>vinblastine</td>
</tr>
<tr>
<td>bortezomib</td>
<td>daunorubicin</td>
<td>linezolid</td>
<td>pomalidomide</td>
<td>vincristine</td>
</tr>
<tr>
<td>bosutinib</td>
<td>decitabine</td>
<td>lomustine</td>
<td>primaqmine</td>
<td>vindesine</td>
</tr>
<tr>
<td>brentuximab vedotin</td>
<td>deferiprone</td>
<td>melphalan</td>
<td>procabazine</td>
<td>vinflunine</td>
</tr>
<tr>
<td>busulfan</td>
<td>docetaxel</td>
<td>mercaptapurine</td>
<td>propylthouracil</td>
<td>vinorelbine</td>
</tr>
<tr>
<td>cabazitaxel</td>
<td>doxorubicin</td>
<td>methotrexate</td>
<td>pyrimethamine</td>
<td>vismodegib</td>
</tr>
<tr>
<td>cabozaclitab</td>
<td>eprubicin</td>
<td>mitomycin</td>
<td>raltrexed</td>
<td></td>
</tr>
<tr>
<td>canakinumab</td>
<td>eribulin</td>
<td>mitotane</td>
<td>ramucirumab</td>
<td></td>
</tr>
<tr>
<td>capectabine</td>
<td>estramustine</td>
<td>mitoxantrone</td>
<td>regorafenib</td>
<td></td>
</tr>
<tr>
<td>carbimazole</td>
<td>ethosuximide</td>
<td>mycoplacenolate</td>
<td>rituximab</td>
<td></td>
</tr>
<tr>
<td>carboplatin</td>
<td>etoposide</td>
<td>nelerabine</td>
<td>rituximab</td>
<td></td>
</tr>
<tr>
<td>carfilzomib</td>
<td>everolimus</td>
<td>nilotinib</td>
<td>siltuximab</td>
<td></td>
</tr>
</tbody>
</table>
### Table 16
**Drugs that increase serum potassium**
The following is a list of some drugs that increase serum potassium concentrations (note that this list is not exhaustive). Concurrent use of two or more drugs from this list might increase the risk of hyperkalaemia (hyperkalaemia is particularly notable when ACE inhibitors or angiotensin-II receptor antagonists are given with spironolactone or eplerenone).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>aceclofenac</td>
<td>diclofenac</td>
<td>heparin (unfractionated)</td>
</tr>
<tr>
<td>aliskiren</td>
<td>drosipirenone</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>amiloride</td>
<td>enalapril</td>
<td>imidapril</td>
</tr>
<tr>
<td>azilsartan</td>
<td>enoxaparin</td>
<td>indometacin</td>
</tr>
<tr>
<td>candesartan</td>
<td>eprenone</td>
<td>irbesartan</td>
</tr>
<tr>
<td>captopril</td>
<td>epeptin alfa</td>
<td>ketoprofen</td>
</tr>
<tr>
<td>celecoxib</td>
<td>epeptin beta</td>
<td>ketalolac</td>
</tr>
<tr>
<td>ciclosporin</td>
<td>epeptin zeta</td>
<td>lisinopril</td>
</tr>
<tr>
<td>dalteparin</td>
<td>eprosartan</td>
<td>losartan</td>
</tr>
<tr>
<td>darbepoetin alfa</td>
<td>etodolac</td>
<td>mefenamic acid</td>
</tr>
<tr>
<td>dexibuprofen</td>
<td>etoricoxib</td>
<td>meloxicam</td>
</tr>
<tr>
<td>dexketoprofen</td>
<td>flurbiprofen</td>
<td>nabumetone</td>
</tr>
</tbody>
</table>

### Table 17
**Drugs that reduce serum potassium**
The following is a list of some drugs that reduce serum potassium concentrations (note that this list is not exhaustive and that other drugs can cause hypokalaemia in overdose). Concurrent use of two or more drugs from this list might increase the risk of hypokalaemia. Hypokalaemia can increase the risk of torsade de pointes, which might be additive with the effects of drugs that prolong the QT interval (see table of drugs that prolong the QT interval). Drugs that reduce serum potassium are predicted to increase the risk of digoxin toxicity.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminophylline</td>
<td>bumetanide</td>
<td>furosemide</td>
</tr>
<tr>
<td>amphotericin</td>
<td>chlorothiazide</td>
<td>hydrochlorothiazide</td>
</tr>
<tr>
<td>bambuterol</td>
<td>chlorotaldione</td>
<td>hydrocortisone</td>
</tr>
<tr>
<td>beclometasone</td>
<td>deflazacort</td>
<td>hydroflumethiazide</td>
</tr>
<tr>
<td>bendroflumethiazide</td>
<td>dexamethasone</td>
<td>indacaterol</td>
</tr>
<tr>
<td>betamethasone</td>
<td>fluidcortisone</td>
<td>indapamide</td>
</tr>
<tr>
<td>budesonide</td>
<td>formoterol</td>
<td>methylprednisolone</td>
</tr>
</tbody>
</table>

### Table 18
**Drugs that cause hyponatraemia**
The following is a list of some drugs that reduce sodium concentrations (note that this list is not exhaustive). Concurrent use of two or more drugs from this list might increase the risk of hyponatraemia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>aceclofenac</td>
<td>desmopressin</td>
<td>flurbiprofen</td>
</tr>
<tr>
<td>amiloride</td>
<td>dexibuprofen</td>
<td>fluvoxamine</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>dixibuprofen</td>
<td>furosemide</td>
</tr>
<tr>
<td>bendroflumethiazide</td>
<td>diclofenac</td>
<td>gabapentin</td>
</tr>
<tr>
<td>bumetanide</td>
<td>dosulepin</td>
<td>hydrochlorothiazide</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>doepezin</td>
<td>hydrocortisone</td>
</tr>
<tr>
<td>celecoxib</td>
<td>duloxetine</td>
<td>hydroflumethiazide</td>
</tr>
<tr>
<td>chlorothiazide</td>
<td>epleeronone</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>chlortalidone</td>
<td>escitalopram</td>
<td>imipramine</td>
</tr>
<tr>
<td>citalopram</td>
<td>etodolac</td>
<td>indapamide</td>
</tr>
<tr>
<td>clomipramine</td>
<td>etoricoxib</td>
<td>indometacin</td>
</tr>
<tr>
<td>dapoxetine</td>
<td>fluoxetine</td>
<td>ketoprofen</td>
</tr>
</tbody>
</table>

### Table 19
**Drugs that cause ototoxicity**
The following is a list of some drugs that cause ototoxicity (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>amikacin</td>
<td>cisplatin</td>
<td>oxaliplatin</td>
</tr>
<tr>
<td>bumetanide</td>
<td>furosemide</td>
<td>streptomyacin</td>
</tr>
<tr>
<td>capreomycin</td>
<td>gentamicin</td>
<td>telavancin</td>
</tr>
<tr>
<td>carboplatin</td>
<td>neomycin</td>
<td>tobramycin</td>
</tr>
</tbody>
</table>

### Table 20
**Drugs with neuromuscular blocking effects**
The following is a list of some drugs with neuromuscular blocking effects (note that this list is not exhaustive). Concurrent use of two or more drugs from the list might increase this risk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>amikacin</td>
<td>botulinum toxin type B</td>
<td>gentamicin</td>
</tr>
<tr>
<td>atracurium</td>
<td>cisatracurium</td>
<td>mivacurium</td>
</tr>
<tr>
<td>botulinum toxin type A</td>
<td>colistimethate</td>
<td>neomycin</td>
</tr>
</tbody>
</table>

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List of drug interactions

The following is an alphabetical list of drugs and their interactions; to avoid excessive cross-referencing each drug or group is listed twice: in the alphabetical list and also against the drug or group with which it interacts.

Abacavir
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to abacavir. Avoid. [Moderate] Theoretical
- HIV-protease inhibitors (tipranavir) slightly decrease the exposure to abacavir. Avoid. [Severe] Study

Abatacept
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with abatacept. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Abatacept is predicted to increase the risk of generalised infection (possibly life-threatening) when given with monoclonal antibodies (golimumab). Avoid. [Severe] Theoretical

Abemaciclib
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to abemaciclib. [Moderate] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to abemaciclib. Avoid. [Severe] Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to abemaciclib. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Aprepitant is predicted to increase the exposure to abemaciclib. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) increase the exposure to abemaciclib. [Moderate] Study
- Cobistat is predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Crizotinib is predicted to increase the exposure to abemaciclib. [Moderate] Study
- Enalapril is predicted to markedly decrease the exposure to abemaciclib. Avoid. [Severe] Study
- Enalapril (tetracycline) is predicted to decrease the efﬁcacy of abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Eprosartan is predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Imatinib is predicted to increase the exposure to abemaciclib. [Moderate] Study
- Macrolides (clarithromycin) are predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Macrolides (erythromycin) are predicted to increase the exposure to abemaciclib. [Moderate] Study
- Mitotane is predicted to markedly decrease the exposure to abemaciclib. Avoid. [Severe] Study
- Netupitant is predicted to increase the exposure to abemaciclib. [Moderate] Study
- Nilotinib is predicted to increase the exposure to abemaciclib. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to abemaciclib. Avoid. [Severe] Study

Abiraterone
- General information Caution with concurrent chemotherapy—safety and efﬁcacy not established.
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to abiraterone. Avoid. [Severe] Study
- Abiraterone is predicted to increase the exposure to beta blockers, selective (metoprolol). [Moderate] Study
- Abiraterone is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to abiraterone. Avoid. [Severe] Study
- Mitotane is predicted to decrease the exposure to abiraterone. Avoid. [Severe] Study
- Rifampicin is predicted to decrease the exposure to abiraterone. Avoid. [Severe] Study

Acarbose → see Table 14 p. 1378 (antidiabetic drugs)
- Acarbose decreases the concentration of digoxin. [Moderate] Study
- HIV-protease inhibitors
- Grapefruit juice
- Enzalutamide
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole)
- Abemaciclib
- Abatacept
- Mitotane
- Netupitant
- Acipollo
- HIV-protease inhibitors
- Antiepileptics
- Abacavir
- TABLE 10 p. 1377 (nephrotoxicity)
- Enalapril
- Imatinib
- Antiarrhythmics (dronedarone)
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole)
- Enalapril (tetracycline)
- Calcium channel blockers (diltiazem, verapamil)
- Imatinib
- Macrolides (clarithromycin)
- Mitotane
- Netupitant
- St John’s Wort
- Abiraterone
- Acarbose → see Table 14 p. 1378 (antidiabetic drugs)
- Acarbose decreases the concentration of digoxin. [Moderate] Study
- HIV-protease inhibitors
- Grapefruit juice
- Enzalutamide
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole)
- Abemaciclib
- Abatacept
- Mitotane
- Netupitant
- Acipollo
- HIV-protease inhibitors
- Antiepileptics
- Abacavir
- TABLE 10 p. 1377 (nephrotoxicity)
Antiepileptics ▶

- **Rifampicin** are predicted to increase the exposure to **agomelatine**. (Moderate) Study

- **Quinolones** are predicted to decrease the exposure to **afatinib**. (Moderate) Study

- **Mexiletine** are predicted to increase the exposure to **agomelatine**. (Moderate) Study

- **HIV-protease inhibitors (ritonavir)** are predicted to decrease the exposure to **agomelatine**. (Moderate) Study

- **Antiepileptics (carbamazepine)** are predicted to decrease the concentration of **albendazole**. (Moderate) Study

**TABLE 15**

<table>
<thead>
<tr>
<th>Adefovir – Aldosterone antagonists</th>
<th>1381</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROUTE-SPECIFIC INFORMATION</strong></td>
<td>Interactions do not generally apply to topical use unless specified.</td>
</tr>
</tbody>
</table>

**Agalsidase**

- **Aminoglycosides** are predicted to decrease the effects of **agalsidase**. Avoid. (Moderate) Theoretical

- **Antiarrhythmics (amiodarone)** are predicted to decrease the effects of **agalsidase**. Avoid. (Moderate) Theoretical

- **Aminoglycosides (chloroquine)** are predicted to decrease the effects of **agalsidase**. Avoid. (Moderate) Theoretical

- **Hydroxychloroquine** is predicted to decrease the effects of **agalsidase**. (Moderate) Theoretical

**Agomelatine** ▶

- **Agomelatine** is predicted to decrease the exposure to **albendazole**. (Moderate) Study

- **H₂ receptor antagonists (cimetidine)** decrease the clearance of **albendazole**. (Moderate) Study

- **HIV-protease inhibitors (ritonavir)** decrease the exposure to **albendazole**. (Moderate) Study

- **Albendazole** slightly decreases the exposure to **levamisole** and **levamisole** moderately decreases the exposure to **albendazole**. (Moderate) Study

**Alcohol (beverage)** ▶

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **anfinsals, azoles (itraconazole, ketoconazole)**. Avoid. (Moderate) Theoretical

- **Alcohol (beverage)** causes serious, potentially fatal, CNS depression when given with **clomethiazole**. Avoid. (Severe) Study ▶ Also see **TABLE 11 p. 1377**

- **Alcohol (beverage)** in those who drink heavily potentially decreases the anticoagulant effect of **coumarins**. (Severe) Study

- **Alcohol (beverage)** (excessive consumption) potentially increases the risk of gastrointestinal side-effects when given with **dimethyl fumarate**. Avoid. (Moderate) Theoretical

- **Alcohol (beverage)** causes an extremely unpleasant systemic reaction when given with **disulfiram**. Avoid for at least 24 hours before and up to 14 days after stopping treatment. (Severe) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **griseofulvin**. (Moderate) Anecdotal

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **levamisole**. (Moderate) Study

- **Alcohol (beverage)** (excessive consumption) potentially increases the risk of lactic acidosis when given with **metformin**. Avoid excessive alcohol consumption. (Moderate) Theoretical

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **metronidazole**. Avoid for at least 48 hours stopping treatment. (Moderate) Study

- **Alcohol (beverage)** causes rapid release of **opioids (hydromorphone, morphine)** (from extended-release preparations). Avoid. (Severe) Study ▶ Also see **TABLE 11 p. 1377**

- **Alcohol (beverage)** in those who drink heavily causes severe liver damage when given with **paracetamol**. (Severe) Study ▶ Also see **TABLE 1 p. 1375**

- **Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical **pimecrolimus**. (Moderate) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **procarbazine**. (Moderate) Anecdotal

- **Alcohol (beverage)** potentially increases the concentration of **retinoids (acitretin)**. Avoid and for 2 months after stopping treatment. (Moderate) Study

- **Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical **tacrolimus**. (Moderate) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **tiadazole**. Avoid for 72 hours stopping treatment. (Moderate) Theoretical

**Alcohol (beverage)** ▶

- **Alcohol (beverage)** causes rapid release of **opioids (hydromorphone, morphine)** (from extended-release preparations). Avoid. (Severe) Study ▶ Also see **TABLE 11 p. 1377**

- **Alcohol (beverage)** causes rapid release of **opioids (hydromorphone, morphine)** (from extended-release preparations). Avoid. (Severe) Study ▶ Also see **TABLE 11 p. 1377**

- **Alcohol (beverage)** causes rapid release of **opioids (hydromorphone, morphine)** (from extended-release preparations). Avoid. (Severe) Study ▶ Also see **TABLE 11 p. 1377**

- **Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical **pimecrolimus**. (Moderate) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **procarbazine**. (Moderate) Anecdotal

- **Alcohol (beverage)** potentially increases the concentration of **retinoids (acitretin)**. Avoid and for 2 months after stopping treatment. (Moderate) Study

- **Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical **tacrolimus**. (Moderate) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with **tiadazole**. Avoid for 72 hours stopping treatment. (Moderate) Theoretical

**Aldosterone antagonists** ▶

- **Aldosterone antagonists** are predicted to increase the exposure to **eplerenone**. Adjust **eplerenone** dose, p. 193. (Severe) Theoretical

- **Aldosterone antagonists (spironolactone)** are predicted to increase the exposure to **eplerenone**. Adjust **eplerenone** dose, p. 193. (Severe) Theoretical

- **Aldosterone antagonists (dronedarone)** are predicted to increase the exposure to **eplerenone**. Adjust **eplerenone** dose, p. 193. (Severe) Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to **eplerenone**. Avoid. (Moderate) Theoretical ▶ Also see **TABLE 18 p. 1379**

- **Antifungals, azoles (fluconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to **eplerenone**. Adjust **eplerenone** dose, p. 193. (Severe) Study

- **Anecdotal**...

**TABLE 16**

<table>
<thead>
<tr>
<th>eplerenone • spironolactone</th>
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</tbody>
</table>
Aldosterone antagonists (continued)

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Busulfan is predicted to decrease the exposure to eplerenone. Avoid or monitor. (Moderate) Study
- Aprepitant is predicted to increase the exposure to eplerenone. Adjust eplerenone dose, p. 193. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to eplerenone. Adjust eplerenone dose, p. 193. (Severe) Study. Also see TABLE 8 p. 1376
- Cobicistat is predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Crizotinib is predicted to increase the exposure to eplerenone. Adjust eplerenone dose, p. 193. (Severe) Study
- Eplerenone very slightly increases the exposure to digoxin. (Mild) Study
- Spironolactone increases the concentration of digoxin. Monitor and adjust dose. (Moderate) Study
- Enalapril is predicted to decrease the exposure to eplerenone. Avoid. (Moderate) Theoretical
- HIV protease inhibitors are predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Imitatinib is predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Eplerenone potentially increases the concentration of lithium. Avoid. (Moderate) Theoretical
- Spironolactone potentially increases the concentration of lithium. (Moderate) Study
- Macrolides (clarithromycin) are predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Macrolides (erythromycin) are predicted to increase the exposure to eplerenone. Adjust eplerenone dose, p. 193. (Severe) Study
- Mitotane is predicted to decrease the exposure to eplerenone. Avoid. (Moderate) Theoretical
- Spironolactone is predicted to decrease the effects of mitotane. Avoid. (Severe) Avoid
- Nilotinib is predicted to increase the exposure to eplerenone. Adjust eplerenone dose, p. 193. (Severe) Study
- Rifampicin is predicted to decrease the exposure to eplerenone. Avoid. (Moderate) Theoretical
- St John’s Wort is predicted to slightly decrease the exposure to eplerenone. Avoid. (Moderate) Study
- Alectinib is predicted to markedly increase the exposure to eplerenone. Avoid. (Severe) Study
- Alimemazine is increased in the concentration of digoxin. Avoid. (Severe) Study
- Alkylating agents
- Anticancer drugs: busulfan is predicted to increase the risk of thromboembolism when given with busulfan. Use with caution and adjust dose. (Moderate) Theoretical
- Avoid. (Severe) Study
- Aliskiren is predicted to markedly increase the exposure to aliskiren. (Moderate) Theoretical
- Calcium channel blockers (verapamil) moderately increase the exposure to aliskiren. [Moderate] Study → Also see TABLE 8 p. 1376
- Calcitriol markedly increases the exposure to aliskiren. Avoid. (Severe) Study → Also see TABLE 16 p. 1379
- Eliglustat is predicted to increase the exposure to aliskiren. Adjust dose. (Moderate) Study
- Grapefruit juice moderately decreases the exposure to aliskiren. Avoid. (Severe) Study
- HIV protease inhibitors (ritonavir, saquinavir) are predicted to increase the exposure to aliskiren. (Moderate) Theoretical
- Lapatinib is predicted to slightly decrease the exposure to aliskiren. (Moderate) Theoretical
- Avoid. (Severe) Study
- Alkylating agents are predicted to increase the exposure to aliskiren. (Moderate) Theoretical
- Aliskiren slightly decreases the exposure to loop diuretics (furosemide). (Moderate) Study → Also see TABLE 8 p. 1376
- Macrolides (azithromycin) are predicted to increase the exposure to aliskiren. (Moderate) Theoretical
- Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to aliskiren. (Moderate) Study
- Mirabegron is predicted to increase the exposure to aliskiren. (Mild) Theoretical
- Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to aliskiren. (Moderate) Study
- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to aliskiren. (Moderate) Study
- Pitolisant is predicted to decrease the exposure to aliskiren. (Mild) Theoretical
- Ranolazine is predicted to increase the exposure to aliskiren. (Moderate) Theoretical
- Rifampicin decreases the exposure to aliskiren. (Moderate) Study
- St John’s Wort decreases the exposure to aliskiren. (Moderate) Study
- Statins (atorvastatin) slightly moderately increase the exposure to aliskiren. (Severe) Study
- Velpatasvir is predicted to increase the exposure to aliskiren. (Severe) Study
- Vemurafenib is predicted to increase the exposure to aliskiren. (Severe) Study
- Also see TABLE 5. p. 1375 (thromboembolism), TABLE 2 p. 1375 (nephrotoxicity), TABLE 5 p. 1375 (thromboembolism)

- Bendamustine • Busulfan • Carmustine • Chlorambucil • Cyclophosphamide • Dacarbazine • Estramustine • Ifosfamide • Lomustine • Melphan • Temozolomide • Thiopeta • Tresufan
- Antacids are predicted to decrease the absorption of estramustine. Avoid. (Moderate) Study
- Antifungals, azoles (itraconazole) are predicted to increase the exposure to cyclophosphamide. (Moderate) Study
- Antifungals, azoles (itraconazole) increase the risk of busulfan toxicity when given with busulfan. Monitor and adjust dose. (Moderate) Study
- Use with caution and adjust dose. (Moderate) Theoretical
- Alitretinoin is predicted to see retinoids
- Alkylating agents → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity), TABLE 5 p. 1375 (thromboembolism)

- Anticancer drugs: busulfan is predicted to increase the risk of thromboembolism when given with busulfan. Use with caution and adjust dose. (Moderate) Theoretical
- Aprepitant is predicted to increase the exposure to ifosfamide. (Severe) Theoretical
- Prophylactic and prophylactic vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with alkylating agents. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- Mitotane is predicted to increase the exposure to ifosfamide. (Severe) Study
- Netupitant very slightly increases the exposure to cyclophosphamide. (Moderate) Study
- Paracetamol is predicted to decrease the clearance of busulfan. (Moderate) Theoretical
- Oral calcium salts decrease the absorption of estramustine. (Severe) Study
- Fosaprepitant is predicted to increase the exposure to ifosfamide. (Severe) Theoretical
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with alkylating agents. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- Metronidazole increases the risk of toxicity when given with busulfan. (Severe) Study
- Netupitant very slightly increases the exposure to cyclophosphamide. (Moderate) Study
- Paracetamol is predicted to decrease the clearance of busulfan. (Moderate) Theoretical

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Alkylating agents – Alprazolam 1383

- Cyclophosphamide (high-dose) increases the risk of toxicity when given with pentostatin. Avoid. (Severe) Anecdotal → Also see TABLE 15 p. 1378 → Also see TABLE 5 p. 1375
- Rolapitant is predicted to increase the exposure to bendamustine. Avoid or monitor. (Moderate) Study
- Cyclophosphamide increases the risk of prolonged neuromuscular blockade when given with suxamethonium. (Moderate) Study

**Allopurinol**

- ACE inhibitors are predicted to increase the risk of hypersensitivity and haematological reactions when given with allopurinol. (Severe) Anecdotal
- Allopurinol potentially increases the risk of haematological toxicity when given with azathioprine. Adjust azathioprine dose. p. 836. (Severe) Study
- Allopurinol is predicted to decrease the effects of capetitabine. Avoid. (Severe) Study
- Allopurinol moderately increases the exposure to didanosine. Avoid. (Severe) Study
- Allopurinol potentially increases the risk of haematological toxicity when given with mercapturine. Adjust mercapturine dose, p. 912. (Severe) Study
- Allopurinol increases the risk of skin rash when given with penicillin (amoxicillin, ampicillin). (Moderate) Study
- Allopurinol is predicted to increase the risk of hyperuricaemia when given with pyrazinamide. (Moderate) Theoretical
- Thiazide diuretics are predicted to increase the risk of hypersensitivity reactions when given with allopurinol. (Severe) Theoretical

**Almotriptan**

→ Also see TABLE 13 p. 1378 (serotonin syndrome)
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) increase the exposure to almotriptan. (Mild) Study
- Cobicistat increases the exposure to almotriptan. (Mild) Study
- Almotriptan is predicted to increase the risk of vasoconstriction when given with ergotamine. Ergotamine should be taken at least 24 hours before or 6 hours after almotriptan. (Severe) Theoretical
- HIV-protease inhibitors increase the exposure to almotriptan. (Mild) Study
- Almotriptan is predicted to increase the exposure to almotriptan. (Mild) Study
- Macrolides (clarithromycin) increase the exposure to almotriptan. (Mild) Study

**Aloilgptin**

→ Also see TABLE 14 p. 1378 (antidiabetic drugs)

**Alpha blockers**

→ Also see TABLE 7 p. 1376 (first-dose hypotension), TABLE 8 p. 1376 (hypotension)
- Alfuzosin - doxazosin - indoramin - prazosin - tamsulosin - terazosin

- Antiarrhythmics (dronedarone) are predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, posaconazole) are predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to doxazosin. (Moderate) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study

- Aprepitant is predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to tamsulosin. (Moderate) Theoretical → Also see TABLE 8 p. 1376
- Cobicistat is predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study
- Cobicistat is predicted to increase the exposure to doxazosin. (Moderate) Study
- Crizotinib is predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- HIV-protease inhibitors are predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study
- HIV-protease inhibitors are predicted to increase the exposure to doxazosin. (Moderate) Study

- Idelalisib is predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study
- Idelalisib is predicted to increase the exposure to doxazosin. (Moderate) Study
- Idelalisib is predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to doxazosin. (Moderate) Study
- Macrolides (erythromycin) are predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Macrolides (clarithromycin) are predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study
- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the effects of indoramini. Avoid. (Severe) Theoretical → Also see TABLE 8 p. 1376
- Netupitant is predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Nilotinib is predicted to increase the exposure to tamsulosin. (Moderate) Theoretical
- Alpha blockers cause significant hypertensive effects when given with phosphodiesterase type-5 inhibitors. Patient should be stabilised on first drug then second drug should be added at the lowest recommended dose. (Severe) Study → Also see TABLE 8 p. 1378
- Ribociclib (high-dose) is predicted to increase the exposure to alfuzosin. Avoid. (Moderate) Theoretical

**Alpha tocopherol**

→ Also see vitamin E substances

**Alpha tocopheryl acetate**

→ Also see vitamin E substances

**Alprazolam**

→ Also see TABLE 11 p. 1377 (CNS depressant effects)
- Antiarhythmics (dronedarone) are predicted to increase the exposure to alprazolam. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to alprazolam. Adjust dose. (Moderate) Theoretical → Also see TABLE 11 p. 1377
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to alprazolam. (Severe) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) moderately increase the exposure to alprazolam. Avoid. (Moderate) Study
- Antifungals, azoles (miconazole) are predicted to increase the exposure to alprazolam. Use with caution and adjust dose. (Moderate) Study
- Aprepitant is predicted to increase the exposure to alprazolam. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to alprazolam. (Severe) Study
- Cobicistat moderately increases the exposure to alprazolam. Avoid. (Moderate) Study
- Crizotinib is predicted to increase the exposure to alprazolam. (Severe) Study
- Enalaprilate is predicted to decrease the exposure to alprazolam. Adjust dose. (Moderate) Theoretical
- Fosaprepitant is predicted to increase the exposure to alprazolam. (Moderate) Study
- HIV-protease inhibitors moderately increase the exposure to alprazolam. Avoid. (Moderate) Study
- Idelalisib moderately increases the exposure to alprazolam. Avoid. (Moderate) Study
- Lomitapide is predicted to increase the exposure to alprazolam. (Severe) Study
- Macrolides (clarithromycin) moderately increase the exposure to alprazolam. Avoid. (Moderate) Study
- Macrolides (erythromycin) are predicted to increase the exposure to alprazolam. (Severe) Study
- Mitotane is predicted to decrease the exposure to alprazolam. Adjust dose. (Moderate) Theoretical
- Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to alprazolam. Monitor and adjust dose. (Moderate) Theoretical
Interactions
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Ataluren
▶ Antifungals, azoles
Amiloride
Amikacin
→ SSRIs
Phenothiazines
▶ Monoamine-oxidase B inhibitors
▶ HIV-protease inhibitors
Amfetamines
Amfetamines
→ Ambrisentan
→ Amantadine
▶ St John
▶ SSRIs
▶ Rifampicin
Alprazolam

Theoretical
is predicted to increase the risk of a hypertensive crisis when given with intravenous
is predicted to increase the risk of nephrotoxicity when given with aminoglycosides. Avoid. [Moderate] Study
Also see TABLE 17 p. 1379 (reduced serum potassium)
Table of Contents
FOOD AND LIFESTYLE
Smoking can increase aminophylline clearance and increased doses of aminophylline are therefore required; dose adjustments are likely to be necessary if smoking started or stopped during treatment.

Aciclovir increases the exposure to aminophylline. Monitor and adjust dose. [Severe] Anecdotal
Aminophylline is predicted to decrease the efficacy of antiarrhythmics (adenosine). Separate administration by 24 hours. [Mild] Theoretical
Antiepileptics (fosphenytoin) are predicted to decrease the exposure to aminophylline. Adjust dose. [Moderate] Study
Antiepileptics (phenobarbital) are predicted to decrease the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
Antiepileptics (primidone) are predicted to increase the clearance of aminophylline. Adjust dose. [Moderate] Theoretical
Beta blockers, non-selective are predicted to increase the risk of bronchospasm when given with aminophylline. Avoid. [Severe] Theoretical
Combined hormonal contraceptives are predicted to increase the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
Aminophylline increases the risk of agitation when given with amfetamines. [Severe] Theoretical
Esketamine is predicted to increase the risk of seizures when given with aminophylline. Avoid. [Severe] Theoretical
H₂ receptor antagonists (cimetidine) increase the concentration of aminophylline. Adjust dose. [Severe] Study
HIV-protease inhibitors (ritonavir) decrease the exposure to aminophylline. Adjust dose. [Moderate] Study
Interferons are predicted to slightly increase the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
Iron chelators (deferasirox) are predicted to increase the exposure to aminophylline. Avoid. [Moderate] Theoretical
Isoniazid is predicted to affect the clearance of aminophylline. [Severe] Theoretical
Leflunomide decreases the exposure to aminophylline. Adjust dose. [Moderate] Study
Aminophylline is predicted to decrease the concentration of lithium. [Moderate] Theoretical
Macrolides (azithromycin) are predicted to increase the exposure to aminophylline. [Moderate] Theoretical
Macrolides (clarithromycin) are predicted to increase the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
Aminophylline is predicted to decrease the exposure to macrolides (erythromycin). Adjust dose. [Severe] Study
Methotrexate is predicted to decrease the clearance of aminophylline. [Moderate] Theoretical
Mexiletine is predicted to increase the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
Monoclonal antibodies (blinatumomab) are predicted to transiently increase the exposure to aminophylline. Monitor and adjust dose. [Moderate] Theoretical
Monoclonal antibodies (carlumab) potentially affect the exposure to aminophylline. Monitor and adjust dose. [Moderate] Theoretical
- Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to aminophylline. Monitor and adjust dose. [Moderate] Theoretical
- Pentoxifylline is predicted to increase the concentration of aminophylline. Use with caution or avoid. [Severe] Theoretical
- Quinolones (ciprofloxacin) are predicted to increase the exposure to aminophylline. Adjust dose. [Moderate] Theoretical
- Rifampicin decreases the exposure to aminophylline. Adjust dose. [Moderate] Study
- Aminophylline is predicted to slightly increase the exposure to aminophylline. Avoid. [Moderate] Theoretical
- Rucaparib is predicted to increase the exposure to aminophylline. Monitor and adjust dose. [Moderate] Study
- SSRIs (fluvoxamine) moderately to markedly increase the exposure to aminophylline. Avoid. [Severe] Study
- ST John’s Wort is predicted to decrease the concentration of aminophylline. [Severe] Theoretical
- Sympathomimetics, vasoconstrictor (ephedrine) increase the risk of side-effects when given with aminophylline. Avoid in children. [Moderate] Study
- Teriflunomide decreases the exposure to aminophylline. Adjust dose. [Moderate] Study
- Valaciclovir is predicted to increase the exposure to aminophylline. [Severe] Anecdotal
- Aminosalicylic acid
  - Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. [Severe] Theoretical
  - Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with dapsone. [Severe] Theoretical
- Amiodarone → see antiarhythmic
- Amsulpride → see TABLE 9 p. 1377 (QT-interval prolongation), TABLE 11 p. 1377 (CNS depressant effects)
- Amisulpride is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- Amisulpride is predicted to decrease the effects of levodopa. Avoid. [Severe] Theoretical
- Amitriptyline → see tricyclic antidepressants
- Amiodipine → see calcium channel blockers
- Amoxicillin → see penicillins
- Amphotericin → see TABLE 2 p. 1275 (nephrotoxicity), TABLE 17 p. 1379 (reduced serum potassium)
- Amphotericin increases the risk of toxicity when given with flucytosine. [Severe] Study
- Micafungin slightly increases the exposure to amphotericin. Avoid or monitor toxicity. [Moderate] Study
- Sodium stibogluconate increases the risk of cardiovascular side-effects when given with amphotericin. Separate administration by 14 days. [Severe] Study
- Ampicillin → see penicillins
- Amsacrine → see TABLE 15 p. 1378 (myelosuppression)
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with amsacrine. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Amsacrine increases the risk of cardiacdepression when given with antiarrhythmics. [Severe] Theoretical → Also see TABLE 11 p. 1377
- Antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical → Also see TABLE 11 p. 1377
- Antiepileptics (phenytoin) are predicted to decrease the exposure to ropivacaine. [Moderate] Theoretical
- Antimalarials (chloroquine, primaquine) are predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- Dapsone is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- HIV- protease inhibitors (ritonavir) are predicted to decrease the exposure to rifampicin. [Moderate] Theoretical
- Leflunomide is predicted to decrease the exposure to ropivacaine. [Moderate] Theoretical
- Metoclopramide is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Avoid. [Severe] Theoretical
- Nitrates are predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Avoid. [Severe] Theoretical
- Nitrofurantoin is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- Paracetamol is predicted to increase the exposure to aminophylline. [Severe] Study
- Sodium nitroprusside is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- SSRIs (fluvoxamine) decrease the clearance of ropivacaine. Avoid prolonged use. [Moderate] Study
- Sulphonamides potentially increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Anecdotal
- Teriflunomide is predicted to decrease the exposure to ropivacaine. [Moderate] Theoretical
- Anagrelide → see TABLE 9 p. 1377 (QT-interval prolongation), TABLE 4 p. 1375 (antiplatelet effects)
- Combined hormonal contraceptives are predicted to increase the exposure to anagrelide. [Moderate] Theoretical
- Mescaline is predicted to increase the exposure to anagrelide. [Moderate] Theoretical
- Quinolones (ciprofloxacin) are predicted to increase the exposure to anagrelide. [Moderate] Theoretical
- SSRIs (fluvoxamine) are predicted to increase the exposure to anagrelide. [Moderate] Theoretical
- Anagrelide is predicted to increase the risk of generalised infection (possibly life-threatening) when given with etanercept. Avoid. [Severe] Theoretical
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with anakinra. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Anakinra is predicted to increase the risk of generalised infection (possibly life-threatening) when given with monoclonal antibodies (golimumab). Avoid. [Severe] Theoretical
- Angiotensin-II receptor antagonists → see TABLE 7 p. 1376 (first-dose hypotension), TABLE 8 p. 1376 (hypotension), TABLE 16 p. 1379 (increased serum potassium)
  - azilsartan - candesartan - eprosartan - irbesartan - losartan - olmesartan - telmisartan - valsartan
- Angiotensin-II receptor antagonists increase the risk of renal impairment when given with aliskiren. Use with caution or avoid aliskiren in selected patients, p. 179. [Severe] Study → Also see TABLE 8 p. 1376 → Also see TABLE 16 p. 1379
- Angiotensin-II receptor antagonists potentially increase the concentration of lithium. Monitor concentration and adjust dose. [Severe] Anecdotal

ROUTE-SPECIFIC INFORMATION
- Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
- Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical
- Antiepileptics (fossphenytoin, phenobarbital, phenytoin, primidone) are predicted to increase the risk of methaemoglobinemia when given with topical prilocaine. Use with caution or avoid. [Severe] Theoretical → Also see TABLE 11 p. 1377
Antacids

Aluminium hydroxide - magnesium carbonate - magnesium trisilicate

**SEPARATION OF ADMINISTRATION** Antacids should preferably not be taken at the same time as other drugs since they might impair absorption. Antacids might damage enteric coatings designed to prevent dissolution in the stomach.

- **Antacids** are predicted to decrease the absorption of alkylating agents (e.g., *estramustine*). Avoid. [Moderate] Study
- **Antacids** decrease the absorption of antiepileptics (e.g., *Gabapentin*). Gabapentin should be taken 2 hours after antacids. [Moderate] Study
- **Antacids** decrease the absorption of antifungals, azoles (e.g., *itraconazole*) (capsule). **Antacids** should be taken 1 hour before or 2 hours after *itraconazole*. [Moderate] Study
- **Antacids** decrease the absorption of antifungals, azoles (e.g., *ketoconazole*). Separate administration by at least 2 hours. [Moderate] Study
- **Antacids** decrease the absorption of aspirin (high-dose). [Moderate] Study
- **Antacids** decrease the exposure to **bictegravir**. Separate administration by at least 2 hours. [Moderate] Study
- **Antacids** decrease the absorption of biphosphonates (e.g., *alendronic acid*). Alendronic acid should be taken at least 30 minutes before antacids. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of biphosphonates (e.g., *ibandronic acid*). Avoid antacids for at least 6 hours before or 1 hour after *ibandronic acid*. [Moderate] Study
- **Antacids** decrease the absorption of biphosphonates (e.g., *risedronate*). Separate administration by at least 2 hours. [Moderate] Study
- **Antacids** decrease the absorption of biphosphonates (e.g., *sodium clodronate*). Avoid antacids for 2 hours before or 1 hour after *sodium clodronate*. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of bosutinib. Bosutinib should be taken at least 12 hours before antacids. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of ceritinib. Separate administration by 2 hours. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of chenodeoxycholic acid. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of cholic acid. Separate administration by 3 hours. [Mild] Study
- **Antacids** are predicted to decrease the absorption of corticosteroids (e.g., *deflazacort*). Separate administration by 2 hours. [Moderate] Study
- **Antacids** decrease the absorption of corticosteroids (e.g., *dexamethasone*). Separate administration by at least 2 hours. [Moderate] Study
- **Aluminium hydroxide** increases the risk of blocked enteral or nasogastric tubes when given with *enteral feeds*. [Moderate] Study
- **Antacids** are predicted to decrease the absorption of *erlotinib*. **Antacids** should be taken 4 hours before or 2 hours after *erlotinib*. (Moderate) Theoretical
- **Antacids** slightly to moderately decrease the exposure to *fibrates* (e.g., *gemfibrozil*). (Moderate) Study
- **Antacids** are predicted to slightly decrease the exposure to *gefitinib*. (Severe) Theoretical
- **Antacids** are predicted to decrease the absorption of HIV-protease inhibitors (e.g., *atazanavir*). Atazanavir should be taken 2 hours before or 1 hour after antacids. (Severe) Theoretical
- **Antacids** are predicted to decrease the absorption of HIV-protease inhibitors (e.g., *tipranavir*). Separate administration by 2 hours. (Moderate) Study
- **Antacids** decrease the absorption of hydroxychloroquine. Separate administration by at least 4 hours. (Moderate) Study
- **Antacids** decrease the absorption of *iron (oral)*. Iron (oral) should be taken 1 hour before or 2 hours after antacids. (Moderate) Study
- **Antacids** decrease the absorption of *nitrofurantoin*. Avoid. (Moderate) Theoretical
- **Antacids** decrease the absorption of nitrofurantoin. Avoid. (Moderate) Theoretical
- **Antacids** are predicted to decrease the absorption of *pazopanib*. Pazopanib should be taken 1 hour before or 2 hours after antacids. (Moderate) Theoretical
- **Antacids** decrease the absorption of *penicillamine*. Separate administration by 2 hours. (Mild) Study
- **Antacids** decrease the absorption of *phenothiazines*. (Moderate) Anecdotal
- **Antacids** increase the risk of metabolic alkalosis when given with *polystyrene sulfonate*. (Severe) Anecdotal
- **Antacids** decrease the absorption of *quinoles*. Quinolones should be taken 2 hours before or 4 hours after antacids. (Moderate) Study
- **Antacids** slightly decrease the exposure to *raltegravir*. Avoid. (Moderate) Study
- **Antacids** decrease the absorption of *rifampicin*. Rifampicin should be taken 1 hour before antacids. (Moderate) Study
- **Antacids** are predicted to decrease the exposure to *rilpivirine*. Antacids should be taken 2 hours before or 4 hours after *rilpivirine*. (Severe) Theoretical
- **Antacids** slightly decrease the exposure to *riociguat*. Antacids should be taken 2 hours before or 1 hour after *riociguat*. (Mild) Study
- **Antacids** moderately decrease the absorption of *statins* (e.g., *rosuvastatin*). Separate administration by 2 hours. (Moderate) Study
- **Antacids** decrease the absorption of *sulpiride*. Separate administration by 2 hours. (Moderate) Study
- **Antacids** decrease the absorption of *tetracyclines*. Separate administration by 2 to 3 hours. (Moderate) Study
- **Antacids** are predicted to decrease the absorption of *thyroid hormones* (e.g., *levothyroxine*). Separate administration by at least 4 hours. (Moderate) Anecdotal
- **Antacids** are predicted to decrease the absorption of *urodeoxycholic acid*. Separate administration by 2 hours. (Moderate) Theoretical
- **Antacids** are predicted to decrease the concentration of *velpatasvir*. Separate administration by 4 hours. (Moderate) Theoretical

**Antazoline** see anti-asthmatics, sedating

**Anthrycines** see TABLE 15 p. 1378 (myelosuppression), TABLE 5 p. 1375 (thromboembolism)
Dronedarone is predicted to increase the exposure to abemaciclib. (Moderate) Study

Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to aflatin. Separate administration is recommended after 12 hours. (Moderate) Study

Amiodarone is predicted to decrease the effects of agalsidase. Avoid. (Moderate) Theoretical

Amiodarone is predicted to increase the exposure to aldosterone antagonists (eplerenone). Adjust eplerenone dose, p. 193. (Severe) Theoretical

Dronedarone is predicted to increase the exposure to aldosterone antagonists (eplerenone). Adjust eplerenone dose, p. 193. (Severe) Study

Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to allekiron. (Severe) Study

Dronedarone is predicted to increase the exposure to alpha blockers (tamsulosin). (Moderate) Theoretical

Dronedarone is predicted to increase the exposure to alprazolam. (Severe) Study

Anaesthetics, local are predicted to increase the risk of cardiovascular side-effects when given with antiarrhythmics. (Severe) Theoretical → Also see TABLE 11 p. 1377

Antiarrhythmics (propafenone) are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, non-selective. Use with caution or avoid. (Severe) Study

Propafenone increases the risk of cardiovascular side-effects when given with beta blockers, non-selective (propranolol). Use with caution or avoid. (Severe) Study
Antiarrhythmics (continued)

- Propafenone is predicted to increase the exposure to beta blockers, non-selective (timolol) and beta blockers, non-selective (timolol) are predicted to increase the risk of cardiodepression when given with propafenone. **(Severe) Anecdotal**

- Antiarrhythmics (amiodarone, diclopyramide, dronedarone, flecainide, lidocaine) are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, selective. Use with caution or avoid. **(Severe) Study** → Also see TABLE 6 p. 1276

- Propafenone is predicted to increase the risk of cardiovascular side-effects when given with beta blockers, selective (acebutolol, atenolol, betaaxolol, bisoprolol, celiprolol, esmolol). Use with caution or avoid. **(Severe) Study**

- Propafenone is predicted to increase the exposure to beta blockers, selective (metoprolol). **(Moderate) Study**

- Dronedarone is predicted to increase the exposure to bosutinib. Avoid or adjust dose. **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- Dronedarone is predicted to increase the exposure to buspirone. Use with caution and adjust dose. **(Moderate) Study**

- Dronedarone is predicted to increase the exposure to cabozantinib. **(Moderate) Theoretical** → Also see TABLE 9 p. 1377

- Caffeine citrate decreases the efficacy of adenosine. Separate administration by 24 hours. **(SEDA) Study**

- Calcium channel blockers (diltiazem, verapamil) increase the exposure to d haze and d lawyers and increase the risk to calcium channel blockers (diltiazem, verapamil). **(Moderate) Study**

- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to propafenone. Monitor and adjust dose. **(Moderate) Study**

- Dronedarone is predicted to increase the risk of cardiodepression when given with calcium channel blockers. **(Severe) Theoretical**

- Dronedarone is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. **(Moderate) Study**

- Amiodarone is predicted to increase the risk of cardiodepression when given with calcium channel blockers (diltiazem, verapamil). Avoid. **(Severe) Theoretical** → Also see TABLE 6 p. 1376

- Disopyramide is predicted to increase the risk of cardiodepression when given with calcium channel blockers (verapamil). **(Severe) Theoretical**

- Dronedarone is predicted to increase the exposure to cariprazine. Avoid. **(Severe) Study**

- Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to ceritinib. **(Moderate) Theoretical** → Also see TABLE 9 p. 1377

- Amiodarone increases the concentration of ciclosporin. Monitor concentration and adjust dose. **(Severe) Study**

- Dronedarone is predicted to increase the concentration of ciclosporin. **(Severe) Study**

- Cobicitaz potentially increases the concentration of antiarrhythmics (amiodarone, disopyramide, flecainide, lidocaine). **(Severe) Theoretical**

- Cobicitaz very markedly increases the exposure to propafenone. Avoid. **(Severe) Study**

- Dronedarone is predicted to increase the exposure to propafenone. Monitor and adjust dose. **(Severe) Study**

- Dronedarone is predicted to increase the exposure to cobimetinib. **(Severe) Theoretical**

- Dronedarone is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. **(Severe) Study**

- Dronedarone is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. **(Moderate) Study**

- Amiodarone increases the anticoagulant effect of coumarins. **(Severe) Study**

- Propafenone increases the anticoagulant effect of coumarins. Monitor INR and adjust dose. **(Moderate) Study**

- Crizotinib is predicted to increase the exposure to propafenone. Monitor and adjust dose. **(Moderate) Study**

- Amiodarone increases the exposure to dabigatran. Adjust dabigatran dose, p. 136. **(Moderate) Study**

- Dronedarone slightly increases the exposure to dabigatran. Avoid. **(Severe) Study**

- Dronedarone is predicted to slightly increase the exposure to darifenacin. **(Moderate) Study**

- Darifenacin is predicted to increase the concentration of flecainide. **(Moderate) Theoretical**

- Dronedarone is predicted to increase the exposure to dasatinib. **(Severe) Study** → Also see TABLE 9 p. 1377

- Antiarrhythmics (amiodarone, dronedarone) are predicted to moderately increase the exposure to digoxin. Monitor and adjust digoxin dose, p. 109. **(Severe) Study** → Also see TABLE 6 p. 1376

- Propafenone increases the concentration of digoxin. Monitor and adjust dose. **(Severe) Study**

- Dipyr idam ole increases the exposure to adenosine. Avoid or adjust dose. **(Severe) Study**

- Dronedarone increases the risk of QT-prolongation when given with domperidone. Avoid. **(Severe) Study**

- Dronedarone is predicted to increase the exposure to dopamine receptor agonists ( bromocriptine). **(Severe) Theoretical**

- Dronedarone is predicted to increase the concentration of dopamine receptor agonists (cabergoline). **(Severe) Anecdotal**

- Dronedarone is predicted to moderately increase the exposure to dutasteride. **(Mild) Study**

- Amiodarone slightly increases the exposure to edoxaban. **(Severe) Study**

- Dronedarone slightly increases the exposure to edoxaban. Adjust edoxaban dose, p. 126. **(Severe) Study**

- Efavirenz is predicted to decrease the exposure to dronedarone. **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- Antiarrhythmics (dronedarone, propafenone) are predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. **(Severe) Study**

- Dronedarone is predicted to moderately increase the exposure to encorafenib. **(Moderate) Study** → Also see TABLE 9 p. 1377

- Enzalutamide is predicted to decrease the exposure to antiarrhythmics (disopyramide, dronedarone). Avoid. **(Severe) Study**

- Enzalutamide is predicted to decrease the efficacy of propafenone. **(Moderate) Study**

- Dronedarone is predicted to increase the risk of ergotism when given with ergometrine. **(Severe) Theoretical**

- Dronedarone is predicted to increase the risk of ergotism when given with ergotamine. **(Severe) Theoretical**

- Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to ergotism. **(Moderate) Theoretical**

- Dronedarone is predicted to increase the concentration of everolimus. Avoid or adjust dose. **(Moderate) Study**

- Dronedarone is predicted to increase the exposure to fostoterodine. Adjust fostoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. **(SEDA) Study**

- Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to fidaxomicin. Avoid. **(Moderate) Study**

- Dronedarone is predicted to increase the exposure to gefitinib. **(Moderate) Theoretical**

- Dronedarone potentially increases the exposure to glecaprevir. **(Moderate) Theoretical**

- Grapefruit juice increases the exposure to amiodarone. Avoid. **(Moderate) Study**

- Grapefruit juice moderately increases the exposure to dronedarone. Avoid. **(Severe) Study**
Grapefruit juice increases the exposure to propafenone. Monitor and adjust dose. Moderate Study

Dronedarone is predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. Moderate Theoretical

H₂ receptor antagonists (cimetidine) increase the exposure to amiodarone. Moderate Study

H₂ receptor antagonists (cimetidine) slightly increase the exposure to flecainide. Monitor and adjust dose. Mild Study

H₂ receptor antagonists (cimetidine) are predicted to increase the exposure to propafenone. Monitor and adjust dose. Moderate Theoretical

HIV-protease inhibitors are predicted to increase the exposure to amiodarone. Avoid. Severe Theoretical

HIV-protease inhibitors are predicted to increase the exposure to disopyramide. Severe Theoretical

HIV-protease inhibitors very markedly increase the exposure to dronedarone. Avoid. Severe Study

HIV-protease inhibitors (ritonavir) are predicted to increase the exposure to flecainide. Avoid or monitor side effects. Severe Theoretical

HIV-protease inhibitors are predicted to increase the exposure to lidoctaine. Avoid. Severe Study

HIV-protease inhibitors are predicted to increase the exposure to amiodarone. Avoid. Moderate Theoretical

Idelalisib is predicted to increase the exposure to ibritunib. Adjust ibritunib dose, p. 983. Theoretical

Dronedarone is predicted to increase the exposure to ibritunib. Adjust ibritunib dose with moderate inhibitors of CYP3A4, p. 983. Study

Idelalisib is predicted to increase the exposure to amiodarone. Avoid. Moderate Theoretical

Idelalisib very markedly increases the exposure to dronedarone. Avoid. Severe Study

Idelalisib is predicted to increase the exposure to propafenone. Monitor and adjust dose. Severe Study

Imatinib is predicted to increase the exposure to propafenone. Monitor and adjust dose. Severe Study

Imatinib is predicted to increase the exposure to propafenone. Monitor and adjust dose. Moderate Study

Dronedarone is predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. Severe Theoretical

Dronedarone is predicted to increase the exposure to ivacator. Adjust ivacator dose, p. 293 or tezacator with ivacator dose, p. 295 dose with moderate inhibitors of CYP3A4. Study

Dronedarone is predicted to increase the exposure to lapatinib. Moderate Study

Leidenivir increases the risk of severe bradycardia or heart block when given with amiodarone. Refer to specialist literature. Severe Anecdotal

Letermovir is predicted to increase the concentration of amiodarone. Moderate Theoretical

Amiodarone is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. Moderate Theoretical

Dronedarone is predicted to increase the exposure to lomitapide. Avoid. Moderate Theoretical

Dronedarone is predicted to increase the exposure to loperamide. Severe Theoretical

Dronedarone is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. Moderate Study

Macrolides (clarithromycin) very markedly increase the exposure to dronedarone. Avoid. Severe Study

Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to lidoctaine. Moderate Theoretical

Macrolides (erythromycin) are predicted to moderately increase the exposure to dronedarone. Avoid. Severe Theoretical

Macrolides (erythromycin) are predicted to increase the exposure to propafenone. Monitor and adjust dose. Moderate Study

Mexitiline increases the risk of torsade de pointes when given with antiarrhythmics. Avoid. Severe Theoretical

Dronedarone is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. Severe Study

Dronedarone is predicted to increase the exposure to midostaurin. Moderate Theoretical

Mitotane is predicted to decrease the exposure to antiarrhythmics (disopyramide, dronedarone). Avoid. Severe Study

Mitotane is predicted to decrease the efficacy of propafenone. Moderate Study

Dronedarone increases the risk of neutropenia when given with monoclonal antibodies (brentuximab vedotin). Monitor and adjust dose. Moderate Study

Dronedarone is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. Moderate Study

Netupitant is predicted to increase the exposure to propafenone. Monitor and adjust dose. Moderate Study

Nevirapine is predicted to decrease the exposure to dronedarone. Severe Theoretical

Nilotinib is predicted to increase the exposure to propafenone. Monitor and adjust dose. Moderate Study

Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to nintedanib. Moderate Study

NSAIDs (celecoxib) are predicted to increase the exposure to antiarrhythmics (flecainide, propafenone). Monitor and adjust dose. Moderate Theoretical

Dronedarone is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. Moderate Theoretical

Dronedarone is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. Moderate Study

Amiodarone is predicted to increase the concentration of opioids (fentanyl). Moderate Theoretical

Dronedarone is predicted to increase the exposure to oxybutynin. Mild Theoretical

Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to panobinostat. Adjust dose. Moderate Theoretical

Dronedarone is predicted to increase the exposure to paxopinib. Moderate Theoretical

Propafenone is predicted to increase the anticoagulant effect of phenindione. Monitor and adjust dose. Moderate Theoretical

Dronedarone is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil). Adjust avanafil dose, p. 812. Moderate Theoretical

Dronedarone is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. Moderate Study

Dronedarone is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). Severe Theoretical

Dronedarone is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (vardenafil). Adjust dose. Moderate Theoretical

Amiodarone is predicted to increase the exposure to piprentasvir. Moderate Theoretical

Dronedarone is predicted to increase the exposure to pimozide. Avoid. Severe Theoretical

Dronedarone is predicted to increase the exposure to guetiapine. Avoid. Moderate Study

Quinolones (ciprofloxacin) slightly increase the exposure to lidocaine. Mild Study

Dronedarone is predicted to increase the exposure to ranolazine. Severe Study

Dronedarone is predicted to increase the exposure to ranolazine. Severe Study

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Antiarrhythmics (continued)

- **Amiodarone** is predicted to increase the exposure to retinoids (all-transretinol). Adjust **all-transretinol** dose, p. 1262. [Moderate] Theoretical
- **Ribocilb** (high-dose) is predicted to increase the exposure to amiodarone. Avoid. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Dronedarone** is predicted to increase the exposure to **amiodarone**. Avoid. [Moderate] Theoretical
- **Rifampicin** is predicted to decrease the efficacy of **propafenone**. [Severe] Theoretical
- **Dronedarone** is predicted to increase the exposure to **rifampicin**. Avoid. [Moderate] Theoretical
- **Amiodarone** is predicted to increase the concentration of sofosbuvir. Avoid. [Moderate] Theoretical
- **Dronedarone** increases the concentration of sirolimus. [Severe] Anecdotal
- **Dronedarone** is predicted to increase the exposure to simvastatin. Adjust dose, p. 482. [Moderate] Theoretical
- **Dronedarone** is predicted to increase the risk of rhabdomyolysis when given with amiodarone. Refer to specialist literature. [Severe] Anecdotal
- **Sofosbuvir** is predicted to increase the risk of severe bradycardia or heart block when given with amiodarone. Refer to specialist literature. [Severe] Anecdotal
- **Dronedarone** is predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. [Moderate] Study
- **Amiodarone** is predicted to increase the exposure to statins (fluvastatin). [Severe] Theoretical
- **Dronedarone** is predicted to increase the exposure to statins (rosuvastatin). Adjust dose. [Severe] Study
- **Dronedarone** increases the risk of rhabdomyolysis when given with statins (simvastatin). Adjust simvastatin dose, p. 205. [Severe] Study
- **Dronedarone** is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. [Severe] Study
- **Amiodarone** is predicted to increase the exposure to sulfonylures. Use with caution and adjust dose. [Moderate] Study
- **Dronedarone** is predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Dronedarone** is predicted to increase the concentration of tacrolimus. [Severe] Anecdotal
- **Dronedarone** is predicted to increase the concentration of tacrolimus. [Severe] Anecdotal
- **Dronedarone** is predicted to increase the concentration of teixobactin. [Severe] Theoretical
- **Dronedarone** is predicted to increase the exposure to tezacafutor. Adjust tezacafutor with vacafoot p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study
- **Theophylline** decreases the efficacy of adenosine. Separate administration by 24 hours. [Mild] Study
- **Amiodarone** is predicted to increase the risk of thyroid dysfunction when given with thyroid hormones. Avoid. [Moderate] Study
- **Amiodarone** is predicted to increase the exposure to ticagrelor. Use with caution or avoid. [Severe] Study
- **Dronedarone** given with a potent CYP3C19 inhibitor is predicted to increase the exposure to tofacitinib. Avoid tofacitinib dose, p. 1105. [Moderate] Study
- **Dronedarone** is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 664. [Moderate] Study
- **Amiodarone** and dronedarone are predicted to increase the exposure to topotecan. [Severe] Study
- **Amiodarone** and dronedarone are predicted to increase the concentration of trametinib. [Moderate] Theoretical
- **Dronedarone** is predicted to increase the exposure to trazodone. [Moderate] Theoretical
- **Dronedarone** is predicted to increase the exposure to tricyclic antidepressants. Avoid. [Severe] Theoretical → Also see TABLE 9 p. 1377
- **Dronedarone** is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. [Moderate] Study
- **Amiodarone** is predicted to increase the concentration of velpatasvir. Avoid or monitor. [Moderate] Theoretical
- **Amiodarone** is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical
- **Dronedarone** is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study
- **Dronedarone** is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical → Also see TABLE 9 p. 1377
- **Dronedarone** is predicted to increase the exposure to donepezil. [Severe] Study
- **Amiodarone** and dronedarone are predicted to increase the exposure to donepezil. [Moderate] Study
- **Dronedarone** is predicted to increase the exposure to donepezil. [Moderate] Study
- **Anticholinesterases, centrally acting** (bradycardia) → see TABLE 9 p. 1376

**donepezil** - **galantamine** - **rivastigmine**

- **Antiarrhythmics** (amiodarone, dronedarone) increase the risk of bradycardia when given with anticholinesterases, centrally acting. [Moderate] Anecdotal → Also see TABLE 6 p. 1376
- **Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to donepezil. [Mild] Study
- **Antifungals**, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study
- **Anticholinesterases, centrally acting** are predicted to increase the risk of bradycardia when given with beta blockers, non-selective. [Moderate] Anecdotal → Also see TABLE 6 p. 1376
- **Anticholinesterases, centrally acting** are predicted to increase the risk of bradycardia when given with beta blockers, selective. [Moderate] Anecdotal → Also see TABLE 6 p. 1376
- **Buproprion** is predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study
- **Calcium channel blockers** (diltiazem, verapamil) increase the risk of bradycardia when given with anticholinesterases, centrally acting. [Moderate] Anecdotal → Also see TABLE 6 p. 1376
- **Cinacalcet** is predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study
- **Cobicistat** is predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study
- **Enzalutamide** is predicted to decrease the exposure to donepezil. [Mild] Study
- **HIV-protease inhibitors** are predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study
- **Idealisib** is predicted to increase the exposure to galantamine. Monitor and adjust dose. [Moderate] Study

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Anticholinesterases, centrally acting – Antiepileptics 1391

- Macrolides (clarithromycin) are predicted to increase the exposure to galantamine. Monitor and adjust dose. (Moderate) Study
- Mitotane is predicted to decrease the exposure to donepezil. (MED) Study
- Anticholinesterases, centrally acting are predicted to decrease the effects of neuromuscular blocking drugs, non-depolarising. (Moderate) Theoretical → Also see TABLE 6 p. 1376
- Rifampicin is predicted to decrease the exposure to donepezil. (MED) Study
- SSRI (fluoxetine, paroxetine) are predicted to increase the exposure to galantamine. Monitor and adjust dose. (Moderate) Study
- Anticholinesterases, centrally acting increase the effects of suxamethonium. (Moderate) Theoretical
- Terbutaline is predicted to increase the exposure to galantamine. Monitor and adjust dose. (Moderate) Study

Antiepileptics → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 18 p. 1379 (hyponatraemia), TABLE 15 p. 1378 (myelosuppression), TABLE 12 p. 1378 (peripheral neuropathy), TABLE 11 p. 1377 (CNS depressant effects)

brivaracetam • carbamazepine • eslicarbazepine • ethosuximide • fosphenytoin • gabapentin • lacosamide • lamotrigine • levetiracetam • oxcarbazepine • paraldehyde • perampanel • phenobarbital • phenytoin • pregabaline • primidone • retigabine • rufinamide • stiripentol • tiagabine • topiramate • valproate • vigabatrin • zonisamide

FOOD AND LIFESTYLE Avoid taking milk, dairy products, carbonated drinks, fruit juices, or caffeine-containing food and drinks at the same time as stiripentol.

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to abacavir. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to abemacil. Avoid. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to abiraterone. Avoid. (Severe) Study
- Acetazolamide potentially increases the risk of toxicity when given with valproate. (Severe) Study
- Acetazolamide potentially increases the risk of overheating and dehydration when given with zonisamide. Avoid in children. (Severe) Theoretical
- Carbamazepine is predicted to decrease the exposure to afatinib. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to apomorphine. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the concentration of albendazole. (Moderate) Study
- Alcohol (beverage) potentially increases the risk of visual disturbances when given with retigabine. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to aldosterone antagonists (epilone). Avoid. (Moderate) Study
- Carbamazepine decreases the exposure to aliskiren. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to alprazolam. Adjust dose. (Moderate) Theoretical → Also see TABLE 11 p. 1377
- Fosphenytoin is predicted to decrease the exposure to aminophylline. Adjust dose. (Moderate) Study
- Phenobarbital is predicted to decrease the exposure to aminophylline. Adjust dose. (Moderate) Theoretical
- Phenytoin decreases the exposure to aminophylline. Adjust dose. (Moderate) Study
- Primidone is predicted to increase the clearance of aminophylline. Adjust dose. (Moderate) Theoretical
- Stiripentol is predicted to increase the exposure to aminophylline. Avoid. (Moderate) Theoretical
- Antiepileptics (fonsphenytoin, phenobarbital, phenytoin, primidone) are predicted to increase the risk of methaemoglobinemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. (Severe) Theoretical → Also see TABLE 11 p. 1377
- Phenytoin is predicted to decrease the exposure to antiepileptics, local (prilocaine). (Moderate) Theoretical
- Antacids decrease the absorption of gabapentin. Gabapentin should be taken 2 hours after antacids. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to antiarrhythmics (disopyramide, dronedarone). Avoid. (Severe) Study
- Antiarrhythmics (amiodarone) are predicted to slightly increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor and adjust dose. (Severe) Study → Also see TABLE 12 p. 1378
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to antiarrhythmics (lidocaine). Avoid. (Severe) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to antiepileptics (propafenone). (Moderate) Study
- Antiepileptics (carbamazepine) decrease the concentration of antiepileptics (brivaracatam). (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) decrease the concentration of antiepileptics (brivaracatam). Adjust lamotrigine dose and monitor carbamazepine concentration, p. 318, p. 311. (Moderate) Study
- Antiepileptics (phenobarbital) affect the concentration of antiepileptics (carbamazepine) and antiepileptics (carbamazepine) increase the concentration of antiepileptics (phenobarbital). Adjust dose. (Moderate) Study
- Antiepileptics (topiramate) increase the risk of carbamazepine toxicity when given with antiepileptics (carbamazepine). (Moderate) Study
- Antiepileptics (stiripentol) increase the concentration of antiepileptics (carbamazepine, phenobarbital). Avoid in Dravet syndrome. (Severe) Study
- Antiepileptics (carbamazepine) slightly decrease the exposure to antiepileptics (eslicarbazepine, oxcarbazepine). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (oxcarbazepine) are predicted to increase the concentration of antiepileptics (fosphenytoin). Monitor concentration and adjust dose. (Moderate) Study
- Antiepileptics (stiripentol) are predicted to increase the concentration of antiepileptics (fosphenytoin). (Severe) Study
- Antiepileptics (carbamazepine) affect the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) decrease the concentration of antiepileptics (carbamazepine). Monitor and adjust dose. (Severe) Study
- Antiepileptics (eslicarbazepine) increase the exposure to antiepileptics (fosprenytoin, phenytoin) and antiepileptics (fosprenytoin, phenytoin) decrease the exposure to antiepileptics (eslicarbazepine). (Moderate) Study
- Antiepileptics (valproate) affect the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) decrease the concentration of antiepileptics (valproate). (Severe) Study
- Antiepileptics (vigabatrin) decrease the concentration of antiepileptics (fossphenytoin, phenytoin). (MGd) Study
- Antiepileptics (fosprenytoin) decrease the concentration of antiepileptics (lamotrigine). Monitor and adjust lamotrigine dose, p. 318. (Moderate) Study
- Antiepileptics (phenobarbital, phenytoin, primidone) decrease the concentration of antiepileptics (lamotrigine). Monitor and adjust lamotrigine dose, p. 318. (Moderate) Study → Also see TABLE 11 p. 1377

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Antiepileptics (continued)

- Antiepileptics (valproate) increase the exposure to antiepileptics (lamotrigine). Adjust lamotrigine dose and monitor rash, p. 318. (Severe) Study
- Antiepileptics (lamotrigine) are predicted to increase the concentration of antiepileptics (oxcarbazepine) and antiepileptics (oxcarbazepine) are predicted to decrease the concentration of antiepileptics (lamotrigine). Monitor side effects and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin) are predicted to decrease the exposure to antiepileptics (perampanel). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (oxcarbazepine) decrease the concentration of antiepileptics (perampanel) and antiepileptics (perampanel) increase the concentration of antiepileptics (oxcarbazepine). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to antiepileptics (perampanel). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (oxcarbazepine) decrease the concentration of antiepileptics (perampanel) and antiepileptics (perampanel) increase the concentration of antiepileptics (oxcarbazepine). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (phenytoin) decrease the concentration of antiepileptics (phenobarbital) and antiepileptics (phenobarbital) affect the concentration of antiepileptics (phenytoin). (Moderate) Study
- Antiepileptics (fosphenytoin) increase the concentration of antiepileptics (phenobarbital) and antiepileptics (phenobarbital, primidone) and antiepileptics (phenobarbital, primidone) affect the concentration of antiepileptics (fosphenytoin). (Moderate) Study
- Antiepileptics (oxcarbazepine) are predicted to increase the concentration of antiepileptics (phenytoin). Monitor concentration and adjust dose. (Moderate) Study
- Antiepileptics (stiripentol) are predicted to increase the concentration of antiepileptics (phenytoin). Avoid in Dravet syndrome. (Severe) Study
- Antiepileptics (primidone) potentially decrease the concentration of antiepileptics (primidone) and antiepileptics (primidone) potentially decrease the concentration of antiepileptics (carbamazepine). Adjust dose. (Moderate) Anecdotal Study
- Antiepileptics (phenytoin) increase the concentration of antiepileptics (primidone) and antiepileptics (primidone) affect the concentration of antiepileptics (phenytoin). (Moderate) Study
- Antiepileptics (stiripentol) are predicted to increase the concentration of antiepileptics (phenytoin). (Moderate) Study
- Antiepileptics (valproate) affect the concentration of antiepileptics (primidone). Monitor and adjust dose. (Severe) Theoretical Study
- Antiepileptics (carbamazepine) slightly increase the clearance of antiepileptics (retigabine). (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) are predicted to slightly increase the clearance of antiepileptics (retigabine). (Moderate) Study
- Antiepileptics (valproate) increase the exposure to antiepileptics (rufinamide). Adjust rufinamide dose, p. 326. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the exposure to antiepileptics (tiagabine). Monitor and adjust tiagabine dose, p. 311. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) decrease the concentration of antiepileptics (topiramate) and antiepileptics (topiramate) increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (phenobarbital, primidone) are predicted to decrease the concentration of antiepileptics (topiramate). (Mild) Study
- Antiepileptics (phenobarbital) decrease the concentration of antiepileptics (valproate) and antiepileptics (valproate) increase the concentration of antiepileptics (phenobarbital). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (topiramate) increase the risk of toxicity when given with antiepileptics (valproate). (Severe) Study
- Antiepileptics (carbamazepine) slightly to moderately decrease the concentration of antiepileptics (zonisamide) and antiepileptics (zonisamide) affect the concentration of antiepileptics (carbamazepine). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) slightly to moderately decrease the concentration of antiepileptics (zonisamide). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (phenobarbital, primidone) are predicted to decrease the concentration of antiepileptics (zonisamide). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (topiramate) are predicted to increase the risk of overheating and dehydration when given with antiepileptics (zonisamide). Avoid in children. (Severe) Theoretical Study
- Antiepileptics (carbamazepine) are predicted to slightly increase the exposure to perampanel. (Mild) Study
- Antiepileptics (szolotone, valproate) increase the risk of phenytoin toxicity when given with carbamazepine. Monitor and adjust dose. (Severe) Anecdotal Study
- Antiepileptics (szolotone, miconazole) increase the risk of phenytoin toxicity when given with fosphenytoin. Monitor and adjust dose. (Severe) Anecdotal Study
- Antiepileptics (szolotone, miconazole) decrease the concentration of antiepileptics (fosphenytoin) and antiepileptics (phenytoin) decrease the concentration of antiepileptics (uremic). Avoid or monitor carbamazepine concentration and adjust dose accordingly, p. 311. (Severe) Theoretical Study
- Antiepileptics (szolotone, miconazole) increase the concentration of antiepileptics (phenytoin, phenytoin). Monitor concentration and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to antiepileptics (phenytoin). (Severe) Study
- Fosphenytoin very markedly decreases the exposure to antiepileptics (azoles). Avoid and for 14 days after stopping fosphenytoin. (Moderate) Study
- Phenobarbital decreases the concentration of antiepileptics, azoles (itraconazole). Avoid and for 14 days after stopping phenobarbital. (Moderate) Study
- Phenytoin very markedly decreases the exposure to antiepileptics, azoles (itraconazole). Avoid and for 14 days after stopping phenytoin. (Moderate) Study
- Primidone is predicted to decrease the concentration of antiepileptics, azoles (itraconazole). (Moderate) Theoretical Study
- Carbamazepine is predicted to decrease the efficacy of antiepileptics, azoles (itraconazole) and antiepileptics, azoles (itraconazole) increase the concentration of carbamazepine. Avoid and adjust dose. (Moderate) Theoretical Study
- Carbamazepine is predicted to decrease the efficacy of antiepileptics, azoles (itraconazole, voriconazole) and antiepileptics, azoles (itraconazole, voriconazole) increase the concentration of carbamazepine. Avoid and adjust dose. (Moderate) Theoretical Study
- Carbamazepine is predicted to decrease the efficacy of antiepileptics, azoles (ketonazole) and antiepileptics, azoles (ketonazole) slightly increase the concentration of carbamazepine. Avoid or monitor carbamazepine concentration and adjust dose accordingly, p. 311. (Moderate) Study
- Carbamazepine is predicted to decrease the concentration of antiepileptics, azoles (ketonazole). Avoid. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) decrease the exposure to antiepileptics, azoles (ketonazole). Avoid. (Moderate) Study
- Primidone is predicted to decrease the concentration of antiepileptics, azoles (ketonazole, posaconazole). Avoid. (Moderate) Study
- Carbamazepine is predicted to decrease the efficacy of antiepileptics, azoles (posaconazole) and antiepileptics, azoles (posaconazole) increase the concentration of carbamazepine. Avoid. (Moderate) Theoretical Study
- Carbamazepine is predicted to decrease the concentration of antiepileptics, azoles (posaconazole). Avoid. (Moderate) Study
- Fosphenytoin decreases the exposure to antiepileptics, azoles (voriconazole) and antiepileptics, azoles (voriconazole) increase
Antiepileptics

Phenytoin decreases the exposure to antifungals, azoles (voriconazole) and antifungals, azoles (voriconazole) increase the exposure to phenytoin. Avoid or adjust voriconazole dose and monitor phenytoin concentration, p. 599. (Moderate) Study

Antiepileptics (phenobarbital, primidone) are predicted to decrease the concentration of antifungals, azoles (voriconazole). Avoid. (Moderate) Theoretical

Antihistamines, sedating (hydroxyzine) potentially increase the risk of overheating and dehydration when given with zonisamide. Avoid in children. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to antimalarials (artemether) (with lumefantrine). Avoid. (Severe) Study

Antimalarials (pyrimethamine) increase the risk of haematological toxicity when given with antiepileptics (phenobarbital, primidone). (Severe) Study

Antimalarials (pyrimethamine) are predicted to increase the risk of toxicitiy when given with antiepileptics (phenobarbital, primidone). (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of antimalarials (piperazine). Avoid. (Moderate) Theoretical

Antiepileptics (carbamazepine, phenobarbital, primidone) potentially increase the risk of toxicity when given with antiepileptics (phenobarbital, primidone). (Unclear) Study

Apalutamide potentially decreases the exposure to valproate. (Med) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) moderately decrease the exposure to apremilast. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to aprepitant. Avoid. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to antipirazole. Adjust antipirazole dose, p. 395. (Moderate) Study. Also see TABLE 1 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to bazedoxifene. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the exposure to bedaquiline. Avoid. (Severe) Study. Also see TABLE 1 p. 1377

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to beta blockers, non-selective (carvedilol, labetalol). (Moderate) Theoretical

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to beta blockers, non-selective (propranolol). (Moderate) Study

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to beta blockers, selective (acetabutol, bisoprolol, metoprolol, nebivolol). (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to bictegravir. Avoid. (Moderate) Study

Oxcarbazepine is predicted to decrease the exposure to bictegravir. Avoid. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) slightly decrease the exposure to bortezomib. Avoid. (Severe) Study. Also see TABLE 12 p. 1378

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) affect the exposure to bosentan. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to very markedly decrease the exposure to bosentan. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to bupropion. (Severe) Study

Valproate increases the exposure to bupropion. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to buspirone. Use with caution and adjust dose. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) moderately decrease the exposure to cabozantinib. Avoid. (Moderate) Study

Antiepileptics (fosphenytoin, phenytoin) are predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. (Moderate) Study

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study

Calcium channel blockers (diltiazem) increase the concentration of carbamazepine and carbamazepine is predicted to decrease the exposure to calcium channel blockers (diltiazem). Monitor concentration and adjust dose. (Severe) Aneodal

Calcium channel blockers (verapamil) increase the concentration of carbamazepine and carbamazepine is predicted to decrease the exposure to calcium channel blockers (verapamil). (Severe) Aneodal

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). Avoid. (Moderate) Study

Calcium channel blockers (diltiazem, verapamil) potentially increase the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to cannabis extract. Avoid. (Severe) Theoretical. Also see TABLE 11 p. 1377

Capcetabine increases the concentration of antiepileptics (fosphenytoin, phenytoin). (Severe) Aneodal

Carbapenems decrease the concentration of valproate. Avoid. (Severe) Aneodal

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to cariprazine. Avoid. (Severe) Theoretical. Also see TABLE 11 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of caspofungin. Adjust caspofungin dose, p. 592. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to cetirizine. Avoid. (Severe) Theoretical

Antiepileptics (phenobarbital, primidone) are predicted to affect the efficacy of chenodeoxycholic acid. Monitor and adjust dose. (Moderate) Theoretical

Antiepileptics (phenobarbital, primidone) decrease the concentration of chloramphenicol. (Moderate) Study

Intravenous chloramphenicol increases the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) affect the concentration of intravenous chloramphenicol. Monitor concentration and adjust dose. (Severe) Study

Chloridiazepoxide affects the concentration of antiepileptics (fosphenytoin, phenytoin). (Severe) Study

Phenobarbital decreases the effects of Cholic acid. Avoid. (Moderate) Study
Antiepileptics (continued)

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the concentration of ciclosporin. [Severe] Study
- Oxcarbazepine decreases the concentration of ciclosporin. [Severe] Anecdotal
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to alter the effects of clobazam. [Moderate] Anecdotal
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to cinacalcet. Monitor and adjust dose. [Moderate] Study
- Carbamazepine is predicted to increase the risk of haematological toxicity when given with oral cladribine. [Moderate] Theoretical
- Clobazam potentially affects the concentration of antiepileptics (fosphenytoin, phenytoin). [Severe] Anecdotal
- Stiripentol increases the concentration of clobazam. [Severe] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the exposure to clozapine. [Moderate] Anecdotal
- Carbamazepine is predicted to increase the risk of myelosuppression when given with clozapine. Avoid. [Severe] Anecdotal
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to cobicistat. Avoid. [Severe] Theoretical
- Oxcarbazepine is predicted to decrease the concentration of cobicistat. [Severe] Theoretical
- Cobicistat is predicted to very slightly increase the exposure to perampanel. [Mild] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to coformycin. Avoid. [Severe] Theoretical
- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rifampicin, topiramate) are predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. [Moderate] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to corticosteroids (fluticasone). [Unknown] Theoretical
- Antiepileptics (fosphenytoin, phenytoin) are predicted to alter the anticoagulant effect of coumarins. [Moderate] Anecdotal
- Antiepileptics (phenobarbital, primidone) decrease the anticoagulant effect of coumarins. Monitor INR and adjust dose. [Moderate] Study
- Carbamazepine decreases the effects of coumarins. Monitor and adjust dose. [Severe] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to crizotinib. Avoid. [Severe] Study
- Carbamazepine is predicted to decrease the exposure to dabigatran. Avoid. [Severe] Study
- Phenytoin is predicted to decrease the exposure to dabigatran. Avoid. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to dabrafenib. Avoid. [Moderate] Theoretical
- Danazol moderately increases the concentration of carbamazepine. Monitor and adjust dose. [Severe] Study
- Antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to increase the risk of methaemoglobinemia when given with dapoxetine. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to darifenacin. [Moderate] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to dasatinib. Avoid. [Severe] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to slightly decrease the exposure to delamanid. Avoid. [Moderate] Study
- Lamotrigine is predicted to increase the risk of hyponatraemia when given with desmopressin. [Severe] Theoretical
- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- Desogestrel is predicted to increase the exposure to lamotrigine. [Moderate] Study
- Diazepam potentially affects the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. [Severe] Study
- Diazoxide decreases the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the effects of diazoxide. Monitor concentration and adjust dose. [Moderate] Anecdotal
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the concentration of digoxin. [Moderate] Anecdotal
- Disulfiram increases the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. [Severe] Study
- Diazoxide is predicted to decrease the exposure to dolasetron. Adjust dose. [Severe] Study
- Oxcarbazepine is predicted to decrease the exposure to dolasetron. Adjust dose. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to dolutegravir. [Severe] Study
- Oxcarbazepine is predicted to decrease the exposure to dolutegravir. Adjust dose. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
- Oxcarbazepine is predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical
- Phenytoin is predicted to decrease the exposure to dolasetron. [Moderate] Theoretical
- Carbamazepine is predicted to decrease the exposure to edoxaban. [Moderate] Study
- Phenytoin is predicted to decrease the exposure to edoxaban. [Moderate] Theoretical
- Antiepileptics (fosphenytoin, phenytoin) slightly decrease the exposure to efavirenz and efavirenz affects the concentration of antiepileptics (fosphenytoin, phenytoin). [Severe] Theoretical
- Carbamazepine slightly decreases the exposure to efavirenz and efavirenz slightly decreases the exposure to carbamazepine. [Severe] Theoretical
- Phenobarbital is predicted to decrease the exposure to efavirenz and efavirenz affects the concentration of phenobarbital. [Severe] Theoretical
- Efavirenz is predicted to affect the efficacy of primidone and primidone is predicted to slightly decrease the exposure to efavirenz. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to elbasvir. Avoid. [Severe] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to eliglustat. Avoid. [Severe] Study
Antiepileptics

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of enzalutamide. Avoid. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to encorafenib. (Severe) Theoretical

Enteral feeds decrease the absorption of phenytoin. (Severe) Study

Enzalutamide is predicted to slightly decrease the exposure to brivaracetam. (Moderate) Theoretical

Enzalutamide is predicted to decrease the exposure to perampanel. Monitor and adjust dose. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the effects of ergotamine. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to erlotinib. Avoid or adjust erlotinib dose, p. 979. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to eslicarbazepine. Avoid or adjust dose. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the efficacy of etosodore. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to etravirine. Avoid. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of everolimus. Avoid or adjust dose. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) moderately decrease the exposure to exemestane. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fosoterodine. Avoid. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fosaprepit. Avoid. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to gefitinib. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to gefitinib. Avoid. (Severe) Study

Antiepileptics (eslicarbazepine, oxcarbazepine) potentially decrease the exposure to glecaprevir. Avoid. (Severe) Study

Valproate potentially opposes the effects of glycerol phenbutyrate. (Moderate) Theoretical

Grapefruit juice slightly increases the exposure to carbamazepine. Monitor and adjust dose. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to grazoprevir. Avoid. (Severe) Study

Antiepileptics (phenobarbital, primidone) decrease the effects of griseofulvin. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Study → Also see TABLE 11 p. 1377

Oxcarbazepine is predicted to decrease the concentration of guanfacine. Monitor and adjust guanfacine dose, p. 352. (Moderate) Theoretical

Guanfacine increases the concentration of valproate. Monitor and adjust dose. (Moderate) Study

H₂ receptor antagonists (cimetidine) transiently increase the concentration of carbamazepine. Monitor concentration and adjust dose. (Moderate) Study

H₂ receptor antagonists (cimetidine) increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the concentration of haloperidol. Adjust dose. (Moderate) Study → Also see TABLE 11 p. 1377

Haloperidol potentially increases the risk of overheating and dehydration when given with zonisamide. Avoid in children. (Severe) Theoretical

HIV-protease inhibitors are predicted to affect the exposure to antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) decrease the concentration of HIV-protease inhibitors. (Severe) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to carbamazepine and carbamazepine is predicted to decrease the exposure to HIV-protease inhibitors. Monitor and adjust dose. (Severe) Theoretical

HIV-protease inhibitors (ritonavir) slightly decrease the exposure to lamotrigine. (Severe) Study

HIV-protease inhibitors are predicted to very slightly increase the exposure to perampanel. (Mild) Study

HIV-protease inhibitors (ritonavir) are predicted to decrease the concentration of valproate. (Severe) Aneotal

Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease the efficacy of etonogestrel. For FSH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) moderately decrease the exposure to exemestane. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fosoterodine. Avoid. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fosaprepit. Avoid. (Moderate) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderate decrease the exposure to gefitinib. Avoid. (Severe) Study

Antiepileptics (eslicarbazepine, oxcarbazepine) potentially decrease the exposure to glecaprevir. Avoid. (Severe) Study

Valproate potentially opposes the effects of glycerol phenbutyrate. (Moderate) Theoretical

Grapefruit juice slightly increases the exposure to carbamazepine. Monitor and adjust dose. (Moderate) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to iron chelators (deferasirox). Monitor serum ferritin and adjust dose. (Moderate) Theoretical

Isoniazid increases the concentration of antiepileptics (fosphenytoin, phenytoin). (Moderate) Study → Also see TABLE 12 p. 1378

Isoniazid markedly increases the concentration of carbamazepine and carbamazepine increases the risk of hepatotoxicity when given with isoniazid. Monitor concentration and adjust dose. (Severe) Study → Also see TABLE 1 p. 1375
Antiepileptics (continued)

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ivabradine. Adjust dose. [Moderate] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to ivacaftor. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Carbamazepine is predicted to decrease the exposure to levetiracetam. [Moderate] Theoretical

- Letermovir is predicted to decrease the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) decrease the effects of levodopa. [Moderate] Study

- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease the effects of levetiracetam. [Severe] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of levodopa. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lomiptadine. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, oxcarbazepine) are predicted to increase the risk of neurotoxicity when given with lithium. [Severe] Anecdotal

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lomiptadine. Monitor and adjust dose. [Moderate] Theoretical

- Antiepileptics (fosphenytoin, phenytoin) decrease the effects of loop diuretics (furosemide). [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to slightly decrease the effects of levofloxacin. [Severe] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to lopinavir. Avoid. [Severe] Study

- Macrolides (clarithromycin) slightly increase the concentration of carbamazepine. Monitor concentration and adjust dose. [Severe] Study

- Macrolides (clarithromycin) are predicted to very slightly increase the exposure to perampanel. [Mild] Study

- Macrolides (erythromycin) markedly increase the concentration of carbamazepine. Monitor concentration and adjust dose. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to maraviroc. Adjust dose. [Severe] Study

- Phenytoin is predicted to decrease the exposure to melatonin. [Moderate] Theoretical

- Phenytoin is predicted to decrease the clearance of methotrexate. [Severe] Anecdotal

- Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to metformin. [Moderate] Study

- Antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the effects of metyrapone. Avoid. [Moderate] Study

- Phenytoin is predicted to increase the clearance of mexiteline. Monitor and adjust dose. [Moderate] Study

- Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to minocycline. [Moderate] Study

- Carbamazepine markedly decreases the exposure to minocycline. Adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to midazolam. Monitor and adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to midostaurin. Avoid. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to mirtazapine. Adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, phenobarbital, primidone) are predicted to decrease the exposure to modafinil. [Mild] Study

- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to modafinil and modafinil is predicted to increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. [Moderate] Theoretical

- Antiepileptics (phenobarbital, primidone) are predicted to increase the effects of monoamine-oxidase A and B inhibitors, irreversible. [Severe] Theoretical

- Carbamazepine is predicted to increase the risk of severe toxic reaction when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. [Severe] Theoretical

- Carbamazepine is predicted to decrease the effects of monoclonal antibodies (brentuximab vedotin). [Severe] Theoretical

- Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to antiepileptics (fosphenytoin, phenytoin). Monitor and adjust dose. [Moderate] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to montelukast. [Mild] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to naloxegol. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to slightly decrease the exposure to nateglinide. [Mild] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to netupitant. Avoid. [Severe] Study

- Carbamazepine is predicted to decrease the effects of (but acute use increases the effects of) neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium). Monitor and adjust dose. [Moderate] Study

- Antiepileptics (fosphenytoin, phenytoin) decrease the effects of (but acute use increases the effects of) neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium). [Moderate] Study

- Nevirapine is predicted to decrease the concentration of antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) and antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of nevirapine. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to nilotinib. Avoid. [Severe] Study

- Carbamazepine is predicted to decrease the exposure to nintedanib. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to nitisinone. Adjust dose. [Moderate] Theoretical

- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease decrease
the efficacy of norethisterone. For FSRH guidance, see
Contraceptives, interactions p. 794. [Severe] Anecdotal

- Carbamazepine potentially decreases the exposure to
valproate. Monitor and adjust dose. [Moderate] Study

- Phenytoin is predicted to decrease the exposure to valproate.
Monitor and adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
olanzapine. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
olanzapine. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
olanzapine. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
olanzapine. Avoid. [Moderate] Study

- Oxybutynin is potentially increased the risk of overheating and
dehydration when given with zonisamide. Avoid in children. [Severe] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
opioids (alfentanil, fentanyl). Monitor and adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
opioids (buprenorphine). Monitor and adjust dose. [Moderate] Study

- Carbamazepine decreases the concentration of opioids
(tramadol). Adjust dose. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
osimertinib. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to moderately decrease
the exposure to ospemifene. [Moderate] Study

- Oxybutynin potentially increases the risk of overheating and
dehydration when given with zonisamide. Avoid in children. [Severe] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
paliperidone. Monitor and adjust dose. [Severe] Study

- Valproate slightly increases the exposure to paliperidone.
Adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
paliperidone. Monitor and adjust dose. [Severe] Study

- Carbamazepine decreases the concentration of opioids
(paracetamol). [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
paracetamol. Avoid. [Moderate] Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
daraprim (with ritonavir and ombitasvir). Avoid. [Severe] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
azithromycin. Avoid. [Severe] Study

- Carbamazepine decreases the concentration of antiepileptics
(phenobarbital, primidone) and antiepileptics (phenobarbital, primidone) decrease the concentration of
antiepileptics (phenobarbital, primidone). [Moderate] Study

- Antiepileptics (phenobarbital, primidone) decrease the concentration of
antiepileptics (phenobarbital, primidone). [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
azithromycin. Adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
rifampicin. Use with caution and adjust dose. [Moderate] Study

- Rifampicin decreases the concentration of antiepileptics
(phenobarbital, primidone). Use with caution and adjust dose. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
rifampicin. Avoid. [Moderate] Study

- Carbamazepine is predicted to decrease the exposure to
rifampicin. Avoid. [Moderate] Study

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure to
rifampicin. Avoid. [Moderate] Study

- Rifampicin markedly increases the clearance of lamotrigine.
Adjust lamotrigine dose, p. 318. [Moderate] Study
Antiepileptics (continued)
- Oxcarbazepine is predicted to decrease the concentration of riipingvirine. Avoid. (Severe) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to riperidone. Adjust dose. (Moderate) Study → Also see TABLE 11 p. 1377
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to rivanoxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to rolipram. Avoid. (Severe) Study
- Rucaparib is predicted to increase the exposure to phenytoin. Monitor and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ruxolitinib. Monitor and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to saxagliptin. (Unknown) Theoretical
- Valproate is predicted to increase the exposure to selexipag. Adjust dose. (Moderate) Study
- Valproate potentially decreases the effects of sodium phenylbutyrate. (Moderate) Anecdotal
- Antiepileptics (fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Carbamazepine is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sorafenib. (Moderate) Theoretical
- SSRIs (fluoxetine, fluvoxamine) are predicted to increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor and adjust dose. (Severe) Anecdotal
- SSRIs (sertraline) potentially increase the risk of toxicity when given with antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Severe) Anecdotal
- Antiepileptics (fosphenytoin, phenytoin) decrease the concentration of SSRIs (paroxetine). (Moderate) Study
- St John's Wort is predicted to decrease the concentration of antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone). Avoid. (Severe) Theoretical
- St John's Wort is predicted to decrease the exposure to brivaracetam. (Moderate) Theoretical
- St John's Wort is predicted to decrease the concentration of carbamazepine. Monitor and adjust dose. (Moderate) Theoretical
- St John's Wort is predicted to decrease the exposure to perampanel. Monitor and adjust dose. (Moderate) Theoretical
- St John's Wort is predicted to decrease the exposure to tiagabine. Avoid. (High) Theoretical
- Antiepileptics (carbamazepine, eslicarbazepine) are predicted to decrease the exposure to statins (atorvastatin). Monitor and adjust dose. (Moderate) Theoretical → Also see TABLE 11 p. 1375
- Antiepileptics (fosphenytoin, phenytoin) potentially decrease the exposure to statins (atorvastatin, simvastatin). (Moderate) Anecdotal
- Carbamazepine moderately decreases the exposure to statins (simvastatin). Monitor and adjust dose. (Severe) Study → Also see TABLE 1 p. 1375
- Eslicarbazepine moderately decreases the exposure to statins (simvastatin). Monitor and adjust dose. (Moderate) Study
- Sulfonamides (sulfadiazine) are predicted to increase the concentration of fosphenytoin. Monitor and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) increase the effects of suxamethonium. (Moderate) Study
- Carbamazepine increases the risk of prolonged neuromuscular blockade when given with suxamethonium. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to taxanes (cabazitaxel, paclitaxel). Avoid. (Severe) Study → Also see TABLE 12 p. 1378
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to taxanes (docetaxel). (Severe) Theoretical → Also see TABLE 12 p. 1378
- Tegafur potentially increases the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Severe) Anecdotal
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of temsirolimus. Avoid. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to tenofovir alafenamide. Avoid. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the exposure to tetracyclines (doxycycline). Monitor and adjust dose. (Moderate) Study → Also see TABLE 1 p. 1375
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to tevacin. (Moderate) Theoretical
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to theophylline. Adjust dose. (Moderate) Study
- Antiepileptics (phenobarbital, primidone) are predicted to increase the clearance of theophylline. Adjust dose. (Moderate) Theoretical
- Carbamazepine potentially increases the clearance of theophylline and theophylline decreases the exposure to carbamazepine. Adjust dose. (Moderate) Anecdotal
- Striperintol is predicted to increase the exposure to theophylline. Avoid. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenytoin) are predicted to increase the risk of hypothyroidism when given with thyroid hormones. (Moderate) Study
- Antiepileptics (phenobarbital, primidone) are predicted to decrease the effects of thyroid hormones. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to ticagrelor. Avoid. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to tizanidine. (Severe) Study
- Antiepileptics (fosphenytoin, phenytoin) moderately decrease the exposure to tofacitinib. Avoid. (Severe) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure...
Antiepileptics

- Oxcarbazepine is predicted to decrease the concentration of voxelaprevir. Avoid. [Severe] Theoretical
- Valproate slightly increases the exposure to zidovudine. [Moderate] Study
- Carbamazepine moderately decreases the exposure to zopiclone. [Moderate] Study
- Carbazatepine (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to zopiclone. [Moderate] Study

Antifungals, azoles

- Since systemic absorption can follow topical application, the possibility of interactions with topical clotrimazole and ketoconazole should be borne in mind.
- In general, clotrimazole interactions relate to multiple-dose treatment.
- The use of carbonated drinks, such as cola, improves itraconazole, ketoconazole and posaconazole bioavailability.
- Interactions of miconazole apply to the oral gel formulation, as a sufficient quantity can be absorbed to cause systemic effects. Systemic absorption from intravaginal and topical formulations might also occur.

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to abemaciclib. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to aldosterone antagonists (eplerenone). Adjust eplerenone dose, p. 193. [Severe] Study
- Itraconazole markedly increases the exposure to aliskiren. Avoid. [Severe] Study
- Ketoconazole moderately increases the exposure to aliskiren. [Moderate] Study
- Itraconazole increases the risk of busulfan toxicity when given with alkylating agents (busulfan). Monitor and adjust dose. [Moderate] Study
- Miconazole is predicted to increase the concentration of alkylating agents (busulfan). Use with caution and adjust dose. [Moderate] Theoretical
- Itraconazole is predicted to increase the exposure to alkylating agents (cyclophosphamide). [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) increase the exposure to almotriptan. [Mild] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to alpha blockers (aluzosin, tamsulosin). Use with caution or avoid. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to alpha blockers (doxazosin). [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to alpha blockers (tamsulosin). [Theoretical]
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to alprazolam. [Severe] Study

Interactions | Appendix 1
Antifungals, azoles (itraconazole, ketoconazole, voriconazole) moderately increase the exposure to alprazolam. Avoid. (Moderate) Study

- Itraconazole is predicted to increase the exposure to alprazolam. Use with caution and adjust dose. (Moderate) Theoretical
- Ketoconazole potentially decreases the exposure to aminoglycosides (tobramycin). (Moderate) Anecdotal
- Ketoconazole decreases the absorption of itraconazole (capsule). Antacids should be taken 1 hour before or 2 hours after itraconazole. (Moderate) Study
- Antacids decrease the absorption of ketoconazole. Separate administration by at least 2 hours. (Moderate) Study
- Ketoconazole is predicted to increase the exposure to antihistamines (disopyramide). Use with caution and adjust dose. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines (disopyramide). Avoid. (Severe) Theoretical
- Posaconazole is predicted to increase the exposure to antihistamines (disopyramide, dronedarone). Avoid. (Severe) Theoretical
- Fluconazole is predicted to increase the exposure to antihistamines (dronedarone). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) very markedly increase the exposure to antihistamines (disopyramide). Avoid or adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine) are predicted to decrease the exposure to antihistamines (carbamazepine). Avoid or adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine), fosphenytoin, phenobarbital, phenytoin, primidone are predicted to decrease the exposure to fluconazole. Avoid. (Severe) Study
- Antiepileptics (fosphenytoin) very markedly decrease the exposure to itraconazole. Avoid and for 14 days after stopping fosphenytoin. (Moderate) Study
- Antiepileptics (fosphenytoin) decrease the exposure to voriconazole and voriconazole increases the exposure to antiepileptics (fosphenytoin). Avoid or adjust voriconazole dose and monitor phenytoin concentration. p. 599, p. 321. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) decrease the exposure to ketocnazole. Avoid. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to posaconazole. Avoid. (Moderate) Study
- Antiepileptics (phenobarbital) decrease the concentration of itraconazole. Avoid and for 14 days after stopping phenobarbital. (Moderate) Study
- Antiepileptics (phenobarbital) are predicted to decrease the concentration of ketoconazole. Avoid. (Moderate) Study
- Antiepileptics (phenobarbital) are predicted to decrease the concentration of posaconazole. Avoid. (Moderate) Study
- Antiepileptics (phenobarbital, primidone) are predicted to decrease the concentration of voriconazole. Avoid. (Moderate) Theoretical
- Antiepileptics (phenytoin) very markedly decrease the exposure to itraconazole. Avoid and for 14 days after stopping phenytoin. (Moderate) Study
- Antiepileptics (phenytoin) decrease the exposure to voriconazole and voriconazole increases the exposure to antiepileptics (phenytoin). Avoid or adjust voriconazole dose and monitor phenytoin concentration. p. 599, p. 321. (Moderate) Study
- Antiepileptics (primidone) are predicted to decrease the concentration of itraconazole. (Moderate) Theoretical
- Miconazole increases the risk of carbamazepine toxicity when given with antiepileptics (carbamazepine). Monitor and adjust dose. (Severe) Anecdotal
- Miconazole increases the risk of phenytoin toxicity when given with antiepileptics (fosphenytoin). Monitor and adjust dose. (Severe) Theoretical
- Fluconazole increases the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine) are predicted to decrease the efficacy of antifungals, azoles (itraconazole, voriconazole) and antifungals, azoles (itraconazole, voriconazole) increase the concentration of antiepileptics (carbamazepine). Avoid or adjust dose. (Moderate) Theoretical → Also see TABLE 9 p. 1377
- Antiepileptics (primidone) are predicted to decrease the concentration of antifungals, azoles (ketocnazole, posaconazole). Avoid. (Moderate) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of carbamazepine (mefloquine). Avoid or monitor side effects. (Severe) Study
- Antifungals, azoles (posaconazole) are predicted to increase the exposure to antifungals, azoles (itraconazole, voriconazole). Avoid. (Severe) Theoretical
- Ketoconazole increases the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid and for 14 days after stopping ketoconazole. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). Avoid. (Severe) Theoretical
Antifungals, azoles – Antifungals, azoles

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to aprepitant. [Moderate] Study

- Fluconazole is predicted to increase the exposure to aprepitant. [Moderate] Theoretical

- Voriconazole is predicted to increase the exposure to isavuconazole. [Moderate] Theoretical

- Posaconazole is predicted to increase the exposure to aprepitant. [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. [Moderate] Study

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to aripiprazole. Avoid or adjust dose. [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Theoretical] Study → Also see TABLE 1 p. 1375 → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Theoretical] Study → Also see TABLE 1 p. 1375 → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to betaxolol. Avoid. [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to beta blockers, non-selective (nadolol). [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to beta, agonists (salmeterol). Avoid. [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bictegravir. Use with caution or avoid. [Moderate] Theoretical

- Posaconazole is predicted to increase the exposure to bictegravir. [Moderate] Theoretical

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) slightly increase the exposure to bortezomib. [Moderate] Study

- Fluconazole is predicted to increase the exposure to bosentan. [Severe] Study

- Bosentan is predicted to decrease the exposure to isavuconazole. Avoid. [Severe] Theoretical

- Itraconazole is predicted to increase the exposure to bosentan. [Moderate] Theoretical

- Ketoconazole moderately increases the exposure to bosentan. [Moderate] Study

- Voriconazole is predicted to increase the exposure to bosentan. Avoid. [Severe] Theoretical

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Study → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bupropion. Adjust dose. [Moderate] Study

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to bupropion. Use with caution and adjust dose. [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bupropion. Adjust bupropion dose, p. 342. [Severe] Study

- Miconazole is predicted to increase the concentration of bupropion. Use with caution and adjust dose. [Moderate] Theoretical

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to cabozantinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) slightly increase the exposure to cabozantinib. [Moderate] Study → Also see TABLE 9 p. 1377

- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to isavuconazole. [Moderate] Theoretical

- Miconazole is predicted to increase the exposure to calcium channel blockers (amlodipine, clevidipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, verapamil). Use with caution and adjust dose. [Moderate] Theoretical

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

- Fluconazole (high-dose) is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). [Moderate] Theoretical

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to calcium channel blockers (lercanidipine). Avoid. [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to cannabis extract. Use with caution and adjust dose. [Moderate] Theoretical

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to cariprazine. Avoid. [Severe] Study

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ceritinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ceritinib. [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to cisapride. [Severe] Theoretical

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to cisapride. Avoid. [Severe] Study

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ciclosporin. [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) increase the concentration of ciclosporin. Monitor and adjust dose. [Severe] Anaesthetic

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. [Moderate] Study

- Fluconazole is predicted to increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. [Moderate] Theoretical

- Miconazole is predicted to increase the exposure to cilostazol. Use with caution and adjust dose. [Moderate] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to cinacalcet. Adjust dose. [Moderate] Study

- Antifungals, azoles (fluconazole, voriconazole) potentially increase the exposure to clomazem. Adjust dose. [Moderate] Theoretical

- Fluconazole is predicted to decrease the efficacy of clopidogrel. Avoid. [Severe] Theoretical

- Voriconazole is predicted to decrease the efficacy of clopidogrel. Avoid. [Severe] Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to cobimetinib. [Moderate] Theoretical

- Cobimetinib is predicted to increase the exposure to antifungals, azoles (fluconazole, isavuconazole). [Moderate] Theoretical

- Cobimetinib is predicted to increase the exposure to antifungals, azoles (itraconazole, ketoconazole). Adjust dose. [Moderate] Theoretical

- Cobimetinib is predicted to increase the exposure to isavuconazole. Avoid or monitor side effects. [Severe] Study

- Cobimetinib is predicted to affect the exposure to voriconazole. Avoid. [Moderate] Theoretical
Antifungals, azoles

- Antifungals, azoles (fluconazole, isavuconazole, miconazole, posaconazole) are predicted to increase the exposure to 
cobimetinib. *Severe* Theoretical  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to 
cobimetinib. Avoid or monitor for toxicity. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to 
colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
colchicine. Avoid potent inhibitors of CYP3A4 or adjust colchicine dose, p. 1120. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
corticosteroids (beclometasone) (risk with beclometasone is likely to be lower than with other corticosteroids). *Moderate* Theoretical  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. *Severe* Study  

- Miconazole is predicted to increase the concentration of 
corticosteroids (methylprednisolone). Monitor and adjust dose. *Moderate* Theoretical  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to 
coumarins. Monitor INR and adjust dose. *Moderate* Study  

- Fluconazole increases the anticoagulant effect of 
coumarins. Monitor INR and adjust dose. *Moderate* Study  

- Itraconazole potentially increases the anticoagulant effect of 
coumarins (warfarin). Monitor INR and adjust dose. *Severe* Anecdotal  

- Ketoconazole potentially increases the anticoagulant effect of 
coumarins (warfarin). Monitor INR and adjust dose. *Severe* Anecdotal  

- Miconazole greatly increases the anticoagulant effect of 
coumarins. MHRA advises avoid unless INR can be monitored closely; monitor for signs of bleeding. *Severe* Study  

- Voriconazole increases the anticoagulant effect of 
coumarins. Monitor INR and adjust dose. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
c绝. Avoid. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderate increase the exposure to 
crizotinib. Avoid. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
dabigatran. Avoid. *Severe* Study  

- Isovucnazol is predicted to increase the exposure to 
dabigatran. Avoid. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
dabrafenib. Use with caution or avoid. *Moderate* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to slightly increase the exposure to 
darifenacin. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly to very markedly increase the exposure to 
darifenacin. Avoid. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to 
dasatinib. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to 
dasatinib. Avoid or adjust dose—consult product literature. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) very slightly increase the exposure to 
delamanid. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) moderately increase the exposure to 
diazepam. Monitor and adjust dose. *Moderate* Study  

- Didanosine (buffered) decreases the exposure to antifungals, azoles (itraconazole, ketoconazole). Separate administration by 2 hours. *Severe* Study  

- Isovucnazol slightly increases the exposure to 
digoxin. Monitor and adjust dose. *Moderate* Study  

- Itraconazole is predicted to markedly increase the concentration of 
digoxin. Monitor and adjust dose. *Severe* Study  

- Ketoconazole is predicted to markedly increase the concentration of 
digoxin. *Severe* Study  

- Isovucnazol is predicted to increase the concentration of 
digoxin. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole) increase the risk of QT-prolongation when given with 
domperidone. Avoid. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to 
dopamine receptor agonists (bromocriptine). *Severe* Theoretical  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) increase the exposure to dopamine receptor agonists (bromocriptine). *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole) are predicted to increase the concentration of dopamine receptor agonists (cabergoline). *Moderate* Anecdotal  

- Isovucnazol is predicted to increase the exposure to 
dopamine receptor agonists (pramipexole). Adjust dose. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
doravirine. *Mild* Study  

- Ketoconazole moderately increases the exposure to 
drospirenone. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to moderately increase the exposure to 
dutasteride. *Mild* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
dutasteride. Monitor side effects and adjust dose. *Moderate* Theoretical  

- Itraconazole is predicted to slightly increase the exposure to 
edoxaban. *Severe* Theoretical  

- Ketoconazole slightly increases the exposure to 
edoxaban. Adjust edoxaban dose, p. 126. *Severe* Study  

- Efavirenz is predicted to decrease the exposure to 
isavuconazole. Avoid. *Severe* Theoretical  

- Efavirenz slightly decreases the exposure to 
itraconazole. Avoid and for 14 days after stopping efavirenz. *Moderate* Study  

- Efavirenz moderately decreases the exposure to ketoconazole. *Severe* Study  

- Efavirenz slightly decreases the exposure to posaconazole. Avoid. *Severe* Study  

- Efavirenz moderately decreases the exposure to 
voriconazole and voriconazole slightly increases the exposure to efavirenz. Adjust dose. *Severe* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to 
eliglustat. Avoid or adjust dose—consult product literature. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to moderately increase the exposure to 
encorafenib. *Moderate* Study  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to 
encorafenib. Avoid or monitor. *Severe* Study  

- Enalapril is predicted to decrease the exposure to 
isavuconazole. Avoid. *Severe* Study  

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the risk of ergotism when given with 
ergomine. *Severe* Theoretical  

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with 
ergomine. Avoid. *Severe* Theoretical  

- Miconazole is predicted to increase the exposure to 
ergomine. Avoid. *Moderate* Theoretical
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the risk of ergotism when given with ergotamine. **(Severe) Theoretical**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergotamine. **(Avoid) (Severe) Theoretical**

- Posaconazole is predicted to increase the exposure to ergotamine. **(Avoid) (Moderate) Theoretical**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to erlotinib. Use with caution and adjust dose. **(Moderate) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to erlotinib. **(Moderate) Theoretical**

- Posaconazole is predicted to increase the concentration of HIV-protease inhibitors. Use with caution and adjust dose. **(Moderate) Theoretical**

- Posaconazole is predicted to increase the exposure to HIV-protease inhibitors. **(Moderate) Study**

- HIV-protease inhibitors are predicted to affect the exposure to voriconazole and posaconazole potentially affects the exposure to HIV-protease inhibitors. **(Severe) Study** → Also see TABLE 9 p. 1377

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ibrutinib. Adjust ibritunib dose with moderate inhibitors of CYP3A4, p. 983. **(Severe) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to very markedly increase the exposure to ibritunib. Avoid potent inhibitors of CYP3A4 or adjust ibritunib dose, p. 983. **(Severe) Study**

- Idealisib is predicted to increase the exposure to isavuconazole. Avoid or monitor side effects. **(Severe) Study**

- Antifungals, azoles (fluconazole, posaconazole) are predicted to increase the exposure to imatinib. **(Moderate) Theoretical**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to isavuconazole and posaconazole. **(Moderate) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to imatinib. **(Moderate) Study**

- Imatinib is predicted to decrease the exposure to isavuconazole. **(Moderate) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. **(Severe) Theoretical**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 with moderate inhibitors of CYP3A4. **(Severe) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 with potent inhibitors of CYP3A4. **(Severe) Study**

- Lanthanum is predicted to decrease the absorption of ketoconazole. Separate administration by at least 2 hours. **(Severe) Theoretical**

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to lapatinib. **(Moderate) Study** → Also see TABLE 9 p. 1377

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to lapatinib. **(Moderate) Study** → Also see TABLE 9 p. 1377

- Letemovir slightly decreases the exposure to voriconazole. **(Moderate) Study**

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to lomitapide. **(Avoid) (Moderate) Theoretical** → Also see TABLE 1 p. 1375

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to lomitapide. **(Avoid) (Severe) Study** → Also see TABLE 1 p. 1375

- Clotrimazole is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. **(Moderate) Theoretical**

- Lumacaftor is predicted to decrease the exposure to antifungals, azoles (itraconazole, ketoconazole, posaconazole, voriconazole). Avoid or monitor efficacy. **(Moderate) Theoretical**

- Lumacaftor is predicted to decrease the exposure to fluconazole. Adjust dose. **(Slid) Theoretical**

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. **(Moderate) Study**

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to lurasidone. **(Avoid) (Severe) Study**

- Posaconazole moderately increases the exposure to lurasidone. **(Avoid) (Severe) Study**
Antifungals, azoles (continued)

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to macitentan. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to fluconazole. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to posaconazole. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to maraviroc. Adjust dose. [Severe] Study
- Macrolides (erythromycin) are predicted to increase the exposure to fluconazole. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to maraviroc. Adjust dose. [Severe] Study
- Miconazole is predicted to increase the exposure to intravenous midazolam. Use with caution and adjust dose. [Moderate] Theoretical
- Miconazole is predicted to increase the exposure to oral midazolam. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to midostaurin. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to voriconazole. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to isavuconazole. [Severe] Study
- Mitotane is predicted to decrease the exposure to isavuconazole. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mirtazapine. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mycophenolate. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to naldixicol. Adjust naldixicol dose and monitor side effects, p. 66. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to netupitant. [Moderate] Study
- Nevirapine is predicted to decrease the exposure to isavuconazole. Avoid. [Severe] Theoretical
- Nevirapine is predicted to decrease the exposure to isavuconazole. Avoid and for 14 days after stopping nevirapine. [Moderate] Study
- Nevirapine moderately decreases the exposure to ketoconazole. Avoid. [Severe] Study
- Nevirapine is predicted to decrease the exposure to voriconazole and voriconazole increases the exposure to nevirapine. Monitor and adjust dose. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to nilotinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to nilotinib. Avoid. [Severe] Study → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to nitidazolam. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to nitisine. Adjust dose. [Moderate] Theoretical
- Fluconazole moderately increases the exposure to NSAIDs. (celecoxib). Adjust celecoxib dose, p. 1132. [Moderate] Study
- Voriconazole slightly increases the exposure to NSAIDs (diclofenac). Monitor and adjust dose. [Moderate] Study
- Voriconazole moderately increases the exposure to NSAIDs. (ibuprofen). Adjust dose. [Moderate] Study
- Fluconazole increases the exposure to NSAIDs. (parecoxib). Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. [Moderate] Study
- Miconazole is predicted to increase the exposure to opioids (alfentanil). Use with caution and adjust dose. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to opioids (methadone). Adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to opioids (methadone, sufentanil). [Moderate] Theoretical → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to osimertinib. Avoid. [Severe] Study
- Fluconazole increases the exposure to osimertinib. Adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxycodone. Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxycodone. Monitor and adjust dose. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxfendazole. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxybutynin. [Mild] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxybutynin. [Mild] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxymorphone. Adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to paritaprevir. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to paritaprevir. Avoid or adjust paritaprevir dose, p. 992. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Study → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to pazopanib. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to pazopanib. Avoid or adjust pazopanib dose, p. 993. [Moderate] Study → Also see TABLE 9 p. 1377
Antifungals, azoles

Miconazole greatly increases the anticoagulant effect of phenindione. [Severe] Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil). Adjust avanafil dose, p. 812. [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study → Also see TABLE 9 p. 1377

Miconazole is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Use with caution and adjust dose. [Severe] Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to pimozide. Avoid. [Severe] Theoretical → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to pimozide. Avoid. [Severe] Study → Also see TABLE 9 p. 1377

Miconazole is predicted to increase the exposure to pimozide. Avoid. [Moderate] Theoretical

Pirogallol theoretically decreases the exposure to isavuconazole. Use with caution. [Theoretical]

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately decrease the exposure to piziquamol. [Bolt] Study

Proton pump inhibitors decrease the absorption of itraconazole. Administer itraconazole capsules with an acidic beverage, p. 597. [Moderate] Study

Proton pump inhibitors decrease the absorption of ketoconazole. Administer ketoconazole with an acidic beverage, p. 681. [Moderate] Study

Proton pump inhibitors decrease the absorption of posaconazole (oral suspension). Avoid. [Moderate] Study

Voriconazole increases the exposure to proton pump inhibitors (esomeprazole, omeprazole). Adjust dose. [Moderate] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to quetiapine. Avoid. [Moderate] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to quetiapine. Avoid. [Severe] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ranolazine. [Severe] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ranolazine. Avoid. [Severe] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole, posaconazole) are predicted to increase the exposure to reboxetine. Avoid. [Moderate] Study

Miconazole is predicted to increase the concentration of reboxetine. Use with caution and adjust dose. [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to regorafenib. Avoid. [Moderate] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to repaglinide. [Moderate] Study

Antifungals, azoles (fluconazole, itraconazole, ketoconazole, miconazole, voriconazole) are predicted to increase the exposure to retinooids (alfatretinoin). Adjust alfatretinoin dose, p. 1362. [Moderate] Theoretical

Antifungals, azoles (fluconazole, ketoconazole, voriconazole) are predicted to increase the risk of tretinoin toxicity when given with retinooids (tretinoin). [Moderate] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, posaconazole) increase the concentration of rifabutin and rifabutin decreases the concentration of antifungals, azoles (itraconazole, posaconazole). Avoid. [Severe] Study

Fluconazole increases the risk of uveitis when given with rifabutin. Adjust dose. [Severe] Study

Rifabutin is predicted to decrease the exposure to isavuconazole. Avoid. [Severe] Theoretical

Ketoconazole is predicted to decrease the concentration of rifabutin and rifabutin is predicted to decrease the concentration of ketoconazole. Avoid. [Severe] Theoretical

Miconazole is predicted to increase the concentration of rifabutin. Use with caution and adjust dose. [Moderate] Theoretical

Rifabutin decreases the concentration of voriconazole and voriconazole increases the concentration of rifabutin. Avoid or adjust voriconazole dose, p. 599. [Severe] Study

Rifampicin slightly decreases the exposure to fluconazole. Adjust dose. [Moderate] Study

Rifampicin is predicted to decrease the exposure to isavuconazole. Avoid. [Severe] Study

Rifampicin markedly decreases the exposure to itraconazole. Avoid and for 14 days after stopping rifampicin. [Moderate] Study

Rifampicin markedly decreases the exposure to ketoconazole and ketoconazole potentially decreases the exposure to rifampicin. Avoid. [Moderate] Study

Rifampicin is predicted to decrease the exposure to posaconazole. Avoid. [Moderate] Anecdotal

Rifampicin very markedly decreases the exposure to voriconazole. Avoid. [Moderate] Study

Itraconazole is predicted to increase the exposure to riociguat. Avoid. [Moderate] Study

Ketoconazole theoretically increases the exposure to riociguat. Avoid. [Moderate] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to risperidone. Adjust dose. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole) are predicted to moderately increase the exposure to rivaroxaban. Avoid. [Severe] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ruoxolitinib. [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ruoxolitinib. Adjust dose and monitor side effects. [Moderate] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to saxagliptin. [Mild] Study

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Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of sirolimus. Monitor and adjust dose. (Severe) Study

Miconazole is predicted to increase the concentration of sirolimus. Monitor and adjust dose. ( Moderate) Study

Oral sodium bicarbonate decreases the absorption of ketoconazole. ( Moderate) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. ( Severe) Study

Voriconazole is predicted to increase the exposure to SSRIs (citalopram). (Severe) Theoretical also see TABLE 9 p. 1377

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to SSRIs (dapoxetine). Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. ( Moderate) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to SSRIs (dapoxetine). Avoid potent inhibitors of CYP3A4 or adjust dapoxetine dose, p. 821. ( Severe) Study

St John's Wort is predicted to decrease the exposure to isavuconazole. Avoid. ( Severe) Theoretical

St John's Wort moderately decreases the exposure to voriconazole. Avoid. (Moderate) Study

Miconazole potentially increases the exposure to statins (atorvastatin). (Severe) Aneuradial

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. (Severe) Study also see TABLE 1 p. 1375

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to statins (atorvastatin). Avoid or adjust dose and monitor rhabdomyolysis. ( Severe) Study also see TABLE 1 p. 1375

Antifungals, azoles (fluconazole, miconazole) are predicted to increase the exposure to statins (fluvasatin). ( Severe) Theoretical also see TABLE 1 p. 1375

Isavuconazole is predicted to increase the exposure to statins (fluvasatin, rosuvastatin). ( Moderate) Theoretical

Miconazole is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. (Severe) Study also see TABLE 1 p. 1375

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to statins (simvastatin). Avoid. (Severe) Study also see TABLE 1 p. 1375

Isavuconazole is predicted to increase the exposure to sulfasalazine. ( Moderate) Theoretical

Antifungals, azoles (fluconazole, miconazole) are predicted to increase the exposure to sulfonyleurases. Use with caution and adjust dose. ( Moderate) Study

Voriconazole is predicted to increase the concentration of sulfonyleurases. Use with caution and adjust dose. ( Moderate) Theoretical also see TABLE 9 p. 1377

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to sunitinib. ( Moderate) Theoretical also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. ( Moderate) Study also see TABLE 9 p. 1377

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the concentration of tacrolimus. (Severe) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of taxanes (docetaxel). Use with caution and adjust dose. (Moderate) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to taxanes (docetaxel). Avoid or adjust dose. (Severe) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to taxanes (paclitaxel). ( Severe) Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the concentration of temsirolimus. ( Moderate) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of temsirolimus. Avoid. (Severe) Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. ( Severe) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. ( Severe) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) given with a potent CYP2C19 inhibitor are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. ( Moderate) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to tofarodine. (Mega) Theoretical also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 669. ( Moderate) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with potent inhibitors of CYP3A4, p. 669. (Severe) Study

Antifungals, azoles (itraconazole, ketoconazole) are predicted to increase the exposure to topotecan. (Severe) Study

Isavuconazole is predicted to increase the exposure to topotecan. ( Moderate) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to toremifene. ( Moderate) Theoretical also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to trabectedin. Avoid or adjust dose. (Severe) Theoretical also see TABLE 1 p. 1375

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of trametinib. ( Moderate) Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to trazodone. ( Moderate) Theoretical

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Antifungals, azoles – Antihistamines, non-sedating

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to **trazodone**. Avoid or adjust dose. [Moderate] Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to **ulipristal**. Avoid if used for uterine fibroids. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **ulipristal**. Avoid if used for uterine fibroids. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **venoferanib**. [Severe] Theoretical
  - Also see Table 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **venoferanib**. [Moderate] Study
  - Also see Table 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **vinca alkaloids**. Use with caution and adjust dose. [Moderate] Theoretical
- Antifungals, azoles (clofazimine, ketoconazole) are predicted to decrease the exposure to **vitamin D substances** (calciferol). [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **vitamin D substances** (paricalcitol). [Moderate] Study
- Fluconazole slightly increases the exposure to **zidovudine**. [Moderate] Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to **zopiclone**. Adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to **zopiclone**. Adjust dose. [Severe] Theoretical
  - Also see Table 9 p. 1377
  - Also see Table I p. 1375
- **Antihistamines, non-sedating** [see Table 9 p. 1377 (QT-interval prolongation)]
  - acrivastine, azelastine, bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine, rupatadine
  - Since systemic absorption can follow topical application, the possibility of interactions with topical azelastine should be borne in mind.
  - Apple juice and orange juice decrease the exposure to fexofenadine.
- **Antacids** decrease the absorption of fexofenadine. Separate administration by 2 hours. [Mild] Study
- **Antiarrhythmics** (dronedarone) are predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Antiarrhythmics** (dronedarone) are predicted to increase the exposure to antihistamines, non-sedating (fexofenadine, mizolastine). [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Aprepitant** is predicted to increase the exposure to mizolastine. [Severe] Theoretical
- **Aprepitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to mizolastine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
  - Also see Table 9 p. 1377
- **Aprepitant** is predicted to increase the exposure to mizolastine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to mizolastine. Avoid. [Moderate] Study
  - Also see Table 9 p. 1377
- **Aprepitant** is predicted to increase the exposure to mizolastine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to mizolastine. Avoid. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Antihistamines, non-sedating** are predicted to decrease the effects of betahistine. [Moderate] Theoretical
- **Calcium channel blockers** (diltiazem, verapamil) are predicted to increase the exposure to mizolastine. [Severe] Theoretical
- **Calcium channel blockers** (diltiazem, verapamil) are predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Ceritinib** is predicted to increase the exposure to fexofenadine. [Moderate] Theoretical
- **Cobicistat** is predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Cobicistat** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Crizotinib** is predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Crizotinib** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Eliglustat** is predicted to increase the exposure to fexofenadine. Adjust dose. [Moderate] Study
- **Grapefruit juice** slightly decreases the exposure to bilastine. Bilastine should be taken 1 hour before or 2 hours after grapefruit juice. [Moderate] Study
- **Grapefruit juice** increases the exposure to rupatadine. Avoid. [Moderate] Study
- **HIV-protease inhibitors** are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **HIV-protease inhibitors** are predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Idelalisib** is predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Idelalisib** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Lapatinib** is predicted to increase the exposure to fexofenadine. [Moderate] Theoretical
- **Leflunomide** is predicted to increase the concentration of fexofenadine. [Moderate] Study
- **Letermovir** is predicted to increase the concentration of fexofenadine. [Moderate] Theoretical
- **Macrolides** (clarithromycin) are predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Macrolides** (clarithromycin, erythromycin) are predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Macrolides** (erythromycin) are predicted to increase the exposure to mizolastine. [Severe] Theoretical
- **Mirabegron** is predicted to increase the exposure to fexofenadine. [Mild] Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of antimuscarinic side-effects when given with antihistamines, non-sedating. Avoid. [Severe] Theoretical
- **Netupitant** is predicted to increase the exposure to mizolastine. [Severe] Theoretical
- **Netupitant** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to mizolastine. Avoid. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to rupatadine. Avoid. [Moderate] Study
- **Pibrentasvir** (with glecaprevir) is predicted to increase the exposure to fexofenadine. [Mild] Study
- **Pitolisant** is predicted to decrease the exposure to fexofenadine. [Mild] Theoretical
- **Rifampicin** is predicted to decrease the exposure to bilastine. [Moderate] Theoretical
- **Rifampicin** increases the clearance of fexofenadine. [Moderate] Study
- **Teriflunomide** is predicted to increase the exposure to fexofenadine. [Moderate] Study
- **Velpatasvir** is predicted to increase the exposure to fexofenadine. [Moderate] Study
- **Venoclax** is predicted to increase the exposure to fexofenadine. [Moderate] Theoretical
Antihistamines, sedating – Antimalarials

### General Information

**Antimalarials**
- **Mefloquine**
- **Pyrimethamine**
- **Antifungals, azoles**
- **Ciproheptadine**
- **Cyproheptadine**
- **Antihistamines, sedating**
- **Hydroxyzine**
- **Monoamine-oxidase A and B inhibitors, irreversible**
- **Antiepileptics**
- **Antiarrhythmics**
- **HIV-protease inhibitors**
- **Efavirenz**
- **H2 receptor antagonists**
- **Efavirenz**
- **Grapefruit juice**
- **Proguanil**
- **Quinine**
- **Digoxin**
- **Imatinib**
- **Aprepitant**
- **Mefloquine**
- **Chloroquine**
- **Piperaquine**

**ROUTE-SPECIFIC INFORMATION**

- Since systemic absorption can follow topical application of **ketotifen**, the possibility of interactions should be borne in mind.

- **Hydroxyzine** potentially increases the risk of overheating and dehydration when given with **antiepileptics (zonisamide)**.
- **Antihistamines, sedating** predicted to decrease the effects of **betahistine**.
- **Cyproheptadine** decreases the effects of **meprapone**.
- **Monoamine oxidase A and B inhibitors, reversible** are predicted to increase the risk of antimuscarinic side-effects when given with **antihistamines, sedating**.
- **Antihistamines, sedating** predicted to decrease the efficacy of **pitolisant**.
- **Cyproheptadine** potentially decreases the effects of **SSRIs**.
- **Antimalarials**
  - **Betahistine**
  - **Mefloquine**
  - **Pyrimethamine**

**PHARMACOLOGY**

**Piperaquine** has a long half-life; there is a potential for drug interaction to occur for up to 3 months after treatment has been stopped.

- **Chloroquine** is predicted to decrease the effects of **agalsidase**.
- **Antimalarials (chloroquine, primaquine)** are predicted to increase the risk of methaemoglobinemia when given with topical **anaesthetics, local (prilocaine)**.
- **Antacids** decrease the absorption of **chloroquine**.
- **Antacids** are predicted to decrease the absorption of **proguanil**.
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to **artemether** (with lumefantrine).
- **Antiepileptics (carbamazepine, phenobarbital, phenytoin, primidone)** are predicted to decrease the concentration of **piperaquine**.
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the concentration of **piperaquine**.
- **Antiepileptics** (**carbamazepine, phenobarbital, primidone**) are predicted to increase the risk of toxicity when given with **quinine**.
- **Pyrimethamine** increases the risk of haematological toxicity when given with **antiepileptics (fosphenytoin, phenytoin)**.
- **Pyrimethamine** is predicted to increase the risk of haematological toxicity when given with **antiepileptics (phenobarbital, primidone)**.
- **Antifungals, azoles** (**fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole**) are predicted to increase the concentration of **piperaquine**.
- **Antifungals, azoles** (**fluconazole, itraconazole, posaconazole, voriconazole**) are predicted to increase the exposure to **mefloquine**.
- **Antifungals, azoles** (**ketoconazole**) increase the exposure to **mefloquine**.
- **Antimalarials (proguanil)** are predicted to increase the risk of side-effects when given with antimalarials (**pyrimethamine**).

**Aprepitant** is predicted to increase the concentration of **piperaquine**.
- **Mefloquine** is predicted to increase the risk of bradycardia when given with **beta blockers, non-selective**.
- **Mefloquine** is predicted to increase the risk of bradycardia when given with **calcium channel blockers**.
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the concentration of **piperaquine**.
- **Calcium salts (calcium carbonate)** decrease the absorption of **chloroquine**.
- **Chloroquine** decreases the efficacy of oral **cholera vaccine**.
- **Cyproheptadine** is predicted to increase the concentration of **piperaquine**.
- **Crizotinib** is predicted to increase the concentration of **piperaquine**.
- **Antimalarials (chloroquine, primaquine)** are predicted to increase the risk of methaemoglobinemia when given with **dapsone**.
- **Mefloquine** is predicted to increase the risk of bradycardia when given with **digoxin**.
- **Quinine** increases the concentration of **digoxin**.
- **Piperaquine** is predicted to decrease the effects of **SSRIs**.
- **Chloroquine** increases the risk of **haematological toxicity** when given with **calcium channel blockers**.
- **Digoxin** is predicted to increase the risk of **haematological toxicity** when given with **calcium channel blockers**.
- **Imatinib** is predicted to increase the concentration of **piperaquine**.
- **Perfluorooctane sulfonate** decreases the effects of **SSRIs**.
- **Efavirenz** decreases the concentration of **artemether**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Enzalutamide** is predicted to decrease the exposure to **artemether** (with lumefantrine).
- **Efavirenz** is predicted to decrease the concentration of **piperaquine**.
- **HIV-protease inhibitors** are predicted to decrease the concentration of **piperaquine**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Grapefruit juice** increases the exposure to **artemether**.
- **Grapefruit juice** is predicted to increase the concentration of **piperaquine**.
- **HIV-protease inhibitors** are predicted to increase the concentration of **piperaquine**.
- **HIV-protease inhibitors** are predicted to decrease the exposure to **proguanil**.
- **HIV-protease inhibitors** are predicted to affect the exposure to **quinine**.
- **HIV-protease inhibitors** are predicted to decrease the exposure to **atovaquone**.
- **Efavirenz** decreases the exposure to **artemether**.
- **Grapefruit juice** increases the exposure to **artemether**.
- **Grapefruit juice** is predicted to increase the concentration of **piperaquine**.
- **Imatinib** is predicted to increase the concentration of **piperaquine**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **artemether**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
- **Efavirenz** decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **proguanil**.
- **Efavirenz** decreases the exposure to **quinine**.
- **Efavirenz** slightly increases the exposure to **quinine**.
- **Efavirenz** moderately decreases the exposure to **atovaquone**.
- **Efavirenz** affects the exposure to **artemether**.
Metoclopramide decreases the concentration of atovaquone.
Avoid. [Moderate] Study

Mitotane is predicted to decrease the exposure to artemether (with lumefantrine). Avoid. [Severe] Study

Mitotane is predicted to decrease the concentration of piperacillin. Avoid. [Moderate] Theoretical

Netupitant is predicted to increase the concentration of piperacillin. [Severe] Theoretical

Pyrimethamine is predicted to increase the risk of side-effects when given with metoprolol. [Severe] Theoretical — Also see TABLE 15 p. 1378

Chloroquine is predicted to increase the risk of haematological toxicity when given with fenoprofen. Avoid. [Severe] Theoretical

Chloroquine decreases the efficacy of rabies vaccine. Avoid. [Moderate] Study

Rifabutin slightly decreases the exposure to atovaquone. Avoid. [Moderate] Study

Rifampicin is predicted to decrease the exposure to artemether (with lumefantrine). Avoid. [Severe] Study

Rifampicin moderately decreases the exposure to atovaquone and artemether. Avoid or monitor. [Moderate] Study

Rifampicin moderately decreases the exposure to mefloquine. [Severe] Study

Rifampicin is predicted to decrease the concentration of piperacillin. Avoid. [Moderate] Theoretical

Rifampicin decreases the exposure to quinine. [Severe] Study

St John’s Wort is predicted to decrease the concentration of piperacillin. Avoid. [Moderate] Theoretical

Pyrimethamine increases the risk of side-effects when given with sulphonamides. [Severe] Study — Also see TABLE 15 p. 1378

Tetracyclines (tetracycline) decrease the concentration of atovaquone. [Moderate] Study

Pyrimethamine increases the risk of side-effects when given with trimethoprim. [Severe] Study

Pyrimethamine is predicted to increase the risk of side-effects when given with zidovudine. [Severe] Theoretical — Also see TABLE 15 p. 1378

Antithymocyte immunoglobulin (rabbit) — see TABLE 9 p. 1377 (QT-interval prolongation)

Apalutamide is predicted to decrease the exposure to aldosterone antagonists (epilone). Avoid or monitor. [Moderate] Study

Apalutamide potentially decreases the exposure to antiepileptics (valproate). [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to apalutamide. [Hill] Study — Also see TABLE 9 p. 1377

Apalutamide slightly decreases the exposure to antihistamines, non-sedating (fenofenadine). [Hill] Study

Apalutamide is predicted to decrease the exposure to beta-blockers (salmetrol). Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to bosutinib. Avoid or monitor. [Moderate] Study — Also see TABLE 9 p. 1377

Apalutamide is predicted to decrease the exposure to buspirone. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to calcium channel blockers (felodipine, lercanidipine). Avoid or monitor. [Moderate] Study

Clodigorel is predicted to increase the exposure to apalutamide. [Hill] Study

Cobicistat is predicted to increase the exposure to apalutamide. [Hill] Study

Apalutamide is predicted to decrease the exposure to colchicine. [Hill] Study

Apalutamide is predicted to decrease the exposure to corticosteroids (budesonide, fluticasone). Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to coumarins. Avoid or monitor. [Hill] Study

Apalutamide is predicted to decrease the exposure to dabigatran. [Hill] Study

Apalutamide is predicted to decrease the exposure to darifenacin. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to dasatinib. Avoid or monitor. [Moderate] Study — Also see TABLE 9 p. 1377

Apalutamide is predicted to decrease the exposure to diazepam. Avoid or monitor. [Hill] Study

Apalutamide is predicted to decrease the exposure to digoxin. [Hill] Study

Apalutamide is predicted to decrease the exposure to everolimus. Avoid or monitor. [Moderate] Study

Fibrates (gemfibrozil) are predicted to increase the exposure to apalutamide. [Hill] Study

HIV-protease inhibitors are predicted to increase the exposure to apalutamide. [Hill] Study — Also see TABLE 9 p. 1377

Iadolisib is predicted to increase the exposure to apalutamide. [Hill] Study

Apalutamide is predicted to decrease the exposure to ivacaftor. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to lomitapide. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to maraviroc. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to methotrexate. [Hill] Study

Apalutamide markedly decreases the exposure to midazolam. Avoid or monitor. [Severe] Study

Apalutamide is predicted to decrease the exposure to moclobemide. Avoid or monitor. [Hill] Study

Apalutamide is predicted to decrease the exposure to naloxegol. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to opioids (alfentanil). Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, sildenafil, vardenafil). Avoid or monitor. [Moderate] Study — Also see TABLE 9 p. 1377

Apalutamide is predicted to decrease the exposure to proton pump inhibitors (lansoprazole, rabeprazole). Avoid or monitor. [Hill] Study

Apalutamide markedly decreases the exposure to proton pump inhibitors (omeprazole). Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to quetiapine. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to sirolimus. Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to SSRIs (citalopram). Avoid or monitor. [Hill] Study — Also see TABLE 9 p. 1377

Apalutamide slightly decreases the exposure to statins (rosuvastatin). [Hill] Study

Apalutamide is predicted to decrease the exposure to statins (simvastatin). Avoid or monitor. [Moderate] Study

Apalutamide is predicted to decrease the exposure to tensirolimus. Avoid or monitor. [Moderate] Study

Apalutamide potentially decreases the exposure to thyroid hormones (levothyroxine). [Hill] Theoretical

Apalutamide is predicted to decrease the exposure to ticagrelor. Monitor and adjust dose. [Moderate] Study

Apalutamide is predicted to decrease the exposure to tolvaptan. Avoid or monitor. [Moderate] Study

Apixaban — see TABLE 3 p. 1375 (anticoagulant effects)

Antihyperglycemics (dronedarone) are predicted to increase the exposure to apixaban. [Moderate] Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease
Apixaban (continued)

the exposure to apixaban. Use with caution or avoid. **Severe** Study

- **Antifungals, azoles (itraconazole)** are predicted to increase the exposure to apixaban. **Avoid.** **Severe** Study
- **Antifungals, azoles (ketoconazole)** slightly to moderately increase the exposure to apixaban. **Avoid.** **Severe** Study
- **Antifungals, azoles (voriconazole)** are predicted to increase the exposure to apixaban. **Avoid.** **Moderate** Theoretical
- **Calcium channel blockers (verapamil)** are predicted to increase the exposure to apixaban. **Moderate** Theoretical
- **Cobicistat** is predicted to increase the exposure to apixaban. **Avoid.** **Severe** Theoretical

**Enzalutamide** is predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. **Severe** Study

**Macrolides (erythromycin)** are predicted to increase the exposure to apixaban. **Moderate** Theoretical

**Mitotane** is predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. **Severe** Study

**Rifampicin** is predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. **Severe** Study

**St John’s Wort** is predicted to decrease the exposure to apixaban. Use with caution or avoid. **Severe** Study

Aprepitant is predicted to increase the exposure to apixaban. **Avoid.** **Severe** Theoretical

**Apixaban** (continued)

Aprepitant is predicted to increase the exposure to antifungals, azoles (isavuconazole). **Moderate** Theoretical

Aprepitant is predicted to increase the exposure to antihistamines, non-selecting (mizolastine). **Severe** Theoretical

Aprepitant is predicted to increase the exposure to antihistamines, non-selecting (rupatadine). **Avoid.** **Moderate** Study

Aprepitant is predicted to increase the concentration of antimalarials (piperaquine). **Severe** Theoretical

Aprepitant is predicted to increase the exposure to axitinib. **Moderate** Theoretical

Aprepitant is predicted to increase the exposure to bedaquiline. Avoid prolonged use. **Mild** Theoretical

Aprepitant is predicted to increase the exposure to beta; agonists (salbutamol). **Moderate** Study

Bosentan is predicted to decrease the exposure to apreiptan. **Moderate** Study

Aprepitant is predicted to increase the exposure to bosutinib. **Avoid or adjust dose.** **Severe** Theoretical

Aprepitant is predicted to increase the exposure to buspirone. Use with caution and adjust dose. **Moderate** Study

Aprepitant is predicted to increase the exposure to cabozantinib. **Avoid.** **Moderate** Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to apreiptan and apreiptan is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). **Avoid.** **Mild** Study

Aprepitant is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. **Avoid.** **Moderate** Study

Aprepitant is predicted to increase the exposure to cariprazine. **Avoid.** **Severe** Study

Aprepitant is predicted to increase the exposure to ceritinib. **Avoid.** **Moderate** Theoretical

Aprepitant is predicted to increase the concentration of ciclosporin. **Avoid.** **Severe** Study

Cobicistat is predicted to markedly increase the exposure to apreiptan. **Avoid.** **Moderate** Study

Cobicistat is predicted to increase the exposure to cobimetinib. **Avoid.** **Severe** Theoretical

Aprepitant is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. **Severe** Study

Aprepitant is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Study

Aprepitant is predicted to increase the exposure to oral corticosteroids (budesonide). **Avoid.** **Moderate** Study

Aprepitant moderately increases the exposure to corticosteroids (dexamethasone). Monitor and adjust dose. **Avoid.** **Moderate** Study

Aprepitant is predicted to increase the exposure to corticosteroids (fluticasone). **Avoid.** **Moderate** Study

Aprepitant is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. **Avoid.** **Moderate** Study

Aprepitant decreases the anticoagulant effect of coumarins. **Avoid.** **Severe** Study

Aprepitant is predicted to slightly increase the exposure to darifenacin. **Avoid.** **Severe** Study

Aprepitant is predicted to increase the exposure to dasatinib. **Avoid.** **Severe** Study

Aprepitant is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Theoretical

Aprepitant increases the risk of QT-prolongation when given with domperidone. **Avoid.** **Severe** Study

Aprepitant is predicted to increase the exposure to dopamine receptor agonists (bromocriptine). **Severe** Theoretical

Aprepitant is predicted to increase the concentration of dopamine receptor agonists (cabergoline). **Avoid.** **Severe** Study

Aprepitant is predicted to moderately increase the exposure to dutasteride. **Mild** Study

Efavirenz is predicted to decrease the exposure to apreiptan. **Avoid.** **Moderate** Study
Aprepitant is predicted to increase the exposure to eletriptan. Avoid or adjust dose—consult product literature. [Severe] Study

Aprepitant is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Aprepitant is predicted to moderately increase the exposure to encorafenib. [Moderate] Study

Enzalutamide is predicted to markedly decrease the exposure to aprepitant. Avoid. [Moderate] Study

Aprepitant is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical

Aprepitant is predicted to increase the risk of ergotism when given with ergonovine. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to ergotamine. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to erlotinib. [Moderate] Study

Aprepitant is predicted to decrease the efficacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Moderate] Study

Aprepitant is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study

Aprepitant is predicted to increase the exposure to fosoterodine. Adjust fosoterodine dose with moderate inhibitors of CYP3A4. [Moderate] Study

Aprepitant is predicted to increase the exposure to fexofenadine. Adjust fexofenadine dose, p. 352. [Moderate] Theoretical

HIV-protease inhibitors are predicted to markedly increase the exposure to aprepitant. [Moderate] Study

Aprepitant is predicted to decrease the effects of hormone replacement therapy. [Moderate] Anecdotal

Aprepitant is predicted to increase the exposure to ibritinib. Adjust ibritinib dose with moderate inhibitors of CYP3A4, p. 813. [Severe] Study

Idealixib is predicted to markedly increase the exposure to aprepitant. [Moderate] Study

Aprepitant is predicted to increase the exposure to imatinib. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to intravenous irinotecan. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study

Aprepitant is predicted to increase the exposure to lapatinib. [Moderate] Study

Aprepitant is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to lomitapide. Avoid. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to luridinsone. Adjust luridinsone dose, p. 396. [Moderate] Study

Macrolides (clarithromycin) are predicted to markedly increase the exposure to aprepitant. [Moderate] Study

Macrolides (erythromycin) are predicted to increase the exposure to aprepitant. [Moderate] Study

Aprepitant is predicted to increase the exposure to maraviroc. [Moderate] Study

Aprepitant is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. [Severe] Study

Aprepitant is predicted to increase the exposure to midostaurin. [Moderate] Theoretical

Mitotane is predicted to markedly decrease the exposure to aprepitant. Avoid. [Moderate] Study

Aprepitant is predicted to increase the exposure to nalorexol. Adjust nalorexol dose and monitor side effects, p. 65. [Moderate] Study

Nevirapine is predicted to decrease the exposure to aprepitant. [Moderate] Study

Aprepitant is predicted to increase the exposure to nilotinib. [Moderate] Theoretical

Aprepitant is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Aprepitant is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. [Moderate] Study

Aprepitant is predicted to increase the exposure to opioids (methadone, sufentanil). [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to oxybutynin. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to pimozide. Avoid. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to quetiapine. Avoid. [Moderate] Study

Aprepitant is predicted to increase the exposure to ranolazine. [Severe] Study

Aprepitant is predicted to increase the exposure to ribociclib. [Moderate] Study

Rifampicin is predicted to markedly decrease the exposure to aprepitant. Avoid. [Moderate] Study

Aprepitant is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to saxagliptin. [Moderate] Study

Aprepitant increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study

Aprepitant is predicted to increase the exposure to SSRIs (dapoxetine). Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 812. [Moderate] Study

St John’s Wort is predicted to decrease the exposure to aprepitant. Avoid. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. [Severe] Study

Aprepitant is predicted to increase the exposure to statins (simvastatin). Use with caution and simvastatin dose, p. 205. [Severe] Study

Aprepitant is predicted to increase the exposure to sunitinib. [Moderate] Theoretical

Aprepitant is predicted to increase the concentration of tacrolimus. [Severe] Study

Aprepitant is predicted to increase the exposure to taxanes (cabazitaxel). [Moderate] Theoretical

Aprepitant is predicted to increase the concentration of temsirolimus. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study

Aprepitant given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1005. [Moderate] Study

Aprepitant is predicted to increase the exposure to tolterodine. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 669. [Moderate] Study

Aprepitant is predicted to increase the exposure to trazodone. [Moderate] Theoretical

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Aprepitant (continued)

▶ Aprepitant decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe)

Anecdotal

▶ Aprepitant is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Severe) Study

▶ Aprepitant is predicted to increase the exposure to vinca alkaloids. (Severe) Theoretical

▶ Aprepitant is predicted to increase the exposure to zopiclone. (Moderate) Study

Argatroban → see TABLE 3 p. 1375 (anticoagulant effects)

▶ Ranibizumab is predicted to increase the risk of bleeding events when given with argatroban. (Severe) Theoretical

Aripiprazole → see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressive effects)

▶ Antidepressants (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study → Also see TABLE 11 p. 1377

▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study

▶ Bupropion is predicted to moderately increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study

▶ Cinacalcet is predicted to moderately increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study

▶ Cocistat is predicted to slightly increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study

▶ Aripiprazole is predicted to decrease the effects of dopamine receptor antagonists. (Moderate) Theoretical → Also see TABLE 8 p. 1376

▶ Enalapril is predicted to moderately decrease the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study

▶ Aripiprazole is predicted to increase the risk of cardiovascular side-effects when given with tannic acid (deferiprone). (Severe) Theoretical

▶ Ascorbic acid is predicted to increase the risk of cardiovascular side-effects when given with iron chelators (desferrioxamine). (Severe) Theoretical

▶ Ascorbic acid is predicted to increase the risk of cardiovascular side-effects when given with iron chelators. (Severe) Theoretical

▶ Ascorbic acid is predicted to increase the effects of levodopa. Adjust dose. (Severe) Theoretical → Also see TABLE 8 p. 1376

▶ Asparaginase → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 15 p. 1378 (myelosuppression)

▶ Asparaginase is predicted to increase the risk of hepatotoxicity when given with imatinib. (Severe) Theoretical → Also see TABLE 15 p. 1378

▶ Asparaginase affects the efficacy of methotrexate. (Severe)

Anecdotal → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378

▶ Asparaginase potentially increases the risk of neurotoxicity when given with vinca alkaloids (vincristine). Vincristine should be taken 5 to 24 hours before asparaginase, p. 933. (Severe)

Anecdotal → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378

Aspirin → see 4 p. 1375 (antiplatelet effects)

▶ Acetazolamide increases the risk of severe toxic reaction when given with aspirin (high-dose). (Severe) Study

▶ Antacids decreases the absorption of aspirin (high-dose). (Moderate) Study

▶ Aspirin (high-dose) is predicted to increase the risk of gastrointestinal irritation when given with bisphosphonates (alendronic acid, ibandronic acid). (Moderate) Study

▶ Aspirin (high-dose) is predicted to increase the risk of gastrointestinal irritation when given with corticosteroids. (Moderate) Study

▶ Aspirin (high-dose) increases the risk of renal impairment when given with bisphosphonates (sodium clodronate). (Severe) Theoretical

▶ Corticosteroids are predicted to decrease the concentration of aspirin (high-dose) and aspirin (high-dose) increases the risk of gastrointestinal bleeding when given with corticosteroids. (Moderate) Study

▶ Aspirin (high-dose) increases the risk of renal impairment when given with dapomycin. (Moderate) Theoretical

▶ Erlotinib is predicted to increase the risk of gastrointestinal perforation when given with aspirin (high-dose). (Severe) Theoretical

▶ Aspirin (high-dose) is predicted to increase the risk of gastrointestinal bleeds when given with iron chelators (deferasirox). (Severe) Theoretical

▶ Aspirin (high-dose) is predicted to increase the risk of toxicity when given with methotrexate. (Severe) Study

▶ Aspirin is predicted to increase the risk of gastrointestinal perforation when given with nicorandil. (Severe) Theoretical

▶ Aspirin (high-dose) potentially increases the exposure to pemetrexed. Use with caution or avoid. (Severe) Theoretical

▶ Aspirin (high-dose) increases the risk of acute renal failure when given with thiazide diuretics. (Severe) Theoretical

▶ Zidovudine increases the risk of haematological toxicity when given with aspirin (high-dose). (Severe) Study

Aralen

▶ Aralen is predicted to increase the risk of nephrotoxicity when given with intravenous aminoglycosides. Avoid. (Severe) Study

▶ Rifampicin decreases the exposure to aralen. (Moderate) Study

Azithromycin → see HIV-protease inhibitors

Atenolol → see beta blockers, selective

Atexozilumab → see monoclonal antibodies

Atomoxetine

▶ Amphetamines are predicted to increase the risk of side-effects when given with atomoxetine. (Severe) Theoretical

▶ Atomoxetine is predicted to increase the risk of cardiovascular side-effects when given with beta agonists (high-dose). (Moderate) Study

▶ Bupropion is predicted to markedly increase the exposure to atomoxetine. Adjust dose. (Severe) Study

▶ Cinacalcet is predicted to markedly increase the exposure to atomoxetine. Adjust dose. (Severe) Study

▶ Eliglustat is predicted to increase the exposure to atomoxetine. Adjust dose. (Moderate) Theoretical

▶ Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of side-effects when given with atomoxetine. Avoid and for 2 weeks after stopping the MAOI. (Severe) Theoretical

▶ Panobasinostat is predicted to increase the exposure to atomoxetine. Monitor and adjust dose. (Severe) Theoretical

▶ SSRIs (fluoxetine, paroxetine) are predicted to markedly increase the exposure to atomoxetine. Adjust dose. (Severe) Study

▶ Terbutaline is predicted to markedly increase the exposure to atomoxetine. Adjust dose. (Severe) Study

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Atorvastatin → see statins
Atovaquone → see antimalarials
Atracurium → see neuromuscular blocking drugs, non-depolarising
Atropine → see TABLE 10 p. 1377 (antimuscarinics)

ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

- Atropine increases the risk of severe hypertension when given with sympathomimetics, vasoconstrictor (phenylephrine). [Severe] Study

Avanafil → see phosphodiesterase type-5 inhibitors
Avelumab → see monoclonal antibodies
Axitinib → see TABLE 15 p. 1378 (myelosuppression)
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to axitinib. [Moderate] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to axitinib. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to axitinib. [Moderate] Study

Aprepitant is predicted to increase the exposure to axitinib. [Moderate] Theoretical

Bosantan is predicted to decrease the exposure to axitinib. [Moderate] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to axitinib. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

Crizotinib is predicted to increase the exposure to axitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Efavirenz is predicted to decrease the exposure to axitinib. [Moderate] Study

Enzalutamide is predicted to decrease the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

Grapefruit juice is predicted to increase the exposure to axitinib. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to axitinib. Avoid or adjust dose. [Moderate] Study → Also see TABLE 15 p. 1378

Imatinib is predicted to increase the exposure to axitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Macrolides (clarithromycin) are predicted to increase the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

Macrolides (erythromycin) are predicted to increase the exposure to axitinib. [Moderate] Theoretical

Netupitant is predicted to increase the exposure to axitinib. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to axitinib. [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to axitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Axitinib is predicted to increase the risk of bleeding events when given with coumarins. [Severe] Theoretical

Axitinib is predicted to decrease the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

St John’s Wort is predicted to decrease the exposure to axitinib. [Moderate] Theoretical

Azeleotide is predicted to increase the exposure to axitinib. [Moderate] Theoretical

ACE inhibitors are predicted to increase the risk of anaemia and/or leucopenia when given with azathioprine. [Severe] Anecdotal

Allopurinol potentially increases the risk of haematological toxicity when given with azathioprine. Adjust azathioprine dose, p. 836. [Severe] Study

Azathioprine decreases the anticoagulant effect of coumarins. [Moderate] Study

Febuxostat is predicted to increase the exposure to azathioprine. Avoid. [Severe] Theoretical

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose). Public Health England advises avoid (refer to Green Book). [Severe] Theoretical

Azelastine is predicted to increase antihistamines, non-sedating

Azilsartan is predicted to increase angiotensin-1 receptor antagonists

Azithromycin is predicted to increase macrolides

Bacillus Calmette-Guérin vaccine is predicted to increase live vaccines

Baclofen is predicted to increase the risk of generalised infection (possibly life-threatening) when given with levodob. [Severe] Anecdotal → Also see TABLE 8 p. 1376

Balsalazide is predicted to increase the concentration of digoxin. [Moderate] Theoretical

Bambuterol is predicted to increase beta, agonists

Bacitracin is predicted to increase exposure to baricitinib. [Theoretical] Theoretical

Baricitinib is predicted to increase exposure to baricitinib. [Theoretical] Theoretical

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with baricitinib. Avoid. [Severe] Theoretical

Teriflunomide potentially increases the exposure to baricitinib. [Moderate] Theoretical

Basiliximab is predicted to increase monoclonal antibodies

Bazedoxifene is predicted to increase the exposure to baricitinib. [Moderate] Theoretical

Bedaquiline is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 9 p. 1377

Baclofen is predicted to increase the exposure to bedaquiline. [Mild] Theoretical → Also see TABLE 9 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to bazedoxifene. [Moderate] Theoretical

rifampin is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 1 p. 1375

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 1 p. 1375

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 9 p. 1377

Aprepitant is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

Bosantan is predicted to decrease the exposure to bedaquiline. Avoid. [Severe] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

Clonazepam is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

cyclosporine is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

Etravirine is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Study → Also see TABLE 9 p. 1377

Bedaquiline is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

Etravirine is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Study

Interactions | Appendix 1

A1
Bedaquiline – Beta blockers, selective

**BNF 78**

**Bedaquiline (continued)**

- **Ibalizumab** is predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**
- **Iloperidone** is predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**

- **Macrolides (erythromycin)** are predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**
  - Also see **TABLE 9** p. 1377
- **Macrolides (clarithromycin)** are predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**
  - Also see **TABLE 9** p. 1377

- **Mitotane** decreases the exposure to bedaquiline. Avoid. **[Severe] Study**
- **Netupitant** is predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**
- **Nevirapine** is predicted to decrease the exposure to bedaquiline. Avoid. **[Severe] Study**
- **Nilotinib** is predicted to increase the exposure to bedaquiline. Avoid prolonged use. **[Mild] Study**
  - Also see **TABLE 9** p. 1377
- **Rifampicin** decreases the exposure to bedaquiline. Avoid. **[Severe] Study**
- **St John’s Wort** is predicted to decrease the exposure to bedaquiline. Avoid. **[Severe] Study**

**Bee venom extract**

**GENERAL INFORMATION** Desensitising vaccines should be avoided in patients taking beta-blockers (adenaline might be ineffective in case of a hypersensitivity reaction) or ACE inhibitors (risk of severe anaphylactoid reactions).

**Belatacept**

- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with belatacept. Public Health England advises avoid (refer to Green Book). **[Severe] Theoretical**
- **Belimumab** → to monoclonal antibodies
- **Bendamustine** → to alkylating agents
- **Bendroflumethiazide** → to thiazide diuretics
- **Benperidol** → to see TABLE 8 p. 1376 (hypotension), **TABLE 11** p. 1377 (CNS depressant effects)
  - Also see **TABLE 8** p. 1376
- **Benperidol** is predicted to decrease the effects of **dopamine receptor agonists**. Avoid. **[Moderate] Theoretical**
  - Also see **TABLE 8** p. 1376
- **Benperidol** is predicted to decrease the effects of **guanethidine**. **[Moderate] Theoretical**
  - Also see **TABLE 8** p. 1376
- **Benperidol** is predicted to decrease the effects of **levodopa**. **[Severe] Study**
  - Also see **TABLE 8** p. 1376
- **Benzydamine** → to see NSAIDs
- **Benzylenepinilic acid** → to see penicillins
- **Beta blockers, non-selective** → to see TABLE 8 p. 1376 (bradycardia), **TABLE 9** p. 1376 (C/F-interval prolongation)
  - Also see **TABLE 6** p. 1376

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application of levobunolol and timolol, the possibility of interactions should be borne in mind.

- **Beta blockers, non-selective** are predicted to increase the risk of bronchospasms when given with **aminophylline**. Avoid. **[Severe] Theoretical**
- **Antithrombosis (aminodarone, disopyramide, dronedarone, flecainide, lidocaine)** are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, non-selective. Use with caution or avoid. **[Severe] Study**
  - Also see **TABLE 6** p. 1376
  - Also see **TABLE 9** p. 1377
- **Antithrombosis (propafenone)** increase the risk of cardiovascular side-effects when given with propranolol. Use with caution or avoid. **[Severe] Study**
- **Antithrombosis (propafenone)** are predicted to increase the exposure to timolol and timolol is predicted to increase the risk of cardiodepression when given with **antithrombosis (propafenone)**. **[Severe] Aneucleate**
- **Antithrombosis (propafenone)** are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, non-selective (labetalol, levobunolol, nadolol, pindolol, sotalol). Use with caution or avoid. **[Severe] Study**

- **Anticholinesterases, centrally acting** are predicted to increase the risk of bradycardia when given with **beta blockers, non-selective**. **[Moderate] Aneucleate**
  - Also see **TABLE 6** p. 1376
- **Antiepileptics (phenobarbital, primidone)** are predicted to decrease the exposure to **propranolol**. **[Moderate] Study**
- **Antiepileptics (phenobarbital, primidone)** are predicted to decrease the exposure to beta blockers, non-selective (carvedilol, labetalol). **[Moderate] Theoretical**
- **Antifungals, azoles** (itraconazole, ketoconazole) are predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Antimalarials (mefloquine)** are predicted to increase the risk of bradycardia when given with **beta blockers, non-selective**. **[Severe] Theoretical**
- **Calcium channel blockers (diltiazem)** are predicted to increase the risk of cardiodepression when given with beta blockers, non-selective. **[Severe] Study**
  - Also see **TABLE 6** p. 1376
  - Also see **TABLE 8** p. 1376
- **Intravenous calcium channel blockers (verapamil)** increase the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid. **[Severe] Study**
  - Also see **TABLE 6** p. 1376
  - Also see **TABLE 8** p. 1376
- **Oral calcium channel blockers (verapamil)** increase the risk of cardiovascular side-effects when given with beta blockers, non-selective. **[Severe] Study**
  - Also see **TABLE 6** p. 1376
  - Also see **TABLE 8** p. 1376
- **Ciclosporin** is predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Eliglustat** is predicted to increase the exposure to **propranolol**. Adjust dose. **[Moderate] Study**
- **Beta blockers, non-selective** are predicted to increase the risk of peripheral vasoconstriction when given with **ergometrine**. **[Severe] Study**
- **Beta blockers, non-selective** are predicted to increase the risk of peripheral vasoconstriction when given with **ergotamine**. **[Severe] Study**
- **HIV-protase inhibitors (lopinavir, ritonavir, saquinavir)** are predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Beta blockers, non-selective** are predicted to increase the risk of bradycardia when given with **lanreotide**. **[Moderate] Theoretical**
- **Lapatinib** is predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Macrolides** are predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Propafenone** are predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Mexiletine** potentially increases the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid or monitor. **[Severe] Theoretical**
- **Ranolazine** is predicted to increase the exposure to **nadolol**. **[Moderate] Study**
- **Rifampicin** moderately decreases the exposure to bedaquiline. **[Moderate] Study**
- **Rifapentine** decreases the exposure to **propranolol**. Monitor and adjust dose. **[Moderate] Study**
- **Propranolol** slightly to moderately increases the exposure to **rifazatran**. Adjust **rifazatran** dose and separate administration by at least 2 hours. **[Moderate] Study**
- **Sildenafil** (fluvoxamine) moderately increase the concentration of **propranolol**. **[Moderate] Study**
- **Beta blockers, non-selective** increase the risk of hypertension and bradycardia when given with **sympathomimetics, inotropic (dobutamine)**. **[Severe] Theoretical**
- **Beta blockers, non-selective** are predicted to increase the risk of hypertension and bradycardia when given with **sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine)**. **[Severe] Study**
- **Beta blockers, non-selective** are predicted to increase the risk of bronchospasms when given with theophylline. Avoid. **[Severe] Theoretical**
- **Vemurafenib** is predicted to increase the exposure to **nadolol**. **[Moderate] Study**

**Beta blockers, selective** → to see **TABLE 6** p. 1376 (bradycardia), **TABLE 8** p. 1376 (hypotension)
• Since systemic absorption can follow topical application of betaxolol, the possibility of interactions should be borne in mind.

• Orange juice greatly decreases the exposure to celiprolol.

• Abiraterone is predicted to increase the exposure to metoprolol. (Moderate) Study

• Beta blockers, selective are predicted to increase the risk of bronchospasm when given with aminophylline. Avoid. (Severe) Theoretical

• Antiarrhythmics (amiodarone, disopyramide, dronedarone, flecainide, lidocaine) are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, selective. Use with caution or avoid. (Severe) Study → Also see TABLE 6 p. 1376

• Antiarrhythmics (propafenone) are predicted to increase the exposure to metoprolol. (Moderate) Study

• Antiarrhythmics (propafenone) are predicted to increase the exposure to nebivolol and nebivolol is predicted to increase the risk of cardiodepression when given with antiarrhythmics (propafenone). Avoid. (Severe) Theoretical

• Antiarrhythmics (propafenone) are predicted to increase the risk of cardiovascular side-effects when given with beta blockers, selective. (Moderate) Anecdotal → Also see TABLE 6 p. 1376

• Antiparkinsonians (phenobarbital, primidone) are predicted to decrease the exposure to beta blockers, selective (acebutolol, bisoprolol, metoprolol, esmolol). Use with caution or avoid. (Severe) Study

• Anticholinesterases, centrally acting are predicted to increase the risk of bradycardia when given with beta blockers, selective. (Moderate) Study → Also see TABLE 6 p. 1376

• Antiinflammatories (mefloquine) are predicted to increase the risk of bradycardia when given with beta blockers, selective. (Moderate) Study

• Bupropion is predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). (Moderate) Study

• Calcium channel blockers (diltiazem) are predicted to increase the risk of cardiodepression when given with beta blockers, selective. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

• Intravenous calcium channel blockers (verapamil) increase the risk of cardiovascular side-effects when given with beta blockers, selective. (Moderate) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

• Oral calcium channel blockers (verapamil) increase the risk of cardiovascular side-effects when given with beta blockers, selective. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

• Cinacalcet is predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). (Moderate) Study

• Duloxetine is predicted to increase the exposure to metoprolol. (Moderate) Study

• Eliglustat is predicted to increase the exposure to metoprolol. Adjust dose. (Moderate) Study

• Beta blockers, selective are predicted to increase the risk of peripheral vasoconstriction when given with ergotamine. (Severe) Study

• Beta blockers, selective are predicted to increase the risk of peripheral vasoconstriction when given with ergotamine. (Severe) Study

• Grapefruit juice greatly decreases the exposure to celiprolol. (Moderate) Study

• HIV- protease inhibitors (ritonavir) are predicted to increase the exposure to metoprolol. (Moderate) Study

• Beta blockers, selective are predicted to increase the risk of bradycardia when given with lanreotide. (Moderate) Theoretical

• Mexiletine potentially increases the risk of cardiovascular side-effects when given with beta blockers, selective. Avoid or monitor. (Severe) Theoretical

• Mirabegron is predicted to increase the exposure to metoprolol. (Moderate) Study

• Panobinostat is predicted to increase the exposure to metoprolol. Monitor and adjust dose. (Moderate) Theoretical

• Panobinostat is predicted to increase the exposure to nebivolol. Monitor and adjust dose. (Mild) Theoretical

• Rifampicin slightly decreases the exposure to beta blockers, selective (bisoprolol, metoprolol). (Mild) Study

• Rifampicin moderately decreases the exposure to celecoxib. (Moderate) Study

• Rolipram is predicted to moderately increase the exposure to metoprolol. (Severe) Study

• SSRIs (fluvastatin, paroxetine) are predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). (Moderate) Study

• Beta blockers, selective increase the risk of hypertension and bradycardia when given with sympathomimetics, isotropic (dobutamine). (Moderate) Theoretical

• Beta blockers, selective are predicted to increase the risk of hypertension and bradycardia when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Severe) Study

• Terbinfine is predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). (Moderate) Study

• Beta blockers, selective are predicted to increase the risk of bronchospasm when given with theophylline. Avoid. (Severe) Theoretical

• Beta, agonists → see TABLE 17 p. 1379 (reduced serum potassium)

• Bambuterol - formoterol - indacaterol - olodaterol - salbutamol - salmeterol - terbutaline - vilanterol

• Antiarrhythmics (amiodarone, disopyramide, dronedarone, flecainide, lidocaine) are predicted to increase the exposure to salmeterol. Avoid. (Severe) Study

• Apalutamide is predicted to decrease the exposure to salmeterol. Avoid or monitor. (Moderate) Study

• Aprileptin is predicted to increase the exposure to salmeterol. (Moderate) Study

• Atorvastatin is predicted to increase the risk of cardiovascular side-effects when given with beta, agonists (high-dose). Avoid. (Severe) Study

• Cobicistat is predicted to increase the exposure to salmeterol. Avoid. (Severe) Study

• HIV-protease inhibitors are predicted to increase the exposure to salmeterol. Avoid. (Severe) Study

• Idecalisib is predicted to increase the exposure to salmeterol. Avoid. (Severe) Study

• Beta, agonists are predicted to increase the risk of glaucoma when given with ipratropium. (Moderate) Anecdotal

• Beta, agonists are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. (Severe) Theoretical

• Macrolides (clarithromycin) are predicted to increase the exposure to salmeterol. Avoid. (Severe) Study

• Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of cardiovascular side-effects when given with beta, agonists. (Moderate) Anecdotal

• Monoamine-oxidase B inhibitors (safinamide) are predicted to increase the risk of severe hypertension when given with beta, agonists. (Severe) Theoretical

• Netupitant is predicted to increase the exposure to salmeterol. (Moderate) Study

• Beta-histamine

• Antihistamines, non-sedating are predicted to decrease the effects of beta-histamine. (Moderate) Theoretical

• Antihistamines, sedating are predicted to decrease the effects of beta-histamine. (Moderate) Theoretical

• Betamethasone → see corticosteroids

• Betaxolol → see beta blockers, selective

• Bevacizumab → see monoclonal antibodies

• Bexarotene → see retinoids

• Bezlafibrate → see fibrates

• Bicalutamide

• Bicalutamide is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical

• Bictegravir

• Antacids decrease the exposure to bictegravir. Separate administration by at least 2 hours. (Moderate) Study
Bictegravir

Interactions

- **Antituberculars** (rifampicin, isoniazid) are predicted to decrease the absorption of oral bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to decrease the absorption of oral bictegravir. Avoid oral for 2 hours before or 1 hour after bictegravir. [Moderate] Theoretical
- **Bleomycin** decreases the absorption of oral alkaline earth salts. Avoid oral for 2 hours before or 1 hour after bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to increase the exposure to bictegravir. Use with caution or avoid. [Moderate] Study
- **Bleomycin** is predicted to decrease the absorption of oral Rashid. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to decrease the absorption of oral alkaline earth salts. Avoid oral for 2 hours before or 1 hour after bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to increase the absorption of oral bictegravir. Avoid oral for 2 hours before or 1 hour after bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to decrease the absorption of oral bictegravir. Avoid oral for 2 hours before or 1 hour after bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Bleomycin** is predicted to decrease the absorption of oral bictegravir. Avoid oral for 2 hours before or 1 hour after bictegravir. Separate administration by at least 2 hours. [Moderate] Study
- **Cobicistat** slightly increases the exposure to **bortezomib**.
  - Study
- **Enalaprilat** slightly decreases the exposure to **bortezomib**. Avoid. (Severe) Study
- HIV-protease inhibitors slightly increase the exposure to **bortezomib**. (Moderate) Study
- **Ilealitis** slightly increases the exposure to **bortezomib**. (Moderate) Study → Also see TABLE 15 p. 1378
- **Macrolides (clarithromycin)** slightly increase the exposure to **bortezomib**. (Moderate) Study
- **Mitotane** slightly decreases the exposure to **bortezomib**. Avoid. (Severe) Study → Also see TABLE 15 p. 1378
- **Rifampicin** slightly decreases the exposure to **bortezomib**. Avoid. (Severe) Study

**Bosentan**

- **Bosentan** is predicted to decrease the exposure to antiarrhythmics (dronedarone). (Severe) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) affect the exposure to **bosentan**. Avoid. (Severe) Study
- **Antifungals, azoles (fluconazole)** are predicted to increase the exposure to **bosentan**. Avoid. (Severe) Study
- **Antifungals, azoles (itraconazole)** are predicted to increase the exposure to **bosentan**. (Moderate) Theoretical
- **Antifungals, azoles (ketoconazole)** moderately increase the exposure to **bosentan**. (Severe) Study
- **Antifungals, azoles (voriconazole)** are predicted to increase the exposure to **bosentan**. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to antipiptan. (Moderate) Study
- **Bosentan** is predicted to decrease the exposure to arixtinib. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to bedaquiline. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to bosutinib. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to cabazitaxel. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nimodipine). Monitor and adjust dose. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to caripazine. Avoid. (Severe) Study
- **Cephalosporins (cefotibiprole)** are predicted to increase the exposure to **bosentan**. (Moderate) Theoretical
- **Bosentan** moderately decreases the exposure to ciclosporin and ciclosporin moderately increases the exposure to **bosentan**. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to cobimetinib. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Study
- **Bosentan** decreases the anticoagulant effect of **coumarins**. (Moderate) Study
- **Bosentan** is predicted to decrease the exposure to crizotinib. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to dasatinib. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- **Bosentan** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. (Severe) Theoretical
- **Bosentan** is predicted to moderately decrease the exposure to elbasvir. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to eliglustat. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the concentration of elteligravir. Avoid. (Severe) Study
- **Enalaprilat** affects the exposure to bosentan. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the effects of ergotamine. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to erlotinib. (Severe) Theoretical
- **Bosentan** is predicted to decrease the effcacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to gefitinib. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the concentration of everolimus. Avoid or adjust dose. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to fosapirant. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to gliclazepir. Avoid. (Severe) Study
- **Bosentan** is predicted to markedly decrease the exposure to grazoprevir. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the concentration of guanfacine. Adjust dose. (Moderate) Theoretical
- HIV-protease inhibitors are predicted to increase the exposure to **bosentan**. (Severe) Study
- **Bosentan** is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal
- **Bosentan** is predicted to decrease the exposure to idelalisib. Avoid. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to imatinib. (Moderate) Study
- **Bosentan** is predicted to decrease the exposure to icatibant. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- **Leflunomide** is predicted to increase the exposure to **bosentan**. (Moderate) Study
- **Letermovir** is predicted to increase the concentration of **bosentan**. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. (Moderate) Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the exposure to bosentan. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to maraviroc. Avoid. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the concentration of midazolam. Monitor and adjust dose. (Moderate) Theoretical
- **Mitotane** affects the exposure to **bosentan**. Avoid. (Severe) Study
- **Bosentan** is predicted to decrease the exposure to netupitant. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to nevirapine. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the exposure to nilotinib. Avoid. (Severe) Theoretical
- **Bosentan** is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal
- **Bosentan** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- **Bosentan** decreases the exposure to opioids (methadone). Avoid. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to osimertinib. Avoid. (Moderate) Theoretical
- **Bosentan** is predicted to decrease the exposure to ospemifene. Avoid. (Moderate) Study

For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal.
Bosentan (continued)

- **Bosentan** is predicted to decrease the exposure to **paritaprevir** (with ritonavir and obitavir). Avoid. **Severe** Study
- **Bosentan** decreases the exposure to **phosphodiesterase type-5 inhibitors**. **Moderate** Study
- **Bosentan** is predicted to decrease the exposure to **pibrentasvir**. Avoid. **Severe** Study
- **Bosentan** is predicted to decrease the exposure to **quetiapine**. **Moderate** Study
- **Bosentan** is predicted to decrease the exposure to **ribozidovir**. Avoid. **Moderate** Study
- **rifampin** affects the exposure to **bosentan**. Avoid. **Severe** Study
- **Bosentan** is predicted to decrease the exposure to **rolapitant**. Avoid. **Severe** Study
- **Bosentan** is predicted to decrease the exposure to **ruuxolitinib**. Monitor and adjust dose. **Moderate** Theoretical
- **Bosentan** is predicted to decrease the concentration of **sirolimus** and **sirolimus** potentially increases the concentration of **bosentan**. Avoid. **Severe** Theoretical
- **st John’s Wort** is predicted to decrease the exposure to **bosentan**. Avoid. **Moderate** Theoretical
- **Bosentan** slightly decreases the exposure to **statins** (**simvastatin**). **Moderate** Study
- **Bosentan** moderately decreases the exposure to **statins** (**atorvastatin**). **Rigi** Study
- **Bosentan** increases the risk of hepatotoxicity when given with **sulfonilureas** (**glipizidamide**). Avoid. **Severe** Study
- **Bosentan** is predicted to decrease the concentration of **tacrolimus** and **taclorolimus** potentially increases the concentration of **bosentan**. Avoid. **Severe** Theoretical
- **Bosentan** is predicted to decrease the exposure to **taxanes** (**cabazitaxel**). Avoid. **Severe** Study
- **Bosentan** is predicted to decrease the concentration of **temsirolimus**. Avoid. **Severe** Theoretical
- **Teriflunomide** is predicted to increase the exposure to **bosentan**. **Moderate** Study
- **Bosentan** is predicted to decrease the exposure to **ticagrelor**. **Moderate** Study
- **Bosentan** is predicted to decrease the exposure to **tofacitinib**. **Moderate** Study
- **Bosentan** decreases the efficacy of **ulipristal**. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Aneodical
- **Bosentan** is predicted to decrease the exposure to **velpatasvir**. Avoid. **Moderate** Theoretical
- **Bosentan** is predicted to decrease the exposure to **venetoclax**. Avoid. **Severe** Study
- **Venetoclax** is predicted to increase the exposure to **bosentan**. **Moderate** Theoretical
- **Bosentan** is predicted to decrease the concentration of **voxilaprevir**. Avoid. **Severe** Theoretical

**Bosutinib** ➔ **Table** 15 p. 1378 (myositis suppression), **Table** 9 p. 1377

- **Antacids** are predicted to decrease the absorption of **bosutinib**. **Severe** Study
- **Bosutinib** should be taken at least 12 hours before **antacids**. **Severe** Theoretical
- **Antineoplastic drugs** (**dronedarone**) are predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical ➔ Also see **Table** 9 p. 1377
- **Antiepileptics** (**carbamazepine**, **fosphenytoin**, **phenobarbital**, **phenytoin**, **primidone**) are predicted to very markedly decrease the exposure to **bosutinib**. Avoid. **Severe** Study
- **Antifungals**, **azole** (**fluconazole**, **itraconazole**, **posesaconazole**) are predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical ➔ Also see **Table** 9 p. 1377
- **Antifungals**, **azole** (**itraconazole**, **ketocanozole**, **voriconazole**) are predicted to markedly increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Study ➔ Also see **Table** 9 p. 1377
- **Apalutamid** is predicted to decrease the exposure to **bosutinib**. Avoid or monitor. **Moderate** Study ➔ Also see **Table** 9 p. 1377
- **Aprepitant** is predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical
- **Bosentan** is predicted to decrease the exposure to **bosutinib**. Avoid. **Severe** Theoretical
- **Calcium channel blockers** (**diltiazem**, **verapamil**) are predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical
- **Cobicistat** is predicted to markedly increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Study
- **Bosutinib** is predicted to increase the risk of bleeding events when given with **coumarins**. **Severe** Theoretical
- **Crizotinib** is predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical ➔ Also see **Table** 15 p. 1378 ➔ Also see **Table** 9 p. 1377
- **Elavirenz** is predicted to decrease the exposure to **bosutinib**. Avoid. **Severe** Theoretical ➔ Also see **Table** 9 p. 1377
- **Enzalutamide** is predicted to very markedly decrease the exposure to **bosutinib**. Avoid. **Severe** Study
- **Etravirine** is predicted to decrease the exposure to **bosutinib**. **Severe** Theoretical
- **Fosaprepitant** is predicted to increase the exposure to **bosutinib**. **Severe** Theoretical
- **Grapefruit juice** is predicted to increase the exposure to **bosutinib**. **Severe** Theoretical
- **H2 receptor antagonists** are predicted to decrease the absorption of **bosutinib**. **Moderate** Theoretical
- **HIV-protase inhibitors** are predicted to markedly increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Study ➔ Also see **Table** 9 p. 1377
- **Idelalisib** is predicted to markedly increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Study ➔ Also see **Table** 15 p. 1378
- **Imatinib** is predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical ➔ Also see **Table** 15 p. 1378
- **Macrolides** (**clarithromycin**) are predicted to markedly increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Study ➔ Also see **Table** 9 p. 1377
- **Macrolides** (**erythromycin**) are predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical
- **Mitotane** is predicted to very markedly decrease the exposure to **bosutinib**. Avoid. **Severe** Study ➔ Also see **Table** 15 p. 1378
- **Modafinil** is predicted to decrease the exposure to **bosutinib**. Avoid. **Severe** Study
- **Netupitant** is predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical
- **Nevirapine** is predicted to decrease the exposure to **bosutinib**. Avoid. **Severe** Theoretical
- **Nilotinib** is predicted to increase the exposure to **bosutinib**. Avoid or adjust dose. **Severe** Theoretical ➔ Also see **Table** 15 p. 1378 ➔ Also see **Table** 9 p. 1377
- **Bosutinib** is predicted to increase the risk of bleeding events when given with **phenindione**. **Severe** Theoretical
- **Pitolisant** is predicted to decrease the exposure to **bosutinib**. **Severe** Theoretical
- **Proton pump inhibitors** are predicted to decrease the absorption of **bosutinib**. **Moderate** Study
- **rifampin** is predicted to very markedly decrease the exposure to **bosutinib**. **Severe** Study
- **St John’s Wort** is predicted to decrease the exposure to **bosutinib**. **Severe** Theoretical

**Botulinum toxin type A** ➔ **Table** 20 p. 1379 (neuromuscular blocking effects)

**Botulinum toxin type B** ➔ **Table** 20 p. 1379 (neuromuscular blocking effects)

**Bowel cleansing preparations**

**SEPARATION OF ADMINISTRATION** Other oral drugs should not be taken 1 hour before, or after, administration of bowel cleansing preparations because absorption may be impaired. Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

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Brentuximab vedotin → see monoclonal antibodies

Brigatinib

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. (Severe) Study
- Bosentan is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Cobicistat is predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. (Severe) Study
- Brigatinib decreases the exposure to combined hormonal contraceptives. Use additional contraceptive precautions. (Severe) Theoretical
- Brigatinib potentially increases the concentration of dabigatran. (Moderate) Theoretical
- Brigatinib potentially increases the concentration of digoxin. (Moderate) Theoretical
- Efavirenz is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Enalapril is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Etravirine is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- HIV- protease inhibitors are predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. (Severe) Study
- Idealab is predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. (Severe) Study
- Macrolides (clarithromycin) are predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. (Severe) Study
- Brigatinib potentially increases the concentration of methotrexate. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Nevirapine is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Brigatinib potentially decreases the concentration of opioids (alfentanil, fentanyl). Avoid. (Moderate) Theoretical
- Rifabutin is predicted to decrease the exposure to brigatinib. Avoid. (Moderate) Theoretical
- Rifampicin is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Brigatinib potentially decreases the concentration of sirolimus. Avoid. (Moderate) Theoretical
- St John’s Wort is predicted to decrease the exposure to brigatinib. Avoid. (Severe) Study
- Brigatinib potentially decreases the concentration of tacrolimus. Avoid. (Moderate) Theoretical
- Brimonidine → see TABLE 6 p. 1376 (bradycardia), TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)

Brinzolamide

ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

Brivaracetam → see antiepileptics
- Brodalumab → see monoclonal antibodies
- Bromfenac → see NSAIDs
- Bromocriptine → see dopamine receptor agonists
- Bucizine → see antihistamines, sedating
- Budesonide → see corticosteroids
- Bumetanide → see loop diuretics
- Bupivacaine → see anaesthetics, local
- Buprenorphine → see opioids
- Bupropion → see TABLE 13 p. 1378 (serotonin syndrome)
- Bupropion is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to bupropion. (Severe) Study
- Antiepileptics (valproate) increase the exposure to bupropion. (Severe) Study
- Antifungals, azoles (isavuconazole) slightly increase the exposure to bupropion. Adjust dose. (Moderate) Study
- Bupropion is predicted to moderately increase the exposure to ariperiprazole. Adjust ariperiprazole dose, p. 295. (Moderate) Study
- Bupropion is predicted to markedly increase the exposure to atorvastatin. Adjust dose. (Severe) Study
- Bupropion is predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). (Moderate) Study
- Bupropion is predicted to slightly increase the exposure to darifenacin. (Mild) Study
- Bupropion increases the risk of side-effects when given with dopamine receptor agonists (amantadine). (Moderate) Study
- Efavirenz is predicted to decrease the exposure to bupropion. (Moderate) Study
- Bupropion is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Study
- HIV-protease inhibitors (tritonavir) are predicted to decrease the exposure to bupropion. (Moderate) Study
- Bupropion increases the risk of side-effects when given with levodopa. (Moderate) Study
- Bupropion is predicted to increase the risk of intraoperative hypotension when given with linezolid. (Severe) Anebotol. Also see TABLE 13 p. 1378
- Methylthioninium chloride is predicted to increase the risk of severe hypertension when given with bupropion. Avoid. (Severe) Theoretical → Also see TABLE 13 p. 1378
- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of severe hypertension when given with bupropion. Avoid and for 14 days after stopping the MAOI. (Severe) Theoretical → Also see TABLE 13 p. 1378
- Monoamine-oxidase B inhibitors are predicted to increase the risk of severe hypertension when given with bupropion. Avoid. (Moderate) Theoretical → Also see TABLE 13 p. 1378
- Bupropion is predicted to decrease the efficacy of opioids (codeine). (Moderate) Theoretical
- Bupropion is predicted to decrease the efficacy of opioids (tramadol). (Severe) Study → Also see TABLE 13 p. 1378
- Bupropion is predicted to moderately increase the exposure to pipotilzam. Use with caution and adjust dose. (Moderate) Study
- Rifampicin is predicted to decrease the exposure to bupropion. (Moderate) Study
- Bupropion is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- Bupropion is predicted to increase the exposure to SSRIs (dapoxetine). (Moderate) Theoretical → Also see TABLE 13 p. 1378
- Bupropion is predicted to decrease the efficacy of tamoxifen. Avoid. (Severe) Study
- Bupropion is predicted to increase the exposure to tricyclic antidepressants. Monitor for toxicity and adjust dose. (Severe) Study → Also see TABLE 13 p. 1378
- Bupropion is predicted to increase the exposure to voriconazole. Monitor and adjust dose. (Moderate) Study → Also see TABLE 13 p. 1378
- Bupropion → see TABLE 13 p. 1378 (serotonin syndrome)
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to bupropione. Use with caution and adjust dose. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to bupropione. Use with caution and adjust dose. (Severe) Study
- Antifungals, azoles (itraconazole, isavuconazole, posaconazole) are predicted to increase the exposure to bupropione. Use with caution and adjust dose. (Moderate) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to bupropione. Adjust bupropione dose, p. 342. (Severe) Study

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Buspirone (continued)
- Antifungals, azoles (miconazole) are predicted to increase the concentration of buspirone. Use with caution and adjust dose. [Moderate] Theoretical
- Apalutamide is predicted to decrease the exposure to buspirone. Avoid or monitor. [Moderate] Study
- Aprepitant is predicted to increase the exposure to buspirone. Use with caution and adjust dose. [Moderate] Study
- Aprepitant is predicted to increase the exposure to buspirone. [Moderate] Theoretical
- Cabozantinib, ▶ Cobicistat, ▶ ▶ ▶ Aprepitant is predicted to increase the exposure to buspirone. Use with caution and adjust dose. [Moderate] Study
- Antiarrhythmics ▶ ▶ ▶ ▶ Nilotinib ▶ ▶ ▶ ▶ ▶ Macrolides ▶ ▶ ▶ HIV-protease inhibitors slightly increase the exposure to cabozantinib. Avoid. [Moderate] Study
- Grapefruit juice is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical ▶ Also see TABLE 9 p. 1377
- Idelalisib slightly increases the exposure to cabozantinib. [Moderate] Study ▶ Also see TABLE 15 p. 1378
- Idelalisib is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical ▶ Also see TABLE 9 p. 1377
- Idelalisib is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical
- Mitotane moderately decreases the exposure to cabozantinib. Avoid. [Moderate] Study ▶ Also see TABLE 15 p. 1378
- Nevirapine is predicted to decrease the exposure to cabozantinib. [Moderate] Theoretical
- Nevirapine is predicted to decrease the exposure to cabozantinib. [Moderate] Theoretical
- HIV-protease inhibitors, irreversible ▶ HIV-protease inhibitors, irreversible
- Rifampicin moderately decreases the exposure to cabozantinib. Avoid. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to cabozantinib. [Moderate] Theoretical
- Theoretical Caffeine citrate
- Caffeine citrate decreases the efficacy of antiarrhythmics (adenosine). Separate administration by 24 hours. [Moderate] Study
- Antiepileptics (fosphenytoin, phenytoin) are predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. [Moderate] Study
- HIV-protease inhibitors (ritonavir) are predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. [Moderate] Study
- Nilotinib is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical ▶ Also see TABLE 9 p. 1377
- Cabozantinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe] Theoretical
- Rifampicin moderately decreases the exposure to cabozantinib. Avoid. [Moderate] Study
- Caffeine citrate decreases the clearance of theophylline. [Moderate] Study
- Caffeine citrate decreases the clearance of theophylline. [Moderate] Study
- Calcitriol ▶ see vitamin D substances
- Calcium acetate ▶ see calcium salts
- Calcium carbonate ▶ see calcium salts
- Calcium channel blockers ▶ see TABLE 6 p. 1376 (bradycardia), TABLE 8 p. 1376 (hypotension)
- Amiodipine ▶ clevidine ▶ diltiazem ▶ felodipine ▶ lacidipine ▶ lercanidipine ▶ nicardipine ▶ nifedipine ▶ nimodipine ▶ verapamil
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to abemaciclib. [Moderate] Study
- Calcitriol is predicted to increase the exposure to abemaciclib. [Moderate] Study
- Verapamil is predicted to increase the exposure to abemaciclib. Separate administration by 12 hours. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to aldosterone antagonists (eplerenone). Adjust eplerenone dose, p. 193. [Severe] Study ▶ Also see TABLE 8 p. 1376
Verapamil moderately increases the exposure to aliskiren. (Moderate) Study → Also see TABLE 8 p. 1376

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to alpha blockers (tamsulosin). (Moderate) Theoretical → Also see TABLE 13 p. 1376

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to alprazolam. (Severe) Study

Verapamil moderately increases the exposure to anthracyclines (doxorubicin). (Moderate) Study

Antiarhythmics (disopyramide) are predicted to increase the risk of cardiodepression when given with verapamil. (Severe) Theoretical

Antiarhythmics (dronedarone) are predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study

Antiarhythmics (amiodarone) are predicted to increase the risk of cardiodepression when given with calcium channel blockers (diltiazem, verapamil). Avoid. (Severe) Theoretical → Also see TABLE 6 p. 1376

Calcium channel blockers (diltiazem, verapamil) increase the exposure to antiarhythmics (flecainide). (Severe) Anecdotal → Also see TABLE 6 p. 1376

Antiarhythmics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study

Diltiazem increases the concentration of antiepileptics (carbamazepine) and antiepileptics (carbamazepine) are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). Avoid. (Severe) Anecdotal

Verapamil increases the concentration of antiepileptics (carbamazepine) and antiepileptics (carbamazepine) are predicted to decrease the exposure to verapamil. (Severe) Anecdotal

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study

Calcium channel blockers (diltiazem, verapamil) potentially increase the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study

Verapamil increases the risk of cardiodepression when given with beta blockers, non-selective. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Intravenous verapamil increases the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Oral verapamil increases the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Verapamil is predicted to increase the exposure to bictegravir. Use with caution or avoid. (Moderate) Theoretical

Bosantan is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Theoretical

Bosantan is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Moderate) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to bosutinib. Avoid or adjust dose. (Severe) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to caboazatinib. (Moderate) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study

Antifungals, azoles (posaconazole) are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Moderate) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to antifungals, azoles (isavuconazole). (Moderate) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to antihistamines, non-sedating (mizolastine). (Severe) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to antihistamines, non-sedating (triptamine). Avoid. (Moderate) Study

Antimalarials (mefloquine) are predicted to increase the risk of bradycardia when given with calcium channel blockers. (Severe) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of antimalarials (piperperazine). (Severe) Theoretical

Aplutamide is predicted to decrease the exposure to calcium channel blockers (felodipine, lercanidipine). Avoid or monitor. (Moderate) Study

Verapamil is predicted to increase the exposure to apixaban. (Moderate) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to aprepitant and aprepitant is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Moderate) Study

Aprepitant is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to axitinib. (Moderate) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to bedaquiline. Avoid prolonged use. (Mild) Theoretical

Diltiazem is predicted to increase the risk of cardiodepression when given with beta blockers, non-selective. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Intravenous verapamil increases the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Oral verapamil increases the risk of cardiovascular side-effects when given with beta blockers, non-selective. Avoid. (Severe) Study → Also see TABLE 6 p. 1376 → Also see TABLE 8 p. 1376

Verapamil is predicted to increase the exposure to bictegravir. Use with caution or avoid. (Moderate) Theoretical

Bosantan is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Theoretical

Bosantan is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). (Moderate) Theoretical
Calcium channel blockers (continued)

- Calcium channel blockers (diltiazem) are predicted to increase the exposure to calcium channel blockers (amlodipine). Monitor and adjust dose. (Moderate) Study → Also see TABLE 8 p. 1376
- Calcium channel blockers (verapamil) are predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study → Also see TABLE 8 p. 1376
- Calcium channel blockers (diltiazem) are predicted to increase the exposure to calcium channel blockers (felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study → Also see TABLE 8 p. 1376
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to cariprazine. Avoid. (Severe) Study → Also see TABLE 8 p. 1376
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ceritinib. (Moderate) Theoretical Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of ciclosporin. (Severe) Study
- Ciclosporin moderately increases the exposure to lercanidipine. Use with caution or avoid. (Severe) Study
- Nicardipine increases the concentration of ciclosporin. (Severe) Study
- Ciclosporin is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study
- Cobicistat is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study
- Cobicistat is predicted to markedly increase the exposure to lercanidipine. Avoid. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. (Moderate) Study
- Crizotinib is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study
- Dapamil increases the exposure to dabigatran. Adjust dabigatran dose, p. 136. (Severe) Study
- Intravenous dantrolene potentially increases the risk of acute hyperkalaemia and cardiovascular collapse when given with calcium channel blockers (diltiazem, verapamil). Avoid. (Severe) Anecdotal Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to slightly increase the exposure to darifenacin. (Moderate) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to dasatinib. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) increase the concentration of digoxin. Monitor and adjust dose. (Severe) Study → Also see TABLE 6 p. 1376
- Calcium channel blockers (diltiazem, verapamil) increase the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to dopamine receptor antagonists (bromocriptine). (Severe) Theoretical Study → Also see TABLE 8 p. 1376
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of dopamine receptor antagonists (cabergoline). (Moderate) Anecdotal → Also see TABLE 8 p. 1376
- Calcium channel blockers (diltiazem, verapamil) are predicted to moderately increase the exposure to dutasteride. (Mild) Study
- Verapamil is predicted to slightly increase the exposure to efavirenz. (Severe) Study
- Efavirenz is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Theoretical Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure toeliglustat. Avoid or adjust dose—consult product literature. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to moderately increase the exposure to encorafenib. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to calcium channel blockers (amlodipine, verapamil). (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the risk of ergotism when given with ergometrine. (Severe) Theoretical Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the risk of ergotism when given with ergotamine. (Severe) Theoretical Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of everolimus. Avoid or adjust dose. (Moderate) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to fexofenadine. Adjust fexofenadine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. (Mild) Study
- Verapamil is predicted to increase the exposure to fidocarbazone. Avoid. (Moderate) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to fingolimod. Avoid. (Moderate) Theoretical Study → Also see TABLE 6 p. 1376
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to gefitinib. (Moderate) Theoretical Study
- Grapefruit juice very slightly increases the exposure to amloprofen. Avoid. (Mild) Study
- Grapefruit juice increases the exposure to calcium channel blockers (nifedipine, verapamil). Avoid. (Mild) Study
- Grapefruit juice increases the exposure to felodipine. Avoid. (Mild) Study
- Grapefruit juice is predicted to increase the exposure to lercanidipine. Avoid. (Mild) Study
- Grapefruit juice increases the exposure to nicardipine. Avoid. (Mild) Study
- Grazoprevir is predicted to increase the concentration of calcium channel blockers. (Moderate) Theoretical Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Theoretical Study → Also see TABLE 8 p. 1376
- H₂ receptor antagonists (cimetidine) (high-dose) are predicted to increase the exposure to lercanidipine. (Moderate) Theoretical Study
- H₂ receptor antagonists (cimetidine) moderately increase the exposure to nifedipine. Monitor and adjust dose. (Severe) Study
- H₂ receptor antagonists (cimetidine) increase the exposure to verapamil. (Moderate) Study
- H₂ receptor antagonists (cimetidine) slightly increase the exposure to calcium channel blockers (diltiazem, nimodipine). Monitor and adjust dose. (Moderate) Study
- HIV-protease inhibitors are predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study
- HIV-protease inhibitors are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study
- HIV-protease inhibitors are predicted to markedly increase the exposure to lercanidipine. Avoid. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to irbutinib. Adjust irbutinib dose with moderate inhibitors of CYP3A4, p. 983. (Severe) Study
- Idelalisib is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study

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Calcium channel blockers — Calcium channel blockers

- **Idelalisib** is predicted to increase the exposure to calcium channel blockers (**diltiazem, verapamil**). **(Severe) Study**
- **Idelalisib** is predicted to markedly increase the exposure to lercanidipine. **Avoid. (Severe) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to imatinib. **(Moderate) Theoretical**
- **Imatinib** is predicted to increase the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to ivabradine. **Avoid. (Moderate) Study** → Also see **TABLE 6** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. **(Severe) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to lapatinib. **(Moderate) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the risk of neurotoxicity when given with lithium. **(Severe) Anecdotal**
- Calcium channel blockers (**amlodipine, lacidipine**) are predicted to increase the exposure to lomitapide. **Separate administration by 12 hours. (Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to lomustine. **Avoid. (Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to lurisdione. Adjust lurisdione dose, p. 398. **(Moderate) Study** → Also see **TABLE 8** p. 1376
- Macrolides (**clarithromycin**) are predicted to markedly increase the exposure to lercanidipine. **Avoid. (Severe) Study**
- **Macrolides (erythromycin)** are predicted to increase the exposure to diltiazem. **(Severe) Theoretical**
- Macrolides (**clarithromycin**) are predicted to increase the exposure to verapamil. **(Severe) Study**
- **Macrolides (erythromycin)** are predicted to increase the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Macrolides (clarithromycin)** are predicted to increase the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Macrolides (clarithromycin)** are predicted to increase the exposure to calcium channel blockers (**diltiazem, verapamil**). **(Severe) Study**
- Intravenous magnesium potentially increases the risk of hypotension when given with calcium channel blockers (**amlodipine, clevidipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, verapamil**) (in pregnant women). **(Severe) Anecdotal**
- **Mexiletine** increases the risk of cardiovascular side-effects when given with diltiazem. Avoid or monitor. **(Severe) Theoretical**
- **Mexiletine** potentially increases the risk of cardiovascular side-effects when given with verapamil. Avoid or monitor. **(Severe) Theoretical**
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. **(Severe) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to midostaurin. **(Moderate) Theoretical**
- **Mitotane** is predicted to decrease the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Monoclonal antibodies (tocilizumab)** are predicted to decrease the exposure to calcium channel blockers. Monitor and adjust dose. **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects. p. 65. **(Moderate) Study**
- **Netupitant** is predicted to increase the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Nevirapine** is predicted to decrease the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Theoretical**
- **Nevirapine** is predicted to decrease the exposure to calcium channel blockers (**diltiazem, verapamil**). **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to nilotinib. **(Moderate) Theoretical**
- **Nilotinib** is predicted to increase the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Verapamil** is predicted to increase the exposure to nintedanib. **(Moderate) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to opioids (**alfentanil, buprenorphine, fentanyl, oxycodone**). Monitor and adjust dose. **(Moderate) Study** → Also see **TABLE 6** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to pantoprazole. **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to pazopanib. **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (**avanafil**). Adjust avanafil dose, p. 812. **(Moderate) Theoretical** → Also see **TABLE 8** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (**sildenafil**). Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. **(Moderate) Study** → Also see **TABLE 8** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (**tadalafil**). **(Severe) Theoretical** → Also see **TABLE 8** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to **givabril**. **(Moderate) Study** → Also see **TABLE 8** p. 1376
- **Verapamil** is predicted to increase the exposure to **fibratestest**. **(Moderate) Theoretical**
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to **pimozide**. Avoid. **(Severe) Study** → Also see **TABLE 8** p. 1376
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to ranolazine. **(Severe) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to ranibizumab. **(Moderate) Study**
- **Rifampicin** is predicted to decrease the exposure to calcium channel blockers (**amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nimodipine**). Monitor and adjust dose. **(Moderate) Study**
- **Rifampicin** greatly decreases the exposure to calcium channel blockers (**diltiazem, verapamil**). **(Severe) Study**
- **Rifampicin** moderately decreases the exposure to nifedipine. Avoid. **(Severe) Study**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to nortriptyline. **(Moderate) Theoretical**
- Calcium channel blockers (**diltiazem, verapamil**) are predicted to increase the exposure to saxagliptin. **(Mild) Study**
- Calcium channel blockers (**diltiazem, verapamil**) increase the concentration of sirolimus. Monitor and adjust dose. **(Moderate) Study**

**TABLE 8**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Calcium Channel Blockers</th>
<th>Notes</th>
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Calcium channel blockers (continued)
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to SSRIs (dapoxetine). Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. [Moderate] Theoretical
- St John's Wort is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Theoretical
- St John's Wort is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. [Severe] Study
- Amlodipine slightly increases the exposure to simvastatin, p. 205. [MG] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. [Severe] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to suntinib. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of tacrolimus. [Severe] Study
- Nicardipine potentially increases the concentration of tacrolimus. Monitor concentration and adjust dose. [Severe] Anecdotal
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to taxanes (cabazitaxel). [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of temsirolimus. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study
- Calcium channel blockers (diltiazem, verapamil) given with a potent CYP2C19 inhibitor are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 105. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to tolorodine, p. 689. [MG] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 669. [Moderate] Study
- Verapamil is predicted to increase the exposure to toptocan. [Severe] Study
- Verapamil is predicted to increase the concentration of trametinib. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to trazodone. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to venooclax. Avoid or adjust dose—consult product literature. [Severe] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to venooclax. Avoid or adjust dose—consult product literature. [Severe] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to zopiclone. Adjust dose. [Moderate] Study
- Calcium chloride → see calcium salts
- Calcium gluconate → see calcium salts
- Calcium lactate → see calcium salts
- Calcium phosphate → see calcium salts
- Calcium salts
- Calcium acetate - calcium carbonate - calcium chloride - calcium gluconate - calcium lactate - calcium phosphate

**SEPARATION OF ADMINISTRATION** Calcium carbonate-containing antacids should preferably not be taken at the same time as other drugs since they might impair absorption. Antacids might damage enteric coatings designed to prevent dissolution in the stomach.
- Oral calcium salts decrease the absorption of alkylating agents (estramustine). [Severe] Study
- Calcium carbonate decreases the absorption of antimalarials (chloroquine). Separate administration by at least 4 hours. [Moderate] Theoretical
- Calcium carbonate is predicted to decrease the absorption of antimalarials (proguanil). Separate administration by at least 2 hours. [Moderate] Study
- Oral calcium salts decrease the absorption of bisphosphonates (alendronic acid). Alendronic acid should be taken at least 30 minutes before calcium salts. [Moderate] Study
- Oral calcium salts are predicted to decrease the absorption of oral bisphosphonates (ibandronic acid). Avoid calcium salts for at least 6 hours before or 1 hour after ibandronic acid. [Moderate] Theoretical
- Oral calcium salts decrease the absorption of bisphosphonates (risendronate). Separate administration by at least 2 hours. [Moderate] Study
- Oral calcium salts decrease the absorption of bisphosphonates (sodium clodronate). Avoid calcium salts for 2 hours before or 1 hour after sodium clodronate. [Moderate] Study
- Calcium carbonate increases the exposure to cannabis extract. Avoid. [Severe] Anecdotal
- Cephalosporins (ceftriaxone) increase the risk of cardiovascular respiratory arrest when given with calcium chloride. Avoid. [Severe] Anecdotal
- Oral calcium salts decrease the concentration of digoxin. Avoid. [Severe] Anecdotal
- Oral calcium salts decrease the absorption of dolutegravir. Dolutegravir should be taken 2 hours before or 6 hours after calcium salts. [Moderate] Study
- Oral calcium salts decrease the absorption of eltorblopag. Eltorblopag should be taken 2 hours before or 4 hours after calcium salts. [Severe] Study
- Calcium carbonate decreases the absorption of hydroxychloroquine. Separate administration by at least 4 hours. [Moderate] Study
- Calcium carbonate decreases the absorption of iron (oral). Calcium carbonate should be taken 1 hour before or 2 hours after iron (oral). [Moderate] Study
- Calcium carbonate is predicted to decrease the exposure to ledipasvir. Separate administration by 4 hours. [Moderate] Theoretical
- Calcium carbonate decreases the absorption of quinolones (ciprofloxacin). Separate administration by 2 hours. [Moderate] Study
- Calcium carbonate greatly decreases the exposure to raltegravir (high-dose). Avoid. [Severe] Study
- Calcium carbonate is predicted to decrease the exposure to rifampicin. Calcium carbonate should be taken 2 hours before or 4 hours after rifampirine. [Severe] Theoretical
- Calcium carbonate is predicted to decrease the absorption of tetracyclines. Separate administration by 2 to 3 hours. [Moderate] Theoretical
- Thiazide diuretics increase the risk of hypercalcaemia when given with calcium salts. [Severe] Anecdotal
- Oral calcium salts are predicted to decrease the absorption of thyroid hormones (levothyroxine). Separate administration by at least 4 hours. [Moderate] Anecdotal
- Calcium carbonate is predicted to decrease the concentration of velpatasvir. Separate administration by 4 hours. [Moderate] Anecdotal
- Oral calcium salts decrease the absorption of zinc. [Moderate] Study

**TABLE 14** See Table 14 p. 1378 (antidiabetic drugs), Table 8 p. 1376 (hypotension)
- Rifampicin moderately decreases the exposure to canagliflozin. Adjust canagliflozin dose, p. 702. [Moderate] Study
- Canakinumab → see monoclonal antibodies
- Canesartan → see angiotensin-II receptor antagonists
- Cangrelor → see Table 4 p. 1375 (platelet effects)
- Cannabis extract → see Table 11 p. 1377 (CBD depressant effects)
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure...
to **cannabis extract**. Avoid. **[Severe] Theoretical** → Also see TABLE 11 p. 1377

- **Antifungals, azoles** *(itraconazole, ketoconazole, voriconazole)* are predicted to increase the exposure to **cannabis extract**. Use with caution and adjust dose. **[Moderate] Theoretical**
- **Cobicistat** is predicted to increase the exposure to **cannabis extract**. Use with caution and adjust dose. **[Moderate] Theoretical**
- **Enzalutamide** is predicted to decrease the exposure to **cannabis extract**. Avoid. **[Severe] Theoretical**
- **HIV-protease inhibitors** are predicted to increase the exposure to **cannabis extract**. Use with caution and adjust dose. **[Moderate] Theoretical**
- **Idealisib** is predicted to increase the exposure to **cannabis extract**. Use with caution and adjust dose. **[Moderate] Theoretical**
- **Macrolides (clarithromycin)** are predicted to increase the exposure to **cannabis extract**. Use with caution and adjust dose. **[Moderate] Theoretical**
- **Mitoctane** is predicted to decrease the exposure to **cannabis extract**. Avoid. **[Severe] Theoretical**
- **Rifampicin** is predicted to increase the exposure to **cannabis extract**. Avoid. **[Severe] Theoretical**
- **Capreomycin** → see TABLE 15 p. 1378 (myelosuppression)
- **Allopurinol** is predicted to decrease the effects of **capreomycin**. Avoid. **[Severe] Study**
- **Capreomycin** increases the concentration of **antiepileptics** *(fosphenytoin, phenytoin)*. **[Severe] Anecdotal**
- **Capreomycin** increases the effects of **coumarins**. Monitor INR and adjust dose. **[Moderate] Theoretical**
- **Folates** are predicted to increase the risk of toxicity when given with **capreomycin**. **[Severe] Anecdotal**
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with **capreomycin**. Public Health England advises avoid (refer to Green Book). **[Severe] Theoretical**
- **Metronidazole** is predicted to increase the risk of capreomycin toxicity when given with **capreomycin**. **[Severe] Theoretical**
- **Capreomycin** → see TABLE 2 p. 1375 (nephrotoxicity), TABLE 19 p. 1379 *(ototoxicity)*
- **Captopril** → see ACE inhibitors
- **Carbamazepine** → see antiepileptics

**Carbenapens**
- erapenem - imipenem - meropenem
- **Carbenapens** decrease the concentration of **antiepileptics** *(valproate)*. Avoid. **[Severe] Anecdotal**
- **Ganciclovir** is predicted to increase the risk of seizures when given with **imipenem**. Avoid. **[Severe] Anecdotal**
- **Valganciclovir** is predicted to increase the risk of seizures when given with **imipenem**. Avoid. **[Severe] Anecdotal**
- **Carbipoda**
  - **Iron (oral)** is predicted to decrease the exposure to **carbipoda**. **[Moderate] Theoretical**
- **Carbimazole** → see TABLE 15 p. 1378 (myelosuppression)
- **Carbimazole** affects the concentration of **digoxin**. Monitor and adjust dose. **[Moderate] Theoretical**
- **Carbimazole** decreases the effects of **metyparone**. Avoid. **[Moderate] Theoretical**
- **Carboplatin** → see platinum compounds
- **Carfilzomib** → see TABLE 15 p. 1378 (myelosuppression)
- **Cariprazine** → see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)
- **Antihyrtuthyphic (dronedarone)** are predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical** → Also see TABLE 11 p. 1377
- **Antifungals, azoles (fluconazole, itraconazole, ketoconazole, posaconazole)** are predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to moderately increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Aprepitant** is predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Bosantan** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study** → Also see TABLE 8 p. 1376
- **Cobicistat** is predicted to moderately increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Crizotinib** is predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Efavirenz** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Enzalutamide** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Grapefruit juice** is predicted to increase the exposure to **cariprazine**. Avoid. **[Moderate] Study**
- **HIV-protease inhibitors** are predicted to moderately increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Idealisib** is predicted to moderately increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Imatinib** is predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Macrolides (clarithromycin)** are predicted to moderately increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Mitoctane** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Netupitant** is predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Nevirapine** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Nilotinib** is predicted to increase the exposure to **cariprazine**. Avoid. **[Severe] Study**
- **Rifampicin** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **St John’s Wort** is predicted to decrease the exposure to **cariprazine**. Avoid. **[Severe] Theoretical**
- **Carmustine** → see alkylating agents
- **Carvedilol** → see beta blockers, non-selective

**Caspofungin**
- **Antiepileptics (carbamazepine, fosphenytoin, phenytoin)** are predicted to decrease the concentration of **caspofungin**. Adjust **caspofungin** dose, p. 592. **[Moderate] Theoretical**
- **Ciclosporin** slightly increases the exposure to **caspofungin**. **[Severe] Study**
- **Corticosteroids (dexamethasone)** are predicted to decrease the concentration of **caspofungin**. Adjust **caspofungin** dose, p. 592. **[Moderate] Theoretical**
- **Efavirenz** is predicted to decrease the concentration of **caspofungin**. Adjust dose. **[Moderate] Study**
- **Nevirapine** is predicted to decrease the concentration of **caspofungin**. Adjust dose. **[Moderate] Theoretical**
- **Rifampicin** decreases the concentration of **caspofungin**. Adjust **caspofungin** dose, p. 592. **[Moderate] Study**
- **Cefadroxil** → see cephalosporins
- **Cefadroxil** → see cephalosporins
- **Cefalexin** → see cephalosporins
- **Cefixime** → see cephalosporins
- **Cefotaxime** → see cephalosporins
- **Cefradine** → see cephalosporins
- **Ceftaroline** → see cephalosporins
- **Ceftazidime** → see cephalosporins
- **Ceftobiprole** → see cephalosporins
- **Ceftolozane** → see cephalosporins
- **Ceftoxime** → see cephalosporins
- **Cefuroxime** → see cephalosporins
- **Celecoxib** → see NSAIDs
- **Celiprolol** → see beta blockers, selective
- **Cefepime** → see cephalosporins
INTERACTIONS

Ceritinib

▶ Ceritinib is predicted to increase the exposure to bosentan. (Moderate) Theoretical

▶ Ceritinib potentially increases the risk of bleeding events when given with coumarins. (Severe) Anecdotal

▶ Ceritinib is predicted to increase the concentration ofstatins. (Moderate) Theoretical

▶ Ceritinib is predicted to increase the exposure to calcium channel blockers. (Moderate) Theoretical

▶ Ceritinib is predicted to increase the concentration of sufonylureas (glibenclamide). (Moderate) Theoretical

▶ Teriflunomide is predicted to increase the exposure to cefaclocil. (Moderate) Study

Ceritinib → see TABLE 15 p. 1377 (myelosuppression), TABLE 9 p. 1377 (QT-interval prolongation)

Ceritinib is predicted to increase the exposure to aliskiren. (Moderate) Theoretical

▶ Antacids are predicted to decrease the absorption of ceritinib. Separate administration by 2 hours. (Moderate) Theoretical

▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 9 p. 1377

▶ Antiepileptics (clobazam, lamotrigine, phenytoin, primidone) are predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 9 p. 1377

▶ Cefuroxime is predicted to decrease the exposure to ceritinib. (Severe) Study

▶ Ceftriaxone is predicted to increase the exposure to ceritinib. Avoid or adjust ceritinib dose, p. 973. (Severe) Study → Also see TABLE 9 p. 1377

▶ Idealisib is predicted to increase the exposure to ceritinib. Avoid or adjust ceritinib dose, p. 973. (Severe) Study → Also see TABLE 15 p. 1378

▶ Imatinib is predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378

▶ Lapatinib is predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 9 p. 1377

▶ Ceritinib is predicted to predict the exposure to loperamide. (Moderate) Theoretical

▶ Macrolides (azithromycin, erythromycin) are predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 9 p. 1377

▶ Macrolides (clarithromycin) are predicted to increase the exposure to ceritinib. Avoid or adjust ceritinib dose, p. 973. (Severe) Study → Also see TABLE 9 p. 1377

▶ Mitotane is predicted to decrease the exposure to ceritinib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378

▶ Neckiptan is predicted to increase the exposure to ceritinib. (Moderate) Theoretical

▶ Nilotinib is predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377

▶ Ceritinib is predicted to increase the exposure to NSAIDs: (celecoxib, diclofenac). Adjust dose. (Moderate) Theoretical

▶ Ceritinib is predicted to increase the exposure to opioids (alfentanil, fentanyl). Avoid. (Severe) Theoretical

▶ Ceritinib is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see TABLE 9 p. 1377

▶ Proton pump inhibitors are predicted to decrease the absorption of ceritinib. (Moderate) Theoretical

▶ Ranolazine is predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378

▶ Rifampicin is predicted to decrease the exposure to ceritinib. Avoid. (Severe) Study

▶ Ceritinib is predicted to increase the exposure to sirolimus. Avoid. (Severe) Theoretical

▶ St John’s Wort is predicted to decrease the exposure to ceritinib. Avoid. (Severe) Theoretical

▶ Ceritinib is predicted to increase the exposure to sulfonylureas (gliclazide). Adjust dose. (Moderate) Theoretical

▶ Ceritinib is predicted to increase the exposure to taxanes (paclitaxel). (Moderate) Theoretical → Also see TABLE 15 p. 1378

▶ Ceritinib is predicted to increase the exposure to tacrolimus. Avoid. (Severe) Theoretical

▶ Ceritinib is predicted to increase the exposure to topotecan. (Moderate) Theoretical → Also see TABLE 15 p. 1378

▶ Ceroticumab pegol is predicted to decrease the exposure to ceritinib. Study

▶ Cetirizine is predicted to decrease the exposure to ceritinib. Avoid. (Severe) Theoretical

▶ Cetuximab is predicted to decrease the exposure to ceritinib. Study

Cefuroxime

ROUTE-SPECIFIC INFORMATION

Interactions do not generally apply to topical use of cefuroxime unless specified.

▶ Cefuroxime is predicted to affect the efficacy of ceritinib. Avoid or adjust ceritinib dose. (Moderate) Theoretical

ROUTE-SPECIFIC INFORMATION

Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
Antiepileptics (phenobarbital, primidone) decrease the concentration of ciclosporin. [Moderate] Study

Intravenous ciclosporin increases the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (topiramate, phenytoin) affect the concentration of intravenous ciclosporin. Monitor concentration and adjust dose. [Severe] Study

Ciclosporin potentially increases the anticoagulant effect of coumarins. [Moderate] Anecdotal

Ciclosporin is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical

Ciclosporin decreases the efficacy of intravenous iron (injectable). [Moderate] Anecdotal

Ciclosporin decreases the efficacy of oral iron (oral). [Moderate] Theoretical

Ciclosporin is predicted to increase the exposure to sulfonylureas. [Severe] Study

Ciclosporin increases the concentration of tacrolimus. [Severe] Study

Chlordiazepoxide ➔ see TABLE 11 p. 1377 (CNS depressant effects)

Chlordiazepoxide affects the concentration of antiepileptics (topiramate, phenytoin). [Severe] Study

Rifampicin is predicted to decrease the exposure to ciclosporin. [Moderate] Theoretical

Chloroquine ➔ see antimalarials

Chlorothiazide ➔ see thiazide diuretics

Chlorphenamene ➔ see antihistamines, sedating

Chlorpromazine ➔ see phenothiazines

Chloraldehyde ➔ see thiazide diuretics

Chlorothiazide is predicted to increase the concentration of ciclosporin. [Severe] Study

Chlorothiazide affects the concentration of ciclosporin. [Severe] Study

Chlorothiazide increases the concentration of tacrolimus. [Severe] Study

Chlorothiazide increases the efficacy of oral cholestyramine. [Moderate] Study

Hydroxychloroquine is predicted to decrease the efficacy of oral cholestyramine. [Moderate] Theoretical

Cholic acid

Antacids are predicted to decrease the absorption of cholic acid. Separate administration by 5 hours. [Mild] Theoretical

Antiepileptics (phenobarbital) decrease the effects of cholic acid. Avoid. [Moderate] Study

Ciclosporin affects the concentration of cholic acid. Avoid. [Moderate] Study

Ciclosporin affects the concentration of cholic acid. [Moderate] Study

Cholic acid

Ciclosporin is predicted to increase the concentration of cholic acid. [Severe] Study

Ciclosporin is predicted to increase the concentration of cholic acid. [Severe] Study

Cholecalciferol is predicted to decrease the concentration of cholecalciferol. [Moderate] Study

Ciclesonide ➔ see corticosteroids

Ciclosporin ➔ see TABLE 2 p. 1375 (nephrotoxicity), TABLE 16 p. 1379 (increased serum potassium)

Pomelo juice is predicted to increase ciclosporin exposure, and grape juice is predicted to decrease ciclosporin exposure.

Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

Ciclosporin is predicted to increase the exposure to afatinib. Separate administration by 12 hours. [Moderate] Study

Ciclosporin markedly increases the exposure to aliskiren. Avoid. [Severe] Study ➔ Also see TABLE 16 p. 1379

Ciclosporin moderately increases the exposure to ambrisantan. Adjust ambrisantan dose, p. 184. [Moderate] Study

Ciclosporin increases the concentration of anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone). [Severe] Study

Antiarhythmics (amiodarone) increase the concentration of ciclosporin. Monitor concentration and adjust dose. [Severe] Study

Antiarhythmics (dronedarone) are predicted to increase the concentration of ciclosporin. [Severe] Study

Antiarhythmics (flecainide, propafenone, sotalol, flecainide, propafenone, sotalol) decrease the concentration of ciclosporin. [Severe] Study

Antiepileptics (oxcarbazepine) decrease the concentration of ciclosporin. [Severe] Anecdotal

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the concentration of ciclosporin. [Severe] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) increase the concentration of ciclosporin. [Severe] Study

Antifungals, azoles (miconazole) increase the concentration of ciclosporin. Monitor and adjust dose. [Severe] Anecdotal

Aprepitant is predicted to increase the concentration of ciclosporin. [Severe] Study

Ciclosporin is predicted to increase the exposure to beta blockers, non-selective (nadolol). [Moderate] Study

Ciclosporin is predicted to increase the exposure to bictegravir. Use with caution or avoid. [Moderate] Theoretical

Bosentan moderately decreases the exposure to ciclosporin and ciclosporin moderately increases the exposure to bosentan. Avoid. [Severe] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of ciclosporin. [Severe] Study

Calcium channel blockers (nicardipine) increase the concentration of ciclosporin. [Severe] Study

Ciclosporin moderately increases the exposure to calcium channel blockers (verapamil). Use with caution or avoid. [Severe] Study

Ciclosporin slightly increases the exposure to caspofungin. [Severe] Study

Ciclosporin is predicted to increase the exposure to cyclosporin. Avoid. [Severe] Theoretical

Ciclosporin is predicted to affect the efficacy of cyclosporin. [Severe] Study

Ciclosporin affects the concentration of cyclosporin. Avoid. [Moderate] Study

Ciclosporin increases the concentration of cyclosporin. [Severe] Study

Ciclosporin increases the exposure to colchicine. Avoid or adjust colchicine dose, p. 1126. [Severe] Study

Ciclosporin is predicted to increase the concentration of cyclosporin. [Severe] Study

Ciclosporin is predicted to increase the exposure to dabigatran. Avoid. [Severe] Theoretical

Ciclosporin is predicted to increase the risk of rhabdomyolysis when given with dapoxetine. [Severe] Theoretical

Ciclosporin is predicted to increase the exposure to darilfenacin. AVOID. [Moderate] Theoretical

Ciclosporin increases the concentration of digoxin. Monitor and adjust dose. [Severe] Theoretical

Ciclosporin slightly increases the exposure to edoxaban. Adjust edoxaban dose, p. 126. [Severe] Study

Ciclosporin decreases the exposure to eltrombopag. Monitor and adjust dose. [Moderate] Study

Ciclosporin decreases the exposure to etoricoxib. Monitor and adjust dose. [Severe] Study

Ciclosporin decreases the exposure to efavirenz. Decreases the concentration of ciclosporin. Monitor concentration and adjust dose. [Moderate] Study

Ciclosporin decreases the exposure to enzalutamide. Decreases the concentration of ciclosporin. [Severe] Study

Ciclosporin is predicted to increase the exposure to erlotinib. [Moderate] Theoretical

Ciclosporin increases the exposure to etoposide. Monitor and adjust dose. [Severe] Study

Ciclosporin moderately increases the exposure to everolimus. Avoid or adjust dose. [Severe] Study

Ciclosporin moderately increases the exposure to ezetimibe and ezetimibe slightly increases the exposure to ciclosporin. [Moderate] Study

Fibates (bezafibrate) are predicted to increase the risk of nephrotoxicity when given with ciclosporin. [Severe] Theoretical

Fibates (fenofibrate) increase the risk of nephrotoxicity when given with ciclosporin. [Severe] Study

Ciclosporin is predicted to increase the exposure to fidaxomicin. Avoid. [Moderate] Study

Ciclosporin increases the exposure to glecaprevir. Avoid or monitor. [Severe] Study

Grapefruit juice increases the concentration of ciclosporin. Avoid. [Severe] Study

Anecdotal

Theoretical

Moderate

Severe
Ciclosporin – Cilostazol

Ciclosporin (continued)

- Ciclosporin greatly increases the exposure to rapamycin. Avoid. (Severe) Study
- H₂ receptor antagonists (cimetidine) increase the concentration of ciclosporin. (Moderate) Study
- HIV-protease inhibitors increase the concentration of ciclosporin. (Severe) Study
- Idelalisib increases the concentration of ciclosporin. (Severe) Study
- Imatinib is predicted to increase the concentration of ciclosporin. (Severe) Study
- Lanthamide is predicted to decrease the absorption of oral ciclosporin. Adjust dose. (Severe) Theoretical
- Letermovir increases the exposure to ciclosporin and ciclosporin increases the exposure to letermovir. Monitor and adjust letermovir dose, p. 636. (Severe) Study
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with ciclosporin. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- Ciclosporin is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical
- Lumacaftor is predicted to decrease the exposure to ciclosporin. Avoid. (Severe) Theoretical
- Macrolides (clarithromycin) increase the concentration of ciclosporin. (Severe) Study
- Macrolides (erythromycin) are predicted to increase the concentration of ciclosporin. (Severe) Study
- Monoclonal antibodies (blinatumomab) are predicted to transiently increase the exposure to ciclosporin. Monitor and adjust dose. (Moderate) Theoretical
- Monoclonal antibodies (sarilumab) potentially affect the exposure to ciclosporin. Monitor and adjust dose. (Moderate) Theoretical
- Netupitant is predicted to increase the concentration of ciclosporin. (Severe) Study
- Nevirapine is predicted to decrease the concentration of ciclosporin. (Moderate) Study
- Nitotinib is predicted to increase the concentration of ciclosporin. (Severe) Study
- Ciclosporin is predicted to increase the concentration of nintedanib. (Moderate) Study
- Ciclosporin decreases the concentration of nintedanib. (Severe) Study
- Octreotide decreases the concentration of ciclosporin. Adjust ciclosporin dose, p. 838. (Severe) AneCotadal
- Palbociclib is predicted to increase the exposure to ciclosporin. Adjust dose. (Moderate) Theoretical
- Ciclosporin is predicted to increase the exposure to panobinostat. Adjust dose. (Moderate) Theoretical
- Pasireotide is predicted to decrease the absorption of oral ciclosporin. Adjust dose. (Severe) Theoretical
- Pitolisant is predicted to decrease the exposure to ciclosporin. Avoid. (Severe) Theoretical
- Ciclosporin is predicted to increase the concentration of ranolazine and ranolazine is predicted to increase the concentration of ciclosporin. (Moderate) Theoretical
- Ciclosporin moderately increases the exposure to repaglinide. (Moderate) Study
- Ribociclib is predicted to increase the exposure to ciclosporin. Use with caution and adjust dose. (Moderate) Theoretical
- Rifampicin decreases the concentration of ciclosporin. (Severe) Study
- Ciclosporin very markedly increases the exposure to rifaximin. (Severe) Study
- Ciclosporin very markedly increases the exposure to riociguat. (Moderate) Theoretical
- Rufaparib is predicted to increase the exposure to ciclosporin. Monitor and adjust dose. (Moderate) Study
- Ciclosporin moderately increases the exposure to sirolimus. Separate administration by 4 hours. (Severe) Study
- St John's Wort decreases the concentration of ciclosporin. Avoid. (Moderate) Study
- Ciclosporin very markedly increases the exposure to statins (atorvastatin). Avoid or adjust atorvastatin dose, p. 202. (Severe) Study
- Ciclosporin moderately increases the exposure to statins (fluvastatin). (Severe) Study
- Ciclosporin markedly very markedly increases the exposure to statins (pravastatin). Adjust dose. (Severe) Study
- Ciclosporin markedly increases the exposure to statins (rosuvastatin, simvastatin). Avoid. (Severe) Study
- Ciclosporin increases the concentration of tacrolimus. Avoid. (Severe) Study → Also see TABLE 2 p. 1375 → Also see TABLE 16 p. 1379
- Ciclosporin is predicted to increase the exposure to tenofovir alafenamide. (Moderate) Theoretical
- Ciclosporin is predicted to increase the exposure to tenofovir disoproxil. (Moderate) Theoretical → Also see TABLE 2 p. 1375
- Ciclosporin is predicted to increase the exposure to ticagrelor. Use with caution or avoid. (Severe) Study
- Ciclosporin increases the exposure to tofacitinib. Avoid. (Severe) Study
- Ciclosporin is predicted to increase the exposure to topotecan. (Severe) Study
- Ciclosporin is predicted to increase the concentration of tramebulin. (Moderate) Theoretical
- Ursodeoxycholic acid affects the concentration of ciclosporin. Use with caution and adjust dose. (Severe) AneCotadal
- Ciclosporin is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. (Severe) Theoretical
- Vitamin E supplements affect the exposure to ciclosporin. (Moderate) Study
- Ciclosporin increases the concentration of voxilaprevir. Avoid. (Severe) Study
- Cidofovir → See TABLE 2 p. 1375 (nephrotoxicity)
- Cilostazol → See TABLE 4 p. 1375 (antiplatelet effects)

GENERAL INFORMATION
Concurrent use with 2 or more antiplatelets or anticoagulants is contra-indicated.

- Antiplatelets (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to alter the effects of cilostazol. (Moderate) Theoretical
- Antifungals, azoles (fluconazole) are predicted to increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Antifungals, azoles (miconazole) are predicted to increase the exposure to cilostazol. Use with caution and adjust dose. (Moderate) Theoretical
- Cobimetapart is predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Enzalutamide is predicted to alter the effects of cilostazol. (Moderate) Theoretical
- HIV-protease inhibitors are predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Idelalisib is predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Cilostazol is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical
- Macroolides (clarithromycin) are predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Macroolides (erythromycin) slightly increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
- Mitotane is predicted to alter the effects of cilostazol. (Moderate) Theoretical
- Moclobemide is predicted to increase the exposure to cilostazol. (Moderate) Theoretical
- Proton pump inhibitors (esomeprazole) are predicted to increase the exposure to cilostazol. (Moderate) Theoretical
### Cimetidine

**FOOD AND LIFESTYLE** Dose adjustment might be necessary if smoking started or stopped during treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinesterases, centrally acting (galantamine)</td>
<td>Monitor and adjust dose.</td>
</tr>
<tr>
<td>Beta blockers, selective (metoprolol, nebivolol)</td>
<td>(Moderate) Study</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>(Moderate) Study</td>
</tr>
<tr>
<td>Clonidine</td>
<td>(Severe) Study</td>
</tr>
<tr>
<td>Etelcalcetide</td>
<td>(Severe) Study</td>
</tr>
<tr>
<td>Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)</td>
<td>Dose adjustment might be necessary if given with etelcalcetide.</td>
</tr>
<tr>
<td>Antihistamines, sedating</td>
<td>Monitor dose, avoid severe doses.</td>
</tr>
<tr>
<td>Antiepileptics (stiripentol)</td>
<td>Monitor and adjust dose.</td>
</tr>
<tr>
<td>Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone</td>
<td>Avoid.</td>
</tr>
<tr>
<td>Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)</td>
<td>Monitor dose, avoid severe doses.</td>
</tr>
<tr>
<td>Antiepileptics (phenobarbital)</td>
<td>Avoid.</td>
</tr>
<tr>
<td>Dapoxetine</td>
<td>Monitor dose, avoid severe doses.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Monitor dose, avoid severe doses.</td>
</tr>
</tbody>
</table>

### **Interactions**

**Cladribine**

- **Separation of administration:** Oral cladribine might affect the absorption of concurrently administered drugs—consider separating administration by at least 3 hours.

- **Antiepileptics (carbamazepine)** are predicted to increase the risk of haematological toxicity when given with oral cladribine.

- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Clarithromycin**

- **Clarithromycin** is predicted to increase the concentration of cladribine. (Severe) Study

**Clofazimine**

- **Clofazimine** potentially increases the risk of generalised infection (possibly life-threatening) when given with clofarabine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Clofarabine**

- **Clofarabine** potentially increases the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Clonazepam**

- **Clonazepam** potentially increases the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Clomipramine**

- **Clomipramine** potentially increases the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Clobazam**

- **Clobazam** potentially decreases the concentration of ropinirole. (Moderate) Study

**CLOPIDOGREL**

- **CLOPIDOGREL** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clomethiazole**

- **Clomethiazole** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clopenthixol**

- **Clopenthixol** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clopindipine**

- **Clopindipine** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clopitan**

- **Clopitan** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clotiapine**

- **Clotiapine** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clonazepam**

- **Clonazepam** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clonazepam**

- **Clonazepam** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Cloonoxazol**

- **Cloonoxazol** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clexane**

- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clexane**

- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

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- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

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- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clexane**

- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study

**Clexane**

- **Clexane** potentially increases the risk of QT-prolongation when given with bedaquiline. (Severe) Study
Clidipogrel (continued)

- **Antifungals, azoles (voriconazole)** are predicted to decrease the efficacy of clidipogrel. Avoid. (Moderate) Study
- **Clidipogrel** is predicted to increase the exposure to apilimide. (Moderate) Study
- **Clidipogrel** is predicted to increase the exposure to dabrafenib. (Moderate) Theoretical
- **Clidipogrel** is predicted to very markedly increase the exposure to dasabuvir. Avoid. (Severe) Study
- **Addison et al.** moderately increases the exposure to enzalutamide. Avoid or adjust enzalutamide dose, p. 947. (Severe) Study
- **Grapefruit juice** markedly decreases the exposure to clidipogrel. (Severe) Study
- **Modemide** is predicted to decrease the efficacy of clidipogrel. Avoid. (Moderate) Study
- **Clidipogrel** is predicted to moderately increase the exposure to montelukast. (Moderate) Study
- **Clidipogrel** increases the exposure to pioglitazone. Monitor blood glucose and adjust dose. (Severe) Study
- **Probenecid increases the exposure to (esomeprazole, omeprazole)** are predicted to decrease the efficacy of clidipogrel. Avoid. (Moderate) Study
- **Clidipogrel** increases the exposure to repaglinide. Avoid. (Moderate) Study
- **Clidipogrel** is predicted to increase the exposure to retinoids (alitretinoin). Adjust alitretinoin dose, p. 1262. (Moderate) Theoretical
- **Clidipogrel** is predicted to increase the exposure to selexipag. Adjust dose. (Moderate) Study
- **SSRIs (fluvoxamine)** are predicted to decrease the efficacy of clidipogrel. Avoid. (Severe) Theoretical → Also see TABLE 4 p. 1375
- **Clidipogrel** increases the exposure to statins (rosuvastatin). Adjust rosuvastatin dose, p. 204. (Moderate) Study
- **Clidipogrel** is predicted to increase the concentration of taxanes (paclitaxel). (Severe) Anecdotal
- **Clotrimazole** is predicted to increase the exposure to antifungals, azoles (itraconazole, ketoconazole). Adjust dose, p. 1376. Avoid or monitor side effects. (Severe) Study
- **Clodipine** is predicted to increase the effects of dopamine receptor antagonists. Avoid. (Moderate) Theoretical → Also see TABLE 2 p. 1376
- **Clonazepam** is predicted to decrease the effects of alprazolam. (Moderate) Study
- **Clonazepam increases the concentration of clozapine. Monitor side effects and adjust dose. (Severe) Study
- **Clozapine** is predicted to increase the concentration of levodopa. (Severe) Theoretical → Also see TABLE 8 p. 1376
- **Enalapril** is predicted to increase the exposure to clozapine. (Moderate) Theoretical
- **Iron chelators (deferasirox)** are predicted to increase the exposure to clozapine. Avoid. (Moderate) Theoretical
- **Leflunomide** is predicted to decrease the exposure to clozapine. (Moderate) Theoretical → Also see TABLE 15 p. 1376
- **Lurasidone** is predicted to increase the exposure to clozapine. (Moderate) Theoretical
- **Mirtazapine** is predicted to increase the exposure to clozapine. (Moderate) Theoretical
- **Rifampicin** decreases the exposure to clozapine. (Severe) Anecdotal
- **SSRIs (fluvoxamine)** increase the concentration of clozapine. Monitor side effects and adjust dose. (Severe) Study
- **Teriflunomide** is predicted to decrease the exposure to clozapine. (Moderate) Theoretical

**Clidipogrel** is predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose, p. 967. (Severe) Study
- **Clidipogrel** is predicted to markedly increase the exposure to abidol. (Severe) Study
- **Clidipogrel** increases the exposure to almotriptan. (Moderate) Study
- **Clidipogrel** is predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. (Moderate) Study
- **Clidipogrel** is predicted to increase the exposure to alfuzosin (doxazosin). (Moderate) Study
- **Clidipogrel** moderately increases the exposure to alprazolam. Avoid. (Moderate) Study
- **Clidipogrel** potentially increases the concentration of antiarrhythmics (amiodarone, disopyramide, flecainide, lidocaine). (Severe) Theoretical
- **Clidipogrel** very markedly increases the exposure to antiarrhythmics (dronedarone). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antiarrhythmics (propafenone). Monitor and adjust dose. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. (Moderate) Study
- **Clidipogrel** is predicted to affect the exposure to antimuscarinics (paclitaxel). (Severe) Anecdotal
- **Clidipogrel** is predicted to decrease the exposure to anthimastatines, non-sedating (mizolastine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antimalarials (halofantrine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to decrease the exposure to antimalarials (piperquine). (Severe) Theoretical
- **Clidipogrel** is predicted to increase the exposure to apilimide, azoles (fluconazole, posaconazole). Avoid or monitor side effects. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antifungals, azoles (itraconazole, ketoconazole). Adjust dose, p. 1376. Avoid or monitor side effects. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antifungals, azoles (itraconazole, ketoconazole). Adjust dose, p. 1376. Avoid or monitor side effects. (Severe) Study
- **Clidipogrel** is predicted to increase the concentration of antimuscarinics (oxitremorin). Avoid. (Severe) Theoretical
- **Clidipogrel** is predicted to increase the concentration of anthimastatines, non-sedating (mizolastine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antimalarials (halofantrine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the concentration of antimalarials (piperquine). (Severe) Theoretical
- **Clidipogrel** is predicted to increase the exposure to apilimide, azoles (fluconazole, posaconazole). Avoid or monitor side effects. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. (Moderate) Study
- **Clidipogrel** is predicted to affect the exposure to antimuscarinics (paclitaxel). (Severe) Anecdotal
- **Clidipogrel** is predicted to decrease the exposure to anthimastatines, non-sedating (mizolastine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to antimalarials (halofantrine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to decrease the exposure to antimalarials (halofantrine). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to beta agonists (salmeterol). Avoid. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to bedaquiline. Avoid prolonged use. (Mild) Study
- **Clidipogrel** is predicted to increase the exposure to beta agonists (salmeterol). Avoid. (Severe) Study
- **Clidipogrel** significantly increases the exposure to bortezomib. (Moderate) Study
- **Clidipogrel** is predicted to decrease the exposure to bosutinib. Avoid or adjust dose. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to bosutinib. Adjust bosutinib dose, p. 971. (Severe) Study
- **Clidipogrel** is predicted to increase the exposure to buspirone. Adjust buspirone dose, p. 342. (Severe) Study

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Cobicistat is predicted to increase the exposure to cabozantinib.  
(Moderate) Study

Cobicistat is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study

Cobicistat is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study

Cobicistat is predicted to markedly increase the exposure to calcium channel blockers (fercandipine). Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to cannabis extract. Use with caution and adjust dose. (Moderate) Theoretical

Cobicistat is predicted to moderately increase the exposure to cariprazine. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to ceritinib. Avoid or adjust ceritinib dose, p. 973. (Severe) Study

Cobicistat increases the concentration of ciclosporin. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to cinacalcet. Adjust dose. (Moderate) Study

Cobicistat is predicted to markedly increase the exposure to colchicine. Avoid or monitor for toxicity. (Severe) Study

Cobicistat is predicted to increase the exposure to colchicine. Avoid or adjust inhibitors of CYP3A4 or adjust colchicine dose, p. 1120. (Severe) Study

Cobicistat is predicted to increase the concentration of combined hormonal contraceptives. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to corticosteroids (beclometasone) (risk with beclometasone is likely to be lower than with other corticosteroids). (Moderate) Theoretical

Cobicistat is predicted to increase the exposure to corticosteroids (budesonide, fusidic acid, ciclosporin, deflazacort, dexamethasone, fluorouracil, itraconazole, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to crizotinib. Avoid. (Moderate) Study

Cobicistat is predicted to increase the exposure to dabigatran. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to dabrafenib. Use with caution or avoid. (Moderate) Study

Cobicistat is predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. (Severe) Study

Cobicistat is predicted to markedly increase the exposure to dasatinib. Avoid or adjust dose—consult product literature. (Severe) Study

Cobicistat very slightly increases the exposure to delamanid. (Severe) Study

Cobicistat increases the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study

Cobicistat increases the exposure to dopamine receptor agonists ( bromocriptine). (Severe) Study

Cobicistat is predicted to increase the concentration of dopamine receptor agonists (cabergoline). (Moderate) Anecdotal

Cobicistat is predicted to increase the exposure to doravirine. (Severe) Study

Cobicistat is predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical

Cobicistat is predicted to increase the exposure to edoxaban. Avoid. (Severe) Theoretical

Efavirenz is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to markedly increase the exposure to eletriptan. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Study

Cobicistat is predicted to increase the exposure to encorafenib. Avoid or monitor. (Severe) Study

Enzalutamide is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the risk of ergotism when given with ergometrine. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the risk of ergotism when given with ergotamine. Avoid. (Severe) Theoretical

Cobicistat is predicted to slightly increase the exposure to eletriptan. Use with caution and adjust dose. (Moderate) Study

Cobicistat is predicted to increase the exposure to esetemate. Adjust dose. (Moderate) Study

Cobicistat is predicted to increase the concentration of everolimus. Avoid. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to fosaprepitant. (Moderate) Theoretical

Cobicistat is predicted to increase the exposure to gefitinib. (Moderate) Study

Cobicistat potentially increases the exposure to glecaprevir. (Moderate) Theoretical

Cobicistat is predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Study

Cobicistat is predicted to very markedly increase the exposure to ibritinib. Avoid potent inhibitors of CYP3A4 or adjust ibritinib dose, p. 983. (Severe) Study

Cobicistat is predicted to increase the exposure to imatinib. (Moderate) Study

Cobicistat is predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

Cobicistat is predicted to increase the exposure to irinotecan. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 292 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 296 dose with potent inhibitors of CYP3A4. (Severe) Study

Cobicistat is predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study

Cobicistat is predicted to markedly increase the exposure to lomiptamide. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to luramidine. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to macitentan. (Moderate) Study

Cobicistat markedly increases the exposure to maraviroc. Refer to specialist literature. (Severe) Study

Cobicistat potentially increases the exposure to mexiletine. (Severe) Theoretical

Cobicistat is predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Severe) Study

Cobicistat is predicted to very markedly increase the exposure to midostaurin. Avoid or monitor for toxicity. (Severe) Study

Cobicistat is predicted to increase the exposure to mirabegron. Adjust mirabegron dose in hepatic and renal impairment, p. 781. (Moderate) Study

Cobicistat is predicted to increase the exposure to mitrazapine. (Moderate) Study

Mitotane is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to modafinil. (Mild) Theoretical

Cobicistat is predicted to increase the exposure to monoclonal antibodies (trastuzumab emtansine). Avoid. (Severe) Theoretical

Cobicistat is predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to netupitant. (Moderate) Study

Nevirapine is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to moderately increase the exposure to nilotinib. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to nitirizine. Adjust dose. (Moderate) Theoretical
Cobicistat – Cobicistat

Cobicistat is predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study

Cobicistat is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodeone, sufentanil). Monitor and adjust dose. (Severe) Study

Cobicistat is predicted to increase the exposure to ospemifene. Avoid in poor CYP2C9 metabolisers. (Moderate) Study

Cobicistat is predicted to increase the exposure to oxybutynin. (Mild) Study

Cobicistat is predicted to increase the exposure to palbociclib. Avoid or adjust palbociclib dose, p. 992. (Severe) Study

Cobicistat is predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. (Moderate) Study

Cobicistat is predicted to increase the exposure to paritaprevir. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to pazopanib. Avoid or adjust pazopanib dose, p. 993. (Moderate) Study

Cobicistat is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to pimozide. Avoid. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to praziquantel. (Mild) Study

Cobicistat is predicted to increase the exposure to quetiapine. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to ranolazine. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to reboxetine. Avoid. (Moderate) Study

Cobicistat is predicted to increase the exposure to regorafenib. Avoid. (Moderate) Study

Cobicistat is predicted to increase the exposure to regorafenib. Avoid. (Moderate) Study

Cobicistat is predicted to increase the exposure to repaglinide. (Moderate) Study

Cobicistat is predicted to increase the exposure to retinoids (all-transretinoic). Adjust all-transretinoic dose, p. 1262. (Moderate) Study

Cobicistat is predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. (Moderate) Study

Rifabutin decreases the concentration of cobicistat and cobicistat increases the exposure to rifabutin. Avoid or adjust dose. (Severe) Study

Rifampicin is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study

Cobicistat is predicted to increase the exposure to rivaroxaban. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to roxanol. Adjust dose and monitor side effects. (Moderate) Study

Cobicistat is predicted to increase the exposure to saxagliptin. (Moderate) Study

Cobicistat is predicted to increase the concentration of sirolimus. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to SSRIs (dapoxetine). Avoid potent inhibitors of CYP3A4 or adjust dapoxetine dose, p. 821. (Severe) Study

St John’s Wort is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to statins (atorvastatin). Avoid or adjust dose and monitor rhabdomyolysis. (Severe) Study

Cobicistat is predicted to increase the exposure to statins (simvastatin). Avoid. (Severe) Study

Cobicistat is predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. (Moderate) Study

Cobicistat is predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

Cobicistat is predicted to increase the exposure to taxanes (cabazitaxel). Avoid. (Severe) Study

Cobicistat is predicted to moderately increase the exposure to taxanes (docetaxel). Avoid or adjust dose. (Severe) Study

Cobicistat is predicted to increase the exposure to taxanes (paclitaxel). Avoid or moderate dose. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to tezacafor. Adjust tezacafor with ivacafor p. 296 dose with potent inhibitors of CYP3A4. (Severe) Study

Cobicistat is predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Cobicistat is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with potent inhibitors of CYP3A4. p. 660 (Severe) Study

Cobicistat is predicted to increase the exposure to toremifene. (Moderate) Theoretical

Cobicistat is predicted to increase the exposure to trabectedin. Avoid or adjust dose. (Severe) Theoretical

Cobicistat is predicted to moderately increase the exposure to trazodone. Avoid or adjust dose. (Moderate) Study

Cobicistat is predicted to slightly increase the exposure to tricyclic antidepressants. (Mild) Study

Cobicistat is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

Cobicistat is predicted to increase the exposure to vemurafenib. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Severe) Study

Cobicistat is predicted to increase the exposure to venlafaxine. (Moderate) Study

Cobicistat is predicted to increase the exposure to vinca alkaloids. (Severe) Theoretical

Cobicistat is predicted to increase the exposure to vitamin D substances (paricalcitol). (Moderate) Study

Cobicistat is predicted to increase the exposure to zopiclone. Adjust dose. (Moderate) Theoretical

Cobimetinib

Antiarrhythmics (dronedarone) are predicted to increase the exposure to cobimetinib. (Severe) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to cobimetinib. Avoid. (Severe) Theoretical

Antifungals, azoles (fluconazole, isavuconazole, miconazole, posaconazole) are predicted to increase the exposure to cobimetinib. (Severe) Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. (Severe) Study

Apremilast is predicted to increase the exposure to cobimetinib. (Severe) Theoretical

Bosentan is predicted to increase the exposure to cobimetinib. Avoid. (Severe) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to cobimetinib. (Severe) Theoretical

Cobicistat is predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. (Severe) Study

Crizotinib is predicted to increase the exposure to cobimetinib. (Severe) Theoretical

Efavirenz is predicted to decrease the exposure to cobimetinib. Avoid. (Severe) Theoretical

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Cobimetinib — Combined hormonal contraceptives

- **Enalapril** is predicted to decrease the exposure to cobimetinib. Avoid. [Moderate] Theoretical
- **Grapefruit juice** is predicted to increase the exposure to cobimetinib. Avoid. [Severe] Theoretical
- **HIV- Protease inhibitors** are predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. [Severe] Study
- **Lapatinib** is predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. [Severe] Study
- **Macrolides (clarithromycin)** are predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. [Severe] Study
- **Macrolides (erythromycin)** are predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to cobimetinib. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study
- **Pibrentasvir (with glecaprevir)** is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study
- **Velpatasvir** is predicted to increase the exposure to colchicine. [Moderate] Study
- **Vemurafenib** is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Theoretical

<table>
<thead>
<tr>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiarhythymics (dronedarone)</strong> are predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Antifungals, azoles (fluconazole, itraconazole, posaconazole)</strong> are predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Antifungals, azoles (itraconazole, ketoconazole, voriconazole)</strong> are predicted to increase the exposure to colchicine. Avoid potent inhibitors of CYP3A4 or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Aprepitant</strong> is predicted to decrease the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong> is predicted to markedly increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Aripiprazole (lamotrigine)</strong> is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Bosantan</strong> is predicted to decrease the exposure to colchicine. Use additional contraceptive precautions. [Moderate] Theoretical</td>
</tr>
<tr>
<td><strong>Brigatinib</strong> decreases the exposure to combined hormonal contraceptives. Use additional contraceptive precautions. [Moderate] Theoretical</td>
</tr>
<tr>
<td><strong>Combined hormonal contraceptives</strong> are predicted to increase the exposure to combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study</td>
</tr>
<tr>
<td><strong>Clobazam</strong> is predicted to decrease the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Coadministration</strong> with saquinavir, ritonavir, atazanavir/ritonavir, darunavir/ritonavir, indinavir/ritonavir, fosamprenavir/ritonavir, darunavir/cobicistat, amprenavir/ritonavir, or nelfinavir/ritonavir is predicted to decrease the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Cocaine</strong> is predicted to decrease the exposure to colchicine. Avoid or adjust colchicine dose, p. 1120. [Severe] Study</td>
</tr>
<tr>
<td><strong>Colchicine</strong> increases the risk of rhabdomyolysis when given with statins. [Severe] Anecdotal</td>
</tr>
<tr>
<td><strong>Combined hormonal contraceptives</strong> are predicted to increase the exposure to combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study</td>
</tr>
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<td><strong>Combined hormonal contraceptives</strong> are predicted to increase the exposure to combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study</td>
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<td><strong>Combination hormonal contraceptives</strong> are predicted to increase the exposure to combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study</td>
</tr>
</tbody>
</table>
Combined hormonal contraceptives (continued)
- Combined hormonal contraceptives increase the concentration of clozapine. Monitor side effects and adjust dose. [Severe] Study
- Cobicistat is predicted to decrease the efficacy of combined hormonal contraceptives. Avoid. [Severe] Study
- Combined hormonal contraceptives (containing ethinylestradiol) increase the risk of increased ALT concentrations when given with dasabuvir. Avoid. [Severe] Study
- Combined hormonal contraceptives are predicted to increase the exposure to dopamine receptor agonists (ropinirole). Adjust dose. [Moderate] Study
- Efavirenz is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- Encorafenib is predicted to affect the exposure to combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- Combined hormonal contraceptives slightly increase the exposure to erlotinib. Monitor side effects and adjust dose. [Moderate] Study
- Combined hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with metyrapone. Avoid. [Severe] Study
- HIV-protease inhibitors (atazanavir) (unboosted) increase the exposure to combined hormonal contraceptives. Adjust dose. [Severe] Study
- HIV-protease inhibitors (ritonavir) are predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal
- Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with lenalidomide. Avoid. [Severe] Theoretical
- Oral combined hormonal contraceptives slightly increase the exposure to lomitapide. Separate administration by 12 hours. [Moderate] Study
- Combined hormonal contraceptives are predicted to increase the exposure to loxapine. Avoid. [Unknown] Theoretical
- Lumacaftor is predicted to decrease the efficacy of combined hormonal contraceptives. Use additional contraceptive precautions. [Severe] Theoretical
- Combined hormonal contraceptives are predicted to increase the exposure to melatonin. [Moderate] Theoretical
- Combined hormonal contraceptives decrease the effects of metformin. Avoid. [Moderate] Theoretical
- Modafinil is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- Combined hormonal contraceptives slightly increase the exposure to monoamine-oxidase B inhibitors (rasagiline). [Moderate] Study
- Combined hormonal contraceptives increase the exposure to monoamine-oxidase B inhibitors (selegiline). Avoid. [Severe] Study
- Monoclonal antibodies (sarilumab) potentially decrease the exposure to combined hormonal contraceptives. [Severe] Theoretical
- Nevirapine is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- NSAIs (etoricoxib) slightly increase the exposure to combined hormonal contraceptives. [Moderate] Study
- Combined hormonal contraceptives potentially oppose the effects of ospemifene. Avoid. [Severe] Theoretical
- Combined hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with paritaprevir (with ritonavir andombitasvir). Avoid. [Severe] Study
- Combined hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with pivrentavir. Avoid. [Severe] Study
- Combined hormonal contraceptives are predicted to increase the exposure to pirfenidone. Use with caution and adjust dose. [Moderate] Study
- Pitolisant is predicted to decrease the efficacy of combined hormonal contraceptives. Avoid. [Severe] Theoretical
- Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with pomalidomide. Avoid. [Severe] Theoretical
- Combined hormonal contraceptives potentially oppose the effects of raloxifene. Avoid. [Severe] Theoretical
- Rifabutin is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- Rifampicin is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study
- Combined hormonal contraceptives are predicted to increase the exposure to roflumilast. [Moderate] Theoretical
- St John’s Wort decreases the efficacy of combined hormonal contraceptives. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal
- Sugammadex is predicted to decrease the exposure to oral combined hormonal contraceptives. Refer to patient information leaflet for missed pill advice. [Severe] Theoretical
- Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with thalidomide. Avoid. [Severe] Study
- Combined hormonal contraceptives are predicted to increase the exposure to theophylline. Monitor and adjust dose. [Moderate] Theoretical
- Combined hormonal contraceptives increase the exposure to tizanidine. Avoid. [Moderate] Study
- Uloprast is predicted to decrease the efficacy of combined hormonal contraceptives. Avoid. [Severe] Theoretical
- Combined hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with voxtalaprevir (with sofosbuvir andvelpatavir). Avoid. [Severe] Study
- Combined hormonal contraceptives are predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Moderate] Theoretical

Corticosteroids — see TABLE 17 p. 1379 (reduced serum potassium)
- beclometasone - betamethasone - budesonide - ciclesonide - deflazacort - dexamethasone - fludrocortisone - fluticasone - hydrocortisone - methylprednisolone - mometasone - prednisolone - triamcinolone
- Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified.
- With intravitreal use of dexamethasone in adults: caution with concurrent administration of anticoagulant or antiplatelet drugs—increased risk of haemorrhagic events.
- Antacids are predicted to decrease the absorption of deflazacort. Separate administration by 2 hours. [Moderate] Theoretical
- Antacids decrease the absorption of dexamethasone. [Moderate] Study
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fluticasone. [Unknown] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to beclometasone (risk with beclometasone is likely to be lower than with other corticosteroids). [Moderate] Theoretical
- Antifungals, azoles (miconazole) are predicted to increase the concentration of methylprednisolone. Monitor and adjust dose. [Moderate] Theoretical
- Antifungals, azoles, antibiotics (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. [Severe] Study
- Idelalisib is predicted to increase the exposure to corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. [Moderate] Theoretical
- Imatinib is predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- Corticosteroids are predicted to increase the risk of gastrointestinal bleeding when given with iron chelators (deferasirox). [Severe] Theoretical
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with corticosteroids (high-dose). Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Lumacaftor is predicted to decrease the exposure to methylprednisolone. Adjust dose. [Severe] Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to beclometasone (risk with beclometasone is likely to be lower than with other corticosteroids). [Moderate] Theoretical
- Macrolides (erythromycin) are predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- Macrolides (erythromycin) are predicted to increase the exposure to corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. [Moderate] Study
- Corticosteroids are predicted to decrease the efficacy of mifamurtide. Avoid. [Severe] Theoretical
- Mifepristone is predicted to decrease the efficacy of corticosteroids. Use with caution and adjust dose. [Moderate] Theoretical
- Mitotane is predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. [Severe] Study
- Mitotane is predicted to decrease the exposure to fluticasone. [Unknown] Theoretical
- Corticosteroids (betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisolone) are predicted to decrease the efficacy of monoclonal antibodies (atezolizumab, ipilimumab, nivolumab, pembrolizumab). Use with caution or avoid. [Severe] Theoretical
- Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to corticosteroids (dexamethasone, methylprednisolone). Monitor and adjust dose. [Moderate] Theoretical
- Corticosteroids are predicted to decrease the risk of immunosuppression when given with monoclonal antibodies (dinutuximab). Avoid except in life-threatening situations. [Severe] Study
- Netupitant is predicted to increase the exposure to oral budesonide. [Moderate] Study
- Netupitant is predicted to increase the exposure to dexamethasone. Adjust dose. [Moderate] Study
- Netupitant is predicted to increase the exposure to fluticasone. [Moderate] Study
- Netupitant is predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- Corticosteroids are predicted to decrease the effects of neuromuscular blocking drugs, non-depolarising. [Severe] Anecdotal
- Corticosteroids increase the risk of gastrointestinal perforation when given with nicardipine. [Severe] Anecdotal
- Nilotinib is predicted to increase the exposure to methylprednisolone. Monitor and adjust dose. [Moderate] Study
- NSAIDs increase the risk of gastrointestinal bleeding when given with corticosteroids. [Severe] Study
- Corticosteroids are predicted to increase the effects of phenindione. [Moderate] Anecdotal
Corticosteroids – Coumarins

**FOOD AND LIFESTYLE** The effects of coumarins can be reduced or abolished by vitamin K, including that found in health foods, food supplements, enteral feeds, or large amounts of some green vegetables or green tea. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption can affect anticoagulant control. Pomegranate juice is predicted to increase the INR in response to acenocumarol and warfarin.

- **Alcohol (beverage)** in those who drink heavily potentially decreases the anticoagulant effect of coumarins. (Severe) Study
- **Antiepileptics (carbamazepine)** decrease the effects of coumarins. Monitor and adjust dose. (Severe) Study
- **Antiepileptics (fosphenytoin, phenytoin)** are predicted to alter the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **Antifungals, azoles (fluconazole)** increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Moderate) Study
- **Antifungals, azoles (itraconazole)** potentially increase the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Antifungals, azoles (ketocanazole)** potentially increase the anticoagulant effect of warfarin. Monitor INR and adjust dose. (Severe) Anecdotal
- **Antifungals, azoles (miconazole)** greatly increase the anticoagulant effect of coumarins. MHRA advises avoid unless INR can be monitored closely; monitor for signs of bleeding. (Severe) Study
- **Antifungals, azoles (voriconazole)** increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Moderate) Study
- **Apalutamide** is predicted to decrease the exposure to coumarins. Avoid or monitor. (Mild) Study
- **Aprepitant** decreases the anticoagulant effect of coumarins. (Moderate) Study
- **Axitinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Azbathioprine** decreases the anticoagulant effect of coumarins. (Moderate) Study
- **Bosentan** decreases the anticoagulant effect of coumarins. (Moderate) Study
- **Bosutinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Cabozantinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Capeciticabine** increases the effects of coumarins. Monitor INR and adjust dose. (Moderate) Anecdotal
- **Cephalosporins (ceftiriazone)** potentially increase the risk of bleeding events when given with coumarins. (Severe) Anecdotal
- **Ceritinib** is predicted to increase the exposure to warfarin. Avoid. (Severe) Theoretical
- **Chloramphenicol** potentially increases the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **Corticosteroids** are predicted to increase the effects of coumarins. (Moderate) Study
- **Cranberry juice** potentially increases the anticoagulant effect of warfarin. Avoid. (Severe) Anecdotal
- **Crizotinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Dabrafenib** is predicted to decrease the anticoagulant effect of coumarins. (Severe) Theoretical
- **Danazol** potentially increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Dasatinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Disulfiram** increases the anticoagulant effect of coumarins. (Moderate) Study
- **Efavirenz** is predicted to affect the concentration of coumarins. Adjust dose. (Moderate) Theoretical
- **Elvitegravir** is predicted to decrease the anticoagulant effect of coumarins. (Moderate) Theoretical
- **Enteral feeds** (vitamin-K containing) potentially decrease the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Enalaprilat** potentially decreases the exposure to coumarins. Avoid or adjust dose and monitor INR. (Severe) Study
- **Erlotinib** increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Etravirine** increases the anticoagulant effect of coumarins. (Moderate) Theoretical
- **Fibrates** are predicted to increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Severe) Study
- **Fluvastatin** increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Fosaprepitant** is predicted to decrease the anticoagulant effect of coumarins. (Moderate) Theoretical
- **Gefitinib** is predicted to increase the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Glucagon** increases the anticoagulant effect of warfarin. (Severe) Study
- **Glucosamine** potentially decreases the anticoagulant effect of acenocumarol. (Moderate) Anecdotal
- **Glucosamine** potentially increases the anticoagulant effect of warfarin. Avoid. (Moderate) Anecdotal
- **Griseofulvin** potentially decreases the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **H2 receptor antagonists (cimetidine)** increase the anticoagulant effect of coumarins. (Severe) Study
- **HIV-protease inhibitors** (ritonavir) potentially decrease the anticoagulant effect of coumarins. Avoid. (Severe) Anecdotal
- **HIV-protease inhibitors** (atazanavir) are predicted to affect the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **HIV-protease inhibitors** (lopinavir) potentially decrease the anticoagulant effect of coumarins. Avoid. (Severe) Anecdotal
- **HIV-protease inhibitors** (ritonavir) are predicted to affect the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **HIV-protease inhibitors** (atazanavir) potentially decrease the anticoagulant effect of coumarins. Avoid. (Severe) Anecdotal
- **HIV-protease inhibitors** (lopinavir) are predicted to affect the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **Imatinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Ivermectin** potentially increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Lapatinib** is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- **Leflunomide** increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Leflunomide** increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- **Letermovir** is predicted to decrease the concentration of warfarin. Monitor and adjust dose. (Moderate) Theoretical
- **Lomitapide** increases the exposure to warfarin. Monitor INR and adjust dose. (Severe) Study
- **Macrolides (clarithromycin, erythromycin)** increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Severe) Anecdotal
- **Mecaptepinur** decreases the anticoagulant effect of coumarins. (Moderate) Anecdotal
- **Metronidazole** increases the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Severe) Study
- **Mesnexine** potentially affects the exposure to warfarin. Avoid. (Unknown) Theoretical
Interactions

### Crizotinib

**Crizotinib** is predicted to increase the exposure to **abemaciclib.** Avoid. (Moderate) Study

**Crizotinib** is predicted to increase the exposure to **aldosterone antagonists (eplerenone).** Adjust eplerenone dose, p. 493. (Severe) Study

**Crizotinib** is predicted to increase the exposure to alpha blockers (tamsulosin). (Moderate) Theoretical

**Crizotinib** is predicted to increase the exposure to **alprazolam.** Avoid. (Moderate) Study

**Crizotinib** is predicted to increase the exposure to **antihistamines, non-sedating (rupatadine).** Avoid. (Moderate) Study

**Crizotinib** is predicted to increase the concentration of **antimalarials (piperazine).** (Severe) Theoretical

**Crizotinib** is predicted to increase the exposure to **axitinib.** Avoid. (Moderate) Theoretical

**Crizotinib** is predicted to increase the exposure to **bedaquiline.** Avoid prolonged use. (Severe) Theoretical

**Crizotinib** is predicted to increase the exposure to **bosutinib.** Avoid or adjust dose. (Severe) Theoretical

**Crizotinib** is predicted to increase the exposure to **buspirone.** Use with caution and adjust dose. (Moderate) Study

**Crizotinib** is predicted to increase the exposure to **cabozantinib.** (Moderate) Theoretical

**Crizotinib** is predicted to increase the exposure to **calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine).** Monitor and adjust dose. (Moderate) Study

**Crizotinib** is predicted to increase the exposure to **cariprazine.** Avoid. (Severe) Study

**Crizotinib** is predicted to increase the exposure to **ceritinib.** Avoid. (Moderate) Study

**Crizotinib** is predicted to increase the concentration of **cilostazol.** (Severe) Study

**Cobicistat** is predicted to moderately increase the exposure to **crizotinib.** Avoid. (Moderate) Study
Crizotinib is predicted to increase the exposure to cabazitaxel.

Crizotinib is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1200 (Severe) Study.

Crizotinib is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. (Moderate) Study.

Crizotinib is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical.

Crizotinib is predicted to slightly increase the exposure to darifenacin. (Moderate) Study.

Crizotinib is predicted to increase the exposure to eltrombopag. Avoid or adjust dose—consult product literature. (Severe) Study.

Crizotinib is predicted to moderately increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Study.

Crizotinib is predicted to moderately increase the exposure to encorafenib. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to markedly decrease the exposure to ergolines. (Severe) Theoretical.

Crizotinib is predicted to increase the risk of ergotism when given with ergotamine. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to erlotinib. (Moderate) Theoretical.

Crizotinib is predicted to increase the concentration of everolimus. Avoid or adjust dose. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to fesoterodine. Adjust fesoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. (Mild) Study.

Crizotinib is predicted to increase the exposure to gefitinib. Avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378.

Crizotinib potentially decreases the exposure to glecaprevir. Avoid. (Severe) Theoretical.

Grapefruit juice is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Theoretical.

Crizotinib is predicted to increase the concentration of guanfacine. Adjust guanfacine dose. (Mild) Study.

HIV-protease inhibitors are predicted to moderately increase the exposure to crizotinib. Avoid. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to ibrutinib. Adjust ibrutinib dose with moderate inhibitors of CYP3A4, p. 983. (Severe) Study → Also see TABLE 15 p. 1378.

Idelalisib is predicted to moderately increase the exposure to crizotinib. Avoid. (Moderate) Study → Also see TABLE 15 p. 1378.

Crizotinib is predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. (Severe) Theoretical → Also see TABLE 6 p. 1376.

Crizotinib is predicted to increase the exposure to ivacaftor. Adjust ivacaftor or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study.

Crizotinib is predicted to increase the exposure to lapatinib. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical.

Crizotinib is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. (Moderate) Study.

Macrolides (clarithromycin) are predicted to moderately increase the exposure to crizotinib. Avoid. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to midostaurin. Monitor side effects and adjust dose. (Severe) Study.

Crizotinib is predicted to increase the exposure to midostaurin. (Moderate) Theoretical.

Mitotane is predicted to markedly decrease the exposure to crizotinib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378.

Crizotinib is predicted to increase the exposure to naxolone. Adjust naxolone dose and monitor side effects, p. 65. (Moderate) Study.

Nevirapine is predicted to decrease the exposure to crizotinib. Avoid. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical → Also see TABLE 15 p. 1378.

Crizotinib is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study → Also see TABLE 6 p. 1376.

Crizotinib is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 6 p. 1376.

Crizotinib is predicted to increase the exposure to oxycodone. (Mild) Theoretical.

Crizotinib is predicted to increase the exposure to pazopanib. (Moderate) Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil). Adjust avanafil dose, p. 812. (Moderate) Theoretical.

Crizotinib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 811. (Moderate) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (vardenafil). Adjust dose. (Severe) Theoretical → Also see TABLE 9 p. 1377.

Crizotinib potentially decreases the exposure to pioglitazone. Avoid. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see TABLE 9 p. 1377.

Pitolisant is predicted to decrease the exposure to crizotinib. Avoid. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study.

Crizotinib is predicted to increase the exposure to ranolazine. (Severe) Study → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the exposure to ribociclib. (Moderate) Study → Also see TABLE 9 p. 1377.

Rifampicin is predicted to markedly decrease the exposure to crizotinib. Avoid. (Severe) Study.

Crizotinib is predicted to increase the exposure to ruxolitinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378.

Crizotinib is predicted to increase the exposure to saxagliptin. (Mild) Study.

Crizotinib increases the concentration of sirolimus. Monitor and adjust dose. (Moderate) Study.

Crizotinib is predicted to increase the exposure to 555RIs (dapoxetine). Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. (Moderate) Theoretical.

St John’s Wort is predicted to decrease the exposure to crizotinib. Avoid. (Severe) Theoretical.

Crizotinib is predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. (Severe) Study.

Crizotinib is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. (Severe) Study.

Crizotinib is predicted to increase the exposure to sunitinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377.

Crizotinib is predicted to increase the concentration of tacrolimus. (Severe) Study.

Also see TABLE 9 p. 1377.
Cyclosporin
Calcium channel blockers
Brigatinib

Antifungals, azoles

Antiepileptics

Live vaccines

Cytarabine decreases the concentration of flucytosine. Avoid. [Severe] Study

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with cytarabine. Public Health England advises avoid (refer to Green Book). [Severe] Study

Cyproheptadine → see antihistamines, sedating

Cyclophosphamide → see alkylating agents

Cycloserine

Cycloserine increases the risk of CNS toxicity when given with isoniazid. Monitor and adjust dose. [Moderate] Study

Cytochrome P450 (CYP3A4) is predicted to increase the exposure to dabigatran. [Moderate] Study

Dabrafenib is predicted to increase the exposure to dabigatran. [Moderate] Study

Dabrafenib increases the exposure to dabigatran. Use with caution and adjust dose. [Severe] Theoretical

Dabrafenib is predicted to increase the exposure to dabigatran. Avoid. [Moderate] Study

Dabrafenib is predicted to decrease the exposure to dabigatran. Use with caution or avoid. [Moderate] Study

Dabrafenib is predicted to decrease the anticoagulant effect of coumarins. [Severe] Theoretical

Dabrafenib is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose. [Severe] Theoretical

Dabrafenib is predicted to decrease the exposure to dabrafenib. Avoid. [Moderate] Theoretical

Clobopirdrel is predicted to increase the exposure to dabrafenib. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to dabrafenib. Use with caution or avoid. [Moderate] Study

Dabrafenib is predicted to decrease the exposure to dabrafenib. Use with caution or avoid. [Moderate] Study

Fibrates (gemfibrozil) are predicted to increase the exposure to dabrafenib. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to dabrafenib. Use with caution or avoid. [Moderate] Study

Dabrafenib decreases the exposure to midazolam. Monitor and adjust dose. [Moderate] Study

Mitotane is predicted to decrease the exposure to dabrafenib. Avoid. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Rifampicin is predicted to decrease the exposure to dabrafenib. Avoid. [Moderate] Theoretical

Dacarbazine → see alkylating agents

Dactinomycin

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with dactinomycin. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
### Dairy products

- **Dairy products** are predicted to decrease the absorption of eltroambog, Eltroambog should be taken 2 hours before or 4 hours after dairy products, **Severe** Theoretical
- **Dairy products** decrease the exposure to tetracyclines (demeclocycline, oxytetracycline, tetracycline). Avoid, **Moderate** Theoretical Study

### Dalteparin

- Dalteparin → see low molecular-weight heparins

### Danaparoid

- Danaparoid → see TABLE 3 p. 1375 (anticoagulant effects)
- **Fibrates** is predicted to increase the risk of bleeding events when given with danaparoid. **Severe** Theoretical Study

### Danazol

- Danazol moderately increases the concentration of antiepileptics (carbamazepine). Monitor and adjust dose. **Severe** Theoretical Study
- Danazol increases the concentration of ciclosporin. **Severe** Theoretical Study
- Danazol potentially increases the anticoagulant effect of coumarins. **Anecdotal**
- Danazol is predicted to increase the risk of rhabdomyolysis when given with statins (atorvastatin). **Severe** Theoretical Study
- Danazol increases the risk of rhabdomyolysis when given with statins (simvastatin). Avoid, **Severe** Anecdotal

### Dapsone

- Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Dapsone is predicted to increase the risk of methaemoglobinemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. **Severe** Theoretical
- Antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Antimalarials (chloroquine, primaquine) are predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Nitrate are predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Nitrofurantoin is predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Paracetamol is predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Rifabutin decreases the exposure to dapsone. **Moderate** Study
- Rifampicin decreases the exposure to dapsone. **Moderate** Study
- Sodium nitroprusside is predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Sulfonamides are predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical
- Dapsone increases the exposure to trimethoprim and trimethoprim increases the exposure to dapsone. **Severe** Study

### Daptomycin

- **Aspirin** (high-dose) increases the risk of renal impairment when given with daptomycin. **Moderate** Theoretical
- Ciclosporin is predicted to increase the risk of rhabdomyolysis when given with daptomycin. **Severe** Theoretical
- Fibrates are predicted to increase the risk of rhabdomyolysis when given with daptomycin. **Severe** Theoretical
- **NSAIDs** increase the risk of renal impairment when given with daptomycin. **Moderate** Theoretical
- **Statins** are predicted to increase the risk of rhabdomyolysis when given with daptomycin. **Severe** Theoretical
- Daratumumab → see monoclonal antibodies
- Darbepoetin alfa → see TABLE 5 p. 1375 (thromboembolism), TABLE 16 p. 1379 (increased serum potassium)
- Darifenacin → see TABLE 10 p. 1377 (antimuscarinics)
- Antiarrhythmics (dronedarone) are predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Darifenacin is predicted to increase the concentration of antiarrhythmics (flecainide). **Moderate** Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to darifenacin. **Moderate** Theoretical
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Antifungals, azoles (itraconazole, ketocazole, voriconazole) are predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. **Severe** Study
- Apalutamide is predicted to decrease the exposure to darifenacin. Avoid or monitor. **Moderate** Study
- Aprepitant is predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Bupropion is predicted to slightly increase the exposure to darifenacin. **Mild** Study
- Calcium channel blockers (diltiazem, verapamip) are predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Ciclosporin is predicted to increase the exposure to darifenacin. Avoid. **Moderate** Theoretical
- Cinacalcet is predicted to slightly increase the exposure to darifenacin. **Mild** Study
- Cobicistat is predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. **Severe** Study
- Crizotinib is predicted to slightly increase the exposure to darifenacin. **Mild** Study
- Enzalutamide is predicted to decrease the exposure to darifenacin. **Moderate** Theoretical
- Grapefruit juice is predicted to increase the exposure to darifenacin. **Moderate** Study
- HIV-protease inhibitors are predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. **Severe** Study
- Idelalisib is predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. **Severe** Study
- Imatinib is predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Macrolides (clarithromycin) are predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. **Severe** Study
- Macrolides (erythromycin) are predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Milotane is predicted to decrease the exposure to darifenacin. **Moderate** Theoretical
- Netupitant is predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Nilotinib is predicted to slightly increase the exposure to darifenacin. **Moderate** Study
- Rifampicin is predicted to decrease the exposure to darifenacin. **Moderate** Study
- Rifaximin is predicted to slightly increase the exposure to darifenacin. **Mild** Study
- St John’s Wort is predicted to decrease the exposure to darifenacin. **Moderate** Theoretical
- Terbinafine is predicted to slightly increase the exposure to darifenacin. **Mild** Study
- Darifenacin is predicted to increase the exposure to tricyclic antidepressants. **Moderate** Theoretical → Also see TABLE 10 p. 1377

### Dasabuvir

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to dasabuvir. Avoid. **Severe** Theoretical
- Clopidogrel is predicted to very markedly increase the exposure to dasabuvir. Avoid. **Severe** Study

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**TABLE 1**

- Dairy products. Use with caution or avoid.

**TABLE 4**

- Aminosalicylic acid is predicted to increase the risk of methaemoglobinemia when given with dapsone. **Severe** Theoretical

**TABLE 5**

- Anecdotal

**TABLE 8**

- **Darifenacin** is predicted to markedly to very markedly increase the exposure to darifenacin. **Mild** Study

**TABLE 10**

- **Darifenacin** is predicted to slightly increase the exposure to darifenacin. **Mild** Study
**Dasabuvir – Desogestrel 1441**

- **Combined hormonal contraceptives** (containing ethinyl estradiol) increase the risk of increased ALT concentrations when given with dasabuvir. Avoid. [Severe] Study
- **Efavirenz** increases the risk of increased ALT concentrations when given with dasabuvir. Avoid. [Severe] Study
- **Enzalutamide** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Etravirine** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Fibates** (gemfibrozil) are predicted to very markedly increase the exposure to dasabuvir. Avoid. [Severe] Study
- **Dasabuvir** (with omibitasvir, paritaprevir, and ritonavir) decreases the concentration of HIV-protease inhibitors (darunavir). Avoid or adjust dose. [Moderate] Study
- **Dasabuvir** (with omibitasvir, paritaprevir, and ritonavir) decreases the concentration of loop diuretics (furosemide). Adjust dose. [Moderate] Study
- **Mitotane** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Nevirapine** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Rifampicin** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **St John’s Wort** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Dasabuvir** increases the exposure to statins (rosuvastatin). Adjust rosuvastatin dose, p. 204. [Moderate] Study

**Dasabuvir**

- → [See Table 15 p. 1378 (myelosuppression), Table 9 p. 1377 (QT-interval prolongation), Table 4 p. 1373 (antipatelet effects)]
- **Antacids** decrease the absorption of dasabuvir. Separate administration by at least 2 hours. [Moderate] Study
- **Antihyperthrmics (dronedarone)** are predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 9 p. 1377
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to markedly decrease the exposure to dasabuvir. Avoid. [Severe] Study
- **Antifungals, azoles (fluconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 9 p. 1377
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to markedly increase the exposure to dasabuvir. Avoid or adjust dose—consult product literature. [Severe] Study → Also see Table 9 p. 1377
- **Apalutamide** is predicted to decrease the exposure to dasabuvir. Avoid or monitor. [Moderate] Study → Also see Table 9 p. 1377
- **Aprepitant** is predicted to increase the exposure to dasabuvir. [Severe] Study
- **Bosentan** is predicted to decrease the exposure to dasabuvir. [Severe] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to dasabuvir. [Severe] Study
- **Cobicistat** is predicted to markedly increase the exposure to dasabuvir. Avoid or adjust dose—consult product literature. [Severe] Study
- **Dasabuvir** is predicted to increase the risk of bleeding events when given with **coumarins**. [Severe] Theoretical
- **Crixotinib** is predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 15 p. 1378 – Also see Table 9 p. 1377
- **Efavirenz** is predicted to decrease the exposure to dasabuvir. [Severe] Study → Also see Table 9 p. 1377
- **Enzalutamide** is predicted to markedly decrease the exposure to dasabuvir. Avoid. [Severe] Study
- **Grapefruit juice** is predicted to increase the exposure to dasabuvir. Avoid. [Moderate] Theoretical
- **H2 receptor antagonists** are predicted to decrease the exposure to dasabuvir. Avoid. [Moderate] Study
- **HIV-protease inhibitors** are predicted to markedly increase the exposure to dasabuvir. Avoid or adjust dose—consult product literature. [Severe] Study → Also see Table 9 p. 1377
- **Idelalisib** is predicted to markedly increase the exposure to dasabuvir. Avoid or adjust dose—consult product literature. [Severe] Study → Also see Table 15 p. 1378
- **Imatinib** is predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 15 p. 1378
- **Macrolides (clarithromycin)** are predicted to markedly increase the exposure to dasabuvir. Avoid or adjust dose—consult product literature. [Severe] Study → Also see Table 9 p. 1377
- **Macrolides (erythromycin)** are predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 9 p. 1377
- **Mitotane** is predicted to markedly decrease the exposure to dasabuvir. Avoid. [Severe] Study → Also see Table 15 p. 1378
- **Netupitant** is predicted to increase the exposure to dasabuvir. [Severe] Study
- **Nevirapine** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to dasabuvir. [Severe] Study → Also see Table 15 p. 1378 – Also see Table 9 p. 1377
- **Dasabuvir** is predicted to increase the risk of bleeding events when given with **phenindione**. [Severe] Theoretical
- **Pitolisant** is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- **Proton pump inhibitors** are predicted to slightly to moderately decrease the exposure to dasabuvir. Avoid. [Severe] Study
- **Rifampicin** is predicted to markedly decrease the exposure to dasabuvir. [Severe] Study
- **Study**
- **St John’s Wort** is predicted to increase the exposure to dasabuvir. [Severe] Study
- **Dasabuvir** is predicted to increase the exposure to statins (simvastatin). [Moderate] Theoretical
- **Dasuquin** → see anticholinergics
- **Decitabine** → see Table 15 p. 1378 (myelosuppression)
- **Deferasirox** → see iron chelators
- **Deferiprone** → see Table 15 p. 1378 (myelosuppression)
- **Antacids (aluminium hydroxide)** are predicted to decrease the absorption of deferiprone. Avoid. [Moderate] Theoretical
- **Ascorbic acid** is predicted to increase the risk of cardiovascular side-effects when given with deferiprone. [Severe] Theoretical
- **Deflazacort** → see corticosteroids
- **Delamanid** → see Table 9 p. 1377 (QT-interval prolongation)
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to slightly decrease the exposure to delamanid. Avoid. [Moderate] Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** very slightly increase the exposure to delamanid. [Severe] Study
- **Cobicistat** very slightly increases the exposure to delamanid. [Severe] Study
- **Enzalutamide** is predicted to slightly decrease the exposure to delamanid. Avoid. [Moderate] Study
- **HIV-protease inhibitors** very slightly increase the exposure to delamanid. [Severe] Study → Also see Table 9 p. 1377
- **Idelalisib** very slightly increases the exposure to delamanid. [Severe] Study
- **Mitotane** is predicted to slightly decrease the exposure to delamanid. Avoid. [Moderate] Study
- **Macrolides (clarithromycin)** very slightly increase the exposure to delamanid. [Severe] Study
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to slightly decrease the exposure to delamanid. [Severe] Study
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to markedly decrease the exposure to delamanid. Avoid. [Moderate] Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** very slightly decrease the exposure to delamanid. [Severe] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to delamanid. [Severe] Study → Also see Table 9 p. 1377
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to slightly decrease the exposure to delamanid. [Severe] Study
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to markedly increase the exposure to delamanid. Avoid. [Moderate] Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** very slightly increase the exposure to delamanid. [Severe] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to delamanid. [Severe] Study → Also see Table 9 p. 1377
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to slightly decrease the exposure to delamanid. [Severe] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to delamanid. [Severe] Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** very slightly increase the exposure to delamanid. [Severe] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to delamanid. [Severe] Study → Also see Table 9 p. 1377
- **Antiepileptics (lamotrigine)** are predicted to increase the risk of hyponatraemia when given with delamanid. [Severe] Theoretical
- **Loperamide** greatly increases the absorption of oral **desmopressin** (and possibly sublingual). [Moderate] Study
- **Phenothiazines (chlorpromazine)** are predicted to increase the risk of hyponatraemia when given with desmopressin. [Severe] Theoretical
- **Desogestrel**
- **Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate)** are predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, Interactions p. 794. [Severe] Theoretical

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Didanosine → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 12 p. 1378 (peripheral neuropathy)

**ROUTE-SPECIFIC INFORMATION**
Antacids in tablet formulation might affect absorption of other drugs—give at least 2 hours apart.

- Allopurinol moderately increases the exposure to didanosine. Avoid. (Severe) Study
- Didanosine (buffered) decreases the exposure to antifungals, azoles (itraconazole, ketoconazole). Separate administration by 2 hours. (Severe) Study → Also see TABLE 1 p. 1375
- Febuxostat is predicted to increase the exposure to didanosine. (Severe) Theoretical
- Ganciclovir is predicted to increase the exposure to didanosine. (Moderate) Study
- HIV-protease inhibitors (tipranavir) decrease the exposure to didanosine. Separate administration by 2 hours. (Moderate) Study
- Didanosine (buffered) decreases the exposure to HIV-protease inhibitors (atazanavir). Didanosine should be taken 2 hours after atazanavir. (Severe) Study
- Didanosine (buffered) is predicted to decrease the exposure to HIV-protease inhibitors (darunavir boosted with ritonavir). Didanosine should be taken 1 hour before or 2 hours after darunavir. (Moderate) Theoretical
- Hydroxyurea increases the risk of toxicity when given with didanosine. Avoid. (Severe) Study
- Isoniazid is predicted to increase the risk of peripheral neuropathy when given with didanosine. (Severe) Theoretical → Also see TABLE 1 p. 1375 – Also see TABLE 12 p. 1378
- Didanosine is predicted to increase the risk of pancreatitis when given with pentamidine. Avoid. (Severe) Study
- Didanosine (buffered) is predicted to greatly decrease the exposure to oral quinolones. Didanosine should be taken 2 hours after quinolones. (Moderate) Study
- Ribavirin is predicted to increase the exposure to didanosine. Avoid. (Severe) Study
- Didanosine increases the risk of toxicity when given with stavudine. Avoid. (Severe) Study → Also see TABLE 12 p. 1378
- Tenofovir disoproxil increases the risk of toxicity when given with didanosine. Avoid. (Severe) Study
- Valganciclovir is predicted to increase the exposure to didanosine. (Moderate) Study

**Digoxin** → see TABLE 6 p. 1376 (bradycardia)

**GENERAL INFORMATION**
Dugs that reduce serum potassium are predicted to increase the risk of digoxin toxicity, see TABLE 17 p. 1379.

- Acarbose decreases the concentration of digoxin. (Moderate) Study
- Aldosterone antagonists (eplerenone) very slightly increase the exposure to digoxin. (Mild) Study
- Aldosterone antagonists (spironolactone) increase the concentration of digoxin. Monitor and adjust dose. (Moderate) Study
- Aminoglycosides potentially increase the concentration of digoxin. Monitor and adjust dose. (Mild) Study
- Antacids decrease the absorption of digoxin. Separate administration by 2 hours. (Mild) Study
- Antiarrhythmics (amiodarone, dronedarone) are predicted to moderately increase the exposure to digoxin. Monitor and adjust digoxin dose, p. 109. (Severe) Study → Also see TABLE 6 p. 1376
- Antiarrhythmics (propafenone) increase the concentration of digoxin. Monitor and adjust dose. (Moderate) Study
- Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the concentration of digoxin. (Moderate) Anecdotall
- Antifungals, azoles (isavuconazole) slightly increase the exposure to digoxin. Monitor and adjust dose. (Moderate) Study
- Antifungals, azoles (itraconazole) are predicted to markedly increase the concentration of digoxin. Monitor and adjust dose. (Severe) Study
- Antimalarials (mefloquine) are predicted to increase the risk of bradycardia when given with digoxin. (Severe) Theoretical
Antimalarials (quinine) increase the concentration of digoxin. Monitor and adjust digoxin dose, p. 109. [Severe] Anecdotal

Aplutamide is predicted to decrease the exposure to digoxin. [Mild] Study

Balsalazide is predicted to decrease the concentration of digoxin. [Moderate] Theoretical

Brigatinib potentially increases the concentration of digoxin. [Moderate] Theoretical

Calcium channel blockers (diltiazem, verapamil) increase the concentration of digoxin. Monitor and adjust dose. [Severe] Study → Also see TABLE 6 p. 1376

Intravenous calcium salts increase the concentration of digoxin. Avoid. [Moderate] Anecdotal

Carbamazepine affects the concentration of digoxin. Monitor and adjust dose. [Moderate] Theoretical

Ceritinib is predicted to increase the exposure to digoxin. [Severe] Study

Ciclosporin increases the concentration of digoxin. [Moderate] Theoretical

Cipralex is predicted to increase the exposure to digoxin. Avoid or adjust dose. [Moderate] Study

Ciclosporin increases the concentration of digoxin. [Severe] Study

Cisapride is predicted to increase the exposure to digoxin. [Severe] Study

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical

Citalopram increases the concentration of digoxin. [Moderate] Theoretical
Dolutegravir (continued)

- **Efavirenz** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Encorafenib** is predicted to increase the exposure to dolutegravir. (Moderate) Theoretical
- **Enzalutamide** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Etravirine** moderately decreases the exposure to dolutegravir. Avoid unless given with atazanavir, darunavir, or lopinavir (all boosted with ritonavir). (Severe) Study
- **HIV-protease inhibitors (fosamprenavir boosted with ritonavir)** slightly decrease the exposure to dolutegravir. Avoid if resistant to HIV-integrase inhibitors. (Severe) Study
- **HIV-protease inhibitors (tipranavir)** moderately decrease the exposure to dolutegravir. Refer to specialist literature. (Severe) Study
- **Iron (oral)** decreases the absorption of dolutegravir. Dolutegravir should be taken 2 hours before or 6 hours after iron (oral). (Moderate) Study
- **Dolutegravir** increases the exposure to **metformin**. Use with caution and adjust dose. (Severe) Study
- **Mitotane** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Nevirapine** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Rifampicin** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **St John’s Wort** decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- **Sucralfate** decreases the absorption of dolutegravir. (Moderate) Study

**Domperidone** → see **TABLE 9** p. 1377 (QT-interval prolongation)

- **Antiarrhythmics (dronedarone)** increase the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study
- **Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole)** increase the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study
- **Aprepitant** increases the risk of QT-prolongation when given with **domperidone**. Avoid. (Severe) Study
- **Domperidone is predicted to decrease the effects of dopamine receptor agonists.** Avoid. (Moderate) Theoretical → Also see **TABLE 9** p. 1377

- **Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole)** are predicted to increase the concentration of **cablegrone.** (Moderate) Anecdotal

- **Aripiprazole** is predicted to decrease the effects of dopamine receptor agonists. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Asenapine** is predicted to decrease the effects of dopamine receptor agonists. Adjust dose. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Benzodiazepines** is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Bupropion** increases the risk of side-effects when given with **amantadine.** (Moderate) Study

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to **bromocriptine.** (Severe) Theoretical → Also see **TABLE 8** p. 1376

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the concentration of **cablegrone.** (Moderate) Anecdotal → Also see **TABLE 8** p. 1376

- **Clobazapine** is predicted to decrease the effects of dopamine receptor agonists. (Moderate) Theoretical → Also see **TABLE 10** p. 1377

- **Cobicistat** increases the exposure to **bromocriptine.** (Severe) Study

- **Cobicistat** is predicted to increase the concentration of **cablegrone.** (Moderate) Anecdotal

- **Combined hormonal contraceptives** are predicted to increase the exposure to ropinirole. Adjust dose. (Moderate) Study

- **Crizotinib** is predicted to increase the exposure to **bromocriptine.** (Severe) Theoretical

- **Domperidone is predicted to increase the concentration of ropinirole.** Adjust dose. (Moderate) Study

- **Dolutegravir** is predicted to increase the exposure to pramipexole. Adjust dose. (Moderate) Study

- **Droperidol** is predicted to decrease the prolactin-lowering effect of dopamine receptor agonists (bromocriptine, cabela IR). (Moderate) Theoretical

- **Dopamine receptor agonists (cabela IR)** are predicted to increase the risk of ergotism when given with dopamine receptor agonists (bromocriptine). Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Dopamine receptor agonists (cabela IR)** are predicted to increase the exposure to dopamine receptor agonists (pramipexole). Adjust dose. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Ergometrine** is predicted to increase the risk of ergotism when given with dopamine receptor agonists (cabela IR, pergolide). Avoid. (Moderate) Theoretical

**Dopamine receptor agonists** → see **TABLE 8** p. 1376 (hypotension), **TABLE 9** p. 1377 (QT-interval prolongation), **TABLE 10** p. 1377 (antimuscarnics)

- **Antimuscarnics**
  - **Dopamine receptor agonists** → see **TABLE 8** p. 1376 (hypotension), **TABLE 9** p. 1377 (QT-interval prolongation), **TABLE 10** p. 1377 (antimuscarnics)

- **Pramipexole** is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see **TABLE 9** p. 1377

- **Antiarrhythmics (dronedarone)** are predicted to increase the exposure to bromocriptine. (Severe) Theoretical

- **Antihypertensives** are predicted to increase the concentration of cabergoline. (Moderate) Anecdotal

- **Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole)** are predicted to increase the exposure to bromocriptine. (Severe) Study

- **Aprepitant** is predicted to increase the exposure to bromocriptine. Adjust dose. (Moderate) Study

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** increase the exposure to bromocriptine. (Severe) Study

- **Aripiprazole** is predicted to decrease the effects of dopamine receptor agonists. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Asenapine** is predicted to decrease the effects of dopamine receptor agonists. Adjust dose. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Benzodiazepines** is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Bupropion** increases the risk of side-effects when given with **amantadine.** (Moderate) Study

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to **bromocriptine.** (Severe) Theoretical → Also see **TABLE 8** p. 1376

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the concentration of **cablegrone.** (Moderate) Anecdotal → Also see **TABLE 8** p. 1376

- **Clobazapine** is predicted to decrease the effects of dopamine receptor agonists. (Moderate) Theoretical → Also see **TABLE 10** p. 1377

- **Cobicistat** increases the exposure to **bromocriptine.** (Severe) Study

- **Cobicistat** is predicted to increase the concentration of **cablegrone.** (Moderate) Anecdotal

- **Combined hormonal contraceptives** are predicted to increase the exposure to ropinirole. Adjust dose. (Moderate) Study

- **Crizotinib** is predicted to increase the exposure to **bromocriptine.** (Severe) Theoretical

- **Domperidone is predicted to increase the concentration of ropinirole.** Adjust dose. (Moderate) Study

- **Dolutegravir** is predicted to increase the exposure to pramipexole. Adjust dose. (Moderate) Study

- **Droperidol** is predicted to decrease the prolactin-lowering effect of dopamine receptor agonists (bromocriptine, cabergoline). (Moderate) Theoretical

- **Dopamine receptor agonists (cabergoline)** are predicted to increase the risk of ergotism when given with dopamine receptor agonists (bromocriptine). Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Dopamine receptor agonists (cabergoline)** are predicted to increase the exposure to dopamine receptor agonists (pramipexole). Adjust dose. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Dopamine receptor agonists (cabergoline, pergolide)** Avoid. (Moderate) Theoretical

- **Dopamine receptor agonists (cabeline)** are predicted to increase the concentration of cabergoline. (Moderate) Anecdotal

- **Domperidone is predicted to increase the concentration of ropinirole.** Adjust dose. (Moderate) Study

- **Dolutegravir** is predicted to increase the exposure to pramipexole. Adjust dose. (Moderate) Study

- **Droperidol** is predicted to decrease the prolactin-lowering effect of dopamine receptor agonists (bromocriptine, cabergoline). (Moderate) Theoretical

- **Dopamine receptor agonists (cabergoline)** are predicted to increase the risk of ergotism when given with dopamine receptor agonists (bromocriptine). Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Steady-state levelsresses** are predicted to increase the exposure to dopamine receptor agonists (pramipexole). Adjust dose. (Moderate) Theoretical → Also see **TABLE 8** p. 1376

- **Ergometrine** is predicted to increase the risk of ergotism when given with dopamine receptor agonists (cabergoline, pergolide). Avoid. (Moderate) Theoretical

**Food and Lifestyle** Dose adjustment might be necessary if smoking started or stopped during treatment with **ropinirole.**
Dopamine receptor agonists – Doravirine

- Ergotamine is predicted to increase the risk of ergotism when given with dopamine receptor agonists (bromocriptine, cabergoline). Avoid. [Moderate] Theoretical
- Ergotamine is predicted to increase the risk of ergotism when given with pergolide. [Moderate] Theoretical
- Flupentixol is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Apomorphine is predicted to increase the risk of severe hypertension when given with granisetron. [Severe] Theoretical
- H₂ receptor antagonists (cimetidine) are predicted to increase the exposure to pramipexole. Adjust dose. [Moderate] Study
- Haloperidol is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- HIV-protase inhibitors increase the exposure to bromocriptine. [Severe] Study
- HIV-protase inhibitors are predicted to increase the concentration of cabergoline. [Moderate] Anecdotal
- Hormone replacement therapy decreases the clearance of ropinirole. Monitor and adjust dose. [Moderate] Study
- Idealisib increases the exposure to bromocriptine. [Severe] Study
- Idealisib is predicted to increase the concentration of cabergoline. [Moderate] Anecdotal
- Imatinib is predicted to increase the exposure to bromocriptine. [Severe] Theoretical
- Imatinib is predicted to increase the concentration of cabergoline. [Moderate] Anecdotal
- Loxapine is predicted to decrease the effects of dopamine receptor agonists. [Moderate] Theoretical
- Macrolides (clarithromycin) increase the exposure to bromocriptine. [Severe] Study
- Macrolides (clarithromycin, erythromycin) are predicted to increase the concentration of cabergoline. [Severe] Study
- Macrolides (erythromycin) are predicted to increase the exposure to bromocriptine. [Severe] Theoretical
- Amantadine increases the risk of CNS toxicity when given with memantine. Use with caution or avoid. [Severe] Theoretical
- Memantine is predicted to increase the effects of dopamine receptor agonists (apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole, rotigotine). [Moderate] Theoretical
- Metoclopramide is predicted to decrease the effects of dopamine receptor agonists (apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole, rotigotine). Avoid. [Moderate] Study
- Mexiletine is predicted to increase the exposure to ropinirole. Adjust dose. [Moderate] Study
- Nilotinib is predicted to increase the exposure to bromocriptine. [Severe] Theoretical
- Nilotinib is predicted to increase the concentration of cabergoline. [Moderate] Anecdotal
- Olanzapine is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Apomorphine increases the risk of severe hypotension when given with ondansetron. Avoid. [Severe] Study
- Paliperidone is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Apomorphine is predicted to increase the risk of severe hypotension when given with palonosetron. [Severe] Theoretical
- Phenothiazines are predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Pimozide is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Quetiapine is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Quinolones (ciproxofloxacine) are predicted to increase the exposure to ropinirole. Adjust dose. [Moderate] Study
- Raloxifene is predicted to decrease the exposure to pramipexole. Adjust dose. [Moderate] Study
- Risperidone is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- SSRIs (fluvoxamine) are predicted to increase the exposure to ropinirole. Adjust dose. [Moderate] Study
- Sulpiride is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Cabergoline is predicted to increase the exposure to pramipexole. Adjust dose. [Moderate] Study
- Vandetanib is predicted to increase the exposure to pramipexole. Adjust dose. [Moderate] Study
- Zuclopenthixol is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
- Antiepileptics (oxcarbazepine) are predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to doravirine. [Moderate] Study
- Bosentan is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
- Cobimetinib is predicted to increase the exposure to doravirine. [Moderate] Study
- Dabrafenib is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
- Efavirenz is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
- HIV-protase inhibitors are predicted to increase the exposure to doravirine. [Moderate] Study
- Idealisib is predicted to increase the exposure to doravirine. [Moderate] Study
- Lumacaftor is predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to doravirine. [Moderate] Study
- Mitotane is predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
- Modafinil is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
- Nevirapine is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
- Rifabutin moderately decreases the exposure to doravirine. Adjust doravirine dose, p. 644. [Severe] Study
- Rifampicin is predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
- Doravirine is predicted to decrease the exposure to sirolimus. Monitor sirolimus concentration and adjust dose, p. 840. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical
- Doravirine is predicted to decrease the exposure to tacrolimus. Monitor tacrolimus concentration and adjust dose, p. 841. [Moderate] Theoretical
- Telotristat ethyl is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. [Severe] Theoretical
**Dorzolamide**

**ROUTE-SPECIFIC INFORMATION**
Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

**Dosulepin** → see tricyclic antidepressants

**Dosaxipram**
- **Aminophylline** increases the risk of agitation when given with dosaxipram. (Moderate) Study
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the effects of dosaxipram. (Moderate) Theoretical
- **Theophylline** increases the risk of agitation when given with dosaxipram. (Moderate) Study
- **Doxazosin** → see alpha blockers
- **Doxepin** → see tricyclic antidepressants
- **Doxorubicin** → see anthracyclines
- **Doxycycline** → see tetracyclines
- **Doxylamine** → see antihistamines, sedating
- **Dronedarone** → see antiarrhythmics

**Dropiprodol** → see TABLE 8 p. 1376 (hypotension), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 11 p. 1377 (CNS depressant effects)

**Dropiprodol** is predicted to decrease the effects of **dopamine receptor agonists**. Avoid. (Moderate) Theoretical → Also see TABLE 8 p. 1376 → Also see TABLE 9 p. 1377

**Dropiprodol** is predicted to decrease the effects of **guanethidine**. Monitor and adjust dose. (Moderate) Theoretical → Also see TABLE 8 p. 1376

**Dropiprodol** decreases the effects of **levodopa**. (Severe) Study → Also see TABLE 8 p. 1376

**Drospirenone** → see TABLE 16 p. 1379 (increased serum potassium)

**Antifungals, azoles** moderately increase the exposure to drospirenone. (Severe) Study

**Dulaglutide** → see TABLE 14 p. 1376 (anti-diabetic drugs)

**Duloxetine** → see TABLE 18 p. 1379 (hypotension), TABLE 13 p. 1378 (serotonin syndrome), TABLE 4 p. 1375 (antiplatelet effects)

- **Antiepileptics (phenytoin)** are predicted to decrease the exposure to duloxetine. (Moderate) Theoretical
- **Duloxetine is predicted to increase the exposure to beta blockers, selective (metoprolol).** (Moderate) Study
- **Duloxetine is predicted to increase the exposure to doxepin.** (Moderate) Theoretical

**Duloxetine** is predicted to decrease the exposure to duloxetine. (Moderate) Theoretical

**Duloxetine is predicted to increase the exposure to pitolisant.** Use with caution and adjust dose. (Moderate) Study

- **Quinolones (ciprofloxacin)** are predicted to increase the exposure to duloxetine. Avoid. (Moderate) Theoretical
- **Rifampicin** is predicted to decrease the exposure to duloxetine. (Moderate) Theoretical

** SSRIs (fluvoxamine) markedly increase the exposure to duloxetine. Avoid. (Severe) Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378 → Also see TABLE 4 p. 1375

**Teriflunomide** is predicted to decrease the exposure to duloxetine. (Moderate) Theoretical

**Dulvalumab** → see monoclonal antibodies

**Durvalumab** → see monoclonal antibodies

**Dutasteride**
- **Antiarhythmic (dronedarone)** are predicted to moderately increase the exposure to dutasteride. (Mild) Study
- **Antifungals, azoles (fluconazole, isavuconazole, posaconazole)** are predicted to moderately increase the exposure to dutasteride. (Mild) Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical
- **Apruptin is predicted to moderately increase the exposure to dutasteride.** (Mild) Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to moderately increase the exposure to dutasteride. (Mild) Study
- **Cobicistat** is predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical
- **Crizotinib** is predicted to moderately increase the exposure to dutasteride. (Mild) Study

**HIV-protease inhibitors are predicted to increase the exposure to dutasteride.** Monitor side effects and adjust dose. (Moderate) Theoretical

**Idelalisib** is predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical

- **Imatinib** is predicted to moderately increase the exposure to dutasteride. (Mild) Study
- **Macrolides (clarithromycin)** are predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical
- **Macrolides (erythromycin)** are predicted to moderately increase the exposure to dutasteride. (Mild) Study

**Netupitant** is predicted to moderately increase the exposure to dutasteride. (Mild) Study

**Nilotinib** is predicted to moderately increase the exposure to dutasteride. (Mild) Study

**Eculizumab** → see monoclonal antibodies

**Edoxaban** → see TABLE 3 p. 1375 (anticoagulant effects)
- **Antiarhythmic (amiodarone)** slightly increase the exposure to edoxaban. (Severe) Study
- **Antiarhythmic (dronedarone)** slightly increase the exposure to edoxaban. Adjust edoxaban dose, p. 126. (Severe) Study
- **Antiepileptics (carbamazepine)** are predicted to decrease the exposure to edoxaban. (Moderate) Study
- **Antiepileptics (phenytoin)** are predicted to decrease the exposure to edoxaban. (Moderate) Theoretical
- **Antifungals, azoles (itraconazole)** are predicted to slightly increase the exposure to edoxaban. (Severe) Theoretical
- **Ceritinib** is predicted to increase the exposure to edoxaban. (Moderate) Theoretical
- **Ciclosporin slightly increases the exposure to edoxaban.** Adjust edoxaban dose, p. 126. (Severe) Study
- **Cobicistat is predicted to increase the exposure to edoxaban.** Avoid. (Severe) Study
- **Edoxaban is predicted to slightly increase the exposure to edoxaban.** (Moderate) Study
- **Edoxaban is predicted to slightly increase the exposure to edoxaban.** Adjust dose. (Moderate) Study
- **HIV-protease inhibitors (lopinavir, ritonavir, saquinavir)** are predicted to slightly increase the exposure to edoxaban. (Severe) Theoretical
- **Lapatinib** is predicted to slightly increase the exposure to edoxaban. (Severe) Theoretical
- **Macrolides (azithromycin, clarithromycin)** are predicted to slightly increase the exposure to edoxaban. (Severe) Theoretical
- **Macrolides (erythromycin)** slightly increase the exposure to edoxaban. Adjust edoxaban dose, p. 126. (Severe) Study
- **Mirabegron is predicted to increase the exposure to edoxaban.** (Mild) Theoretical
- **Paritaprevir (with ritonavir and obinutuzumab)** is predicted to increase the exposure to edoxaban. (Severe) Study
- **Pibrentasvir (with glecaprevir)** is predicted to increase the exposure to edoxaban. (Moderate) Study
- **Pitolisant is predicted to decrease the exposure to edoxaban.** (Mild) Theoretical
- **Ranolazine is predicted to slightly increase the exposure to edoxaban.** (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to edoxaban. (Moderate) Study
- **St John’s Wort is predicted to decrease the exposure to edoxaban.** (Moderate) Study
- **Velpatasvir is predicted to increase the exposure to edoxaban.** (Severe) Theoretical
- **Vemurafenib is predicted to slightly increase the exposure to edoxaban.** (Severe) Theoretical
- **Voxilaprevir (with sofosbuvir and velpatasvir)** is predicted to increase the concentration of edoxaban. Avoid. (Severe) Theoretical

**Efavirenz** → see TABLE 9 p. 1377 (QT-interval prolongation)

**Efavirenz is predicted to decrease the exposure to antiarhythmics (dronedarone).** (Severe) Theoretical → Also see TABLE 9 p. 1377
Efavirenz decreases the exposure to **dolutegravir**. Adjust dose. **Severe** Study

Efavirenz is predicted to decrease the exposure to **doravirine**. Avoid or adjust doravirine dose, p. 644. **Severe** Theoretical

Efavirenz is predicted to moderately decrease the exposure to efaviravir. Avoid. **Severe** Study

Efavirenz is predicted to decrease the exposure to **elgilustat**. **Moderate** Theoretical

Efavirenz is predicted to decrease the concentration of elvitegravir. Avoid. **Severe** Study

Efavirenz is predicted to decrease the effects of **ergotamine**. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to **erlotinib**. **Severe** Theoretical

Efavirenz is predicted to decrease the efficacy of **etnogestrel**. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to **etrafivirine**. Avoid. **Severe** Study

Efavirenz is predicted to decrease the concentration of everolimus. Avoid or adjust dose. **Severe** Study

Efavirenz is predicted to decrease the exposure to fosaprepitant. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to gefitinib. Avoid. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to glecaprevir. Avoid. **Severe** Study

Efavirenz is predicted to markedly decrease the exposure to **grazoprevir**. Avoid. **Severe** Study

Efavirenz is predicted to decrease the concentration of guanine. Adjust dose. **Moderate** Theoretical

Efavirenz decreases the exposure to **HIV-protease inhibitors**. Refer to specialist literature. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the effects of **Hormone replacement therapy**. **Moderate** Anecdotal

Efavirenz is predicted to decrease the exposure to idelalisib. Avoid. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to **Imatinib**. **Moderate** Study

Efavirenz is predicted to decrease the exposure to **Ivacatant**. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to **lapatinib**. Avoid. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the concentration of letemovir. **Moderate** Theoretical

Efavirenz is predicted to decrease the efficacy of **levonordestrel**. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to **Lurasidone**. Monitor and adjust dose. **Moderate** Theoretical

Efavirenz decreases the exposure to macrolides (clarithromycin). **Moderate** Study → Also see TABLE 9 p. 1377

Efavirenz decreases the exposure to maraviroc. Refer to specialist literature. **Severe** Theoretical

Efavirenz is predicted to alter the effects of **midazolam**. Avoid. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to **netupitant**. **Moderate** Theoretical

Nevirapine decreases the concentration of **efavirenz**. Avoid. **Severe** Study

Efavirenz is predicted to decrease the exposure to **nitoxolinib**. Avoid. **Severe** Theoretical → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the exposure to **noretinone**. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Anecdotal

Efavirenz is predicted to decrease the exposure to **olaparib**. Avoid. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to **omnitvasir**. Avoid. **Severe** Theoretical

Efavirenz decreases the exposure to opioids (methadone). Monitor and adjust dose. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the exposure to **osimertinib**. **Moderate** Theoretical → Also see TABLE 9 p. 1377

Antiepileptics (carbamazepine) slightly decrease the exposure to efavirenz and efavirenz slightly decreases the exposure to antiepileptics (carbamazepine). **Severe** Study

Antiepileptics (fosphenytoin, phenytoin) slightly decrease the exposure to efavirenz and efavirenz affects the concentration of antiepileptics (fosphenytoin, phenytoin). **Severe** Theoretical

Antiepileptics (phenobarbital) are predicted to decrease the exposure to efavirenz and efavirenz affects the concentration of antiepileptics (phenobarbital). **Severe** Theoretical

Efavirenz is predicted to affect the efficacy of antiepileptics (primidone) and antiepileptics (primidine) are predicted to slightly decrease the exposure to efavirenz. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to antifungals, azoles (itraconazole). Avoid. For 14 days after stopping efavirenz. **Moderate** Study

Efavirenz slightly decreases the exposure to antifungals, azoles (itraconazole). Avoid. **Severe** Theoretical

Efavirenz moderately decreases the exposure to antifungals, azoles (ketocanazole). **Severe** Study

Efavirenz slightly decreases the exposure to antifungals, azoles (posaconazole). Avoid. **Moderate** Study

Efavirenz moderately decreases the exposure to antifungals, azoles (voriconazole) and antifungals, azoles (voriconazole) slightly increase the exposure to efavirenz. Adjust dose. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz decreases the concentration of antimalarial (artemether). **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz moderately decreases the exposure to antimalarial (atovaquone). Avoid. **Moderate** Study

Efavirenz affects the exposure to antimalarial (proguanil). Avoid. **Moderate** Study

Efavirenz is predicted to decrease the exposure to aprepitant. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to axitinib. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to bedaquiline. Avoid. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the exposure to bosutinib. Avoid. **Severe** Theoretical → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the exposure to brigatinib. Avoid. **Severe** Study

Efavirenz is predicted to decrease the exposure to bruproprion. **Moderate** Study

Efavirenz is predicted to decrease the exposure to cabazitaxel. **Moderate** Theoretical → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to cariprazine. Avoid. **Severe** Theoretical

Efavirenz is predicted to decrease the concentration of caspofungin. Adjust dose. **Moderate** Study

Efavirenz decreases the concentration of ciclosporin. Monitor concentration and adjust dose. **Moderate** Study

Efavirenz is predicted to decrease the exposure to cobicistat. **Severe** Theoretical

Efavirenz is predicted to decrease the exposure to cobimetinib. **Severe** Theoretical

Efavirenz is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Study

Efavirenz is predicted to affect the concentration of coumarins. Adjust dose. **Moderate** Theoretical

Efavirenz is predicted to decrease the exposure to crizotinib. Avoid. **Severe** Theoretical → Also see TABLE 9 p. 1377

Efavirenz increases the risk of increased ALT concentrations when given with dasabuvir. Avoid. **Severe** Study

Efavirenz is predicted to decrease the exposure to dasatinib. **Severe** Study → Also see TABLE 9 p. 1377

Efavirenz is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. **Severe** Theoretical

Antiepileptics (azoles) are predicted to decrease the exposure to efavirenz. **Severe** Theoretical

Antiepileptics (ergotamine, triptans) slightly decrease the exposure to efavirenz and efavirenz slightly decreases the exposure to antiepileptics (ergotamine, triptans). **Severe** Theoretical

Antiepileptics (methylphenidate, amphetamines) are predicted to decrease the exposure to efavirenz and efavirenz increases the risk of increased ALT concentrations when given with mianserin. Avoid. **Severe** Study

Antiepileptics (valproate) is predicted to alter the effects of efavirenz. **Severe** Study
Efavirenz (continued)  
▶ Efavirenz is predicted to decrease the exposure to osplmenfene.  
   Moderate Study
▶ Efavirenz is predicted to decrease the exposure to paritaprevir  
   (with ritonavir and ombitasvir). Avoid.  
   Severely Study
▶ Efavirenz is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors.  
   Moderate Theoretical — Also see TABLE 9 p. 1377
▶ Efavirenz is predicted to decrease the exposure to ribociclib.  
   Moderate Study — Also see TABLE 9 p. 1377
▶ Efavirenz slightly decreases the exposure to rilpivirine. Adjust dose.  
   Severely Study
▶ Rifampicin slightly decreases the exposure to efavirenz. Adjust dose.  
   Severely Theoretical
▶ Efavirenz is predicted to decrease the exposure to quetiapine.  
   Moderate Study
▶ Efavirenz is predicted to decrease the exposure to sirolimus.  
   Moderate and adjust dose.  
   Moderate Theoretical
▶ St John’s Wort is predicted to decrease the concentration of  
   atorvastatin.  
   Severe Study
▶ Efavirenz moderately decreases the exposure to statins  
   (atorvastatin).  
   Severe Study
▶ Efavirenz is predicted to decrease the concentration of  
   tacrolimus. Monitor and adjust dose.  
   Moderate Theoretical
▶ Efavirenz is predicted to decrease the exposure to taxanes  
   (cabazitaxel). Avoid.  
   Severe Study
▶ Efavirenz is predicted to decrease the concentration of  
   temsirolimus. Avoid.  
   Severe Theoretical
▶ Efavirenz is predicted to decrease the exposure to ticagrelor.  
   Moderate Theoretical
▶ Efavirenz is predicted to decrease the exposure to tofacitinib.  
   Moderate Study
▶ Efavirenz decreases the efficacy of ulipristal. For FSRH  
   guidance, see Contraceptives, interactions p. 794.  
   Severe Anecdotal
▶ Efavirenz is predicted to decrease the exposure to velpatasvir. Avoid.  
   Moderate Theoretical
▶ Efavirenz is predicted to decrease the exposure to venetoclax.  
   Severe Study
▶ Efavirenz is predicted to decrease the concentration of  
   voriparirev. Avoid.  
   Severe Theoretical

Elbasvir  
▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,  
   phenytoin, primidone) are predicted to decrease the exposure  
   to elbasvir. Avoid.  
   Severe Study
▶ Bosantan is predicted to moderately decrease the exposure to  
   elbasvir. Avoid.  
   Severe Study
▶ Cabazitaxel is predicted to increase the concentration of  
   dabigatran.  
   Moderate Theoretical
▶ Efavirenz is predicted to moderately decrease the exposure  
   to elbasvir. Avoid.  
   Severe Study
▶ Enzalutamide is predicted to decrease the exposure to elbasvir.  
   Avoid.  
   Severe Study
▶ Etravirine is predicted to decrease the exposure to elbasvir.  
   Avoid.  
   Unknown Theoretical
▶ Mitotane is predicted to decrease the exposure to elbasvir.  
   Avoid.  
   Severe Study
▶ Modafinil is predicted to decrease the exposure to elbasvir.  
   Avoid.  
   Unknown Theoretical
▶ Nevirapine is predicted to moderately decrease the exposure  
   to elbasvir. Avoid.  
   Severe Study
▶ Rifampicin is predicted to decrease the exposure to elbasvir.  
   Avoid.  
   Severe Study
▶ St John’s Wort is predicted to moderately decrease the exposure  
   to elbasvir. Avoid.  
   Severe Study
▶ Elbasvir increases the exposure to statins (atorvastatin). Adjust  
   Moderate Study
▶ Elbasvir is predicted to increase the exposure to statins  
   Unknown Theoretical
▶ Elbasvir increases the exposure to statins (rosuvastatin). Adjust  
   rosuvastatin dose, p. 204.  
   Moderate Study
▶ Elbasvir is predicted to increase the exposure to statins  
   (simvastatin). Adjust simvastatin dose, p. 205.  
   Unknown Theoretical
▶ Elbasvir is predicted to increase the concentration of sunitinib.  
   Use with caution and adjust dose.  
   Moderate Theoretical
▶ Eletriptan  
   → see TABLE 13 p. 178 (serotonin syndrome)
▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole)  
   are predicted to markedly increase the exposure to eletriptan.  
   Avoid.  
   Severe Study
▶ Aprepitant is predicted to increase the exposure to eletriptan.  
   Moderate Study
▶ Cobicistat is predicted to markedly increase the exposure to  
   eletriptan. Avoid.  
   Severe Study
▶ Eletriptan increases the risk of vasovaginalismus when given  
   with ergotamine. Separate administration by 24 hours.  
   Severe Study
▶ HIV-protease inhibitors are predicted to markedly increase  
   the exposure to eletriptan. Avoid.  
   Severe Study
▶ Idelalisib is predicted to markedly increase the exposure to  
   eletriptan. Avoid.  
   Severe Study
▶ Macrolides (clarithromycin) are predicted to markedly increase  
   the exposure to eletriptan. Avoid.  
   Severe Study
▶ Macrolides (erythromycin) moderately increase the exposure  
   to eletriptan.  
   Moderate Study
▶ Netupitant is predicted to increase the exposure to eletriptan.  
   Moderate Study

Eliglustat  
▶ Abiraterone is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Eliglustat is predicted to increase the exposure to alicriken.  
   Adjust dose.  
   Moderate Study
▶ Antiarrhythmics (dronedarone, propafenone) are predicted  
   to increase the exposure to eliglustat. Avoid or adjust dose—  
   consult product literature.  
   Severe Study
▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,  
   phenytoin, primidone) are predicted to decrease the exposure  
   to eliglustat. Avoid.  
   Severe Study
▶ Antifungals, azoles (fluconazole, itraconazole, ketoconazole,  
   posaconazole, voriconazole) are predicted to increase the exposure  
   to eliglustat. Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Eliglustat is predicted to increase the exposure to antihistamines,  
   non-sedating (fexofenadine). Adjust dose.  
   Moderate Study
▶ Aprepitant is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Eliglustat is predicted to increase the exposure to atomoxetine.  
   Adjust dose.  
   Moderate Theoretical
▶ Antiarhythmics are predicted to increase the exposure to beta  
   blockers, non-selective (propranolol). Adjust dose.  
   Moderate Study
▶ Eliglustat is predicted to increase the exposure to beta blockers,  
   selective (metoprolol). Adjust dose.  
   Moderate Study
▶ Bosantan is predicted to decrease the exposure to eliglustat.  
   Moderate Theoretical
▶ Bupropion is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Calcium channel blockers (diltiazem, verapamil) are predicted  
   to increase the exposure to eliglustat. Avoid or adjust dose—  
   consult product literature.  
   Severe Study
▶ Cinacalcet is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Cobicistat is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
▶ Eliglustat is predicted to increase the exposure to colchicine.  
   Avoid or adjust colchicine dose, p. 1120.  
   Severe Theoretical
▶ Crizotinib is predicted to increase the exposure to eliglustat.  
   Avoid or adjust dose—consult product literature.  
   Severe Study
Eliglustat is predicted to increase the exposure to dacarbazine. Adjust dose. [Moderate] Study

Eliglustat increases the exposure to digoxin. Adjust dose. [Moderate] Study

Duloxetine is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Eliglustat is predicted to increase the exposure to edoxaban. Adjust dose. [Moderate] Study

Efavirenz is predicted to decrease the exposure to eliglustat. [Moderate] Theoretical

Enalapril is predicted to decrease the exposure to eliglustat. Avoid. [Severe] Study

Eliglustat is predicted to increase the exposure to everolimus. Adjust dose. [Moderate] Study

Grapefruit juice is predicted to increase the exposure to eliglustat. Avoid. [Severe] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Idelalisib is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Imatinib is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Eliglustat is predicted to increase the exposure to loperamide. Adjust dose. [Moderate] Study

Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Theoretical

Mirabegron is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Moclobemide is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Netupitant is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Nevirapine is predicted to decrease the exposure to eliglustat. [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Quinolones (ciprofloxacin) are predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Rifampicin is predicted to decrease the exposure to eliglustat. Avoid. [Severe] Study

Eliglustat is predicted to increase the exposure to sirolimus. Adjust dose. [Moderate] Study

SSRIs (fluoxetine, paroxetine) are predicted to decrease the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

St John’s Wort is predicted to increase the exposure to eliglustat. Avoid. [Severe] Study

Eliglustat is predicted to increase the exposure to taxanes (paclitaxel). Adjust dose. [Moderate] Study

Terbinfine is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Eliglustat is predicted to increase the exposure to tolterodine. Adjust dose. [Moderate] Theoretical

Eliglustat is predicted to increase the exposure to topotecan. Adjust dose. [Moderate] Study

Eliglustat is predicted to increase the exposure to tricyclic antidepressants (nortriptyline). Adjust dose. [Moderate] Theoretical

Elotuzumab → see monoclonal antibodies

Elotrombopag

Antacids decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after antacids. [Severe] Study

Oral calcium salts decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after calcium salts. [Severe] Study

Ciclosporin decreases the exposure to elotrombopag. Monitor and adjust dose. [Moderate] Study

Dairy products are predicted to decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after dairy products. [Severe] Theoretical

Iron (oral) is predicted to decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after iron (oral). [Severe] Theoretical

Elotrombopag is predicted to increase the concentration of ivermectin. [Moderate] Study

Elotrombopag is predicted to increase the concentration of methotrexate. [Moderate] Theoretical

Rifampicin is predicted to decrease the exposure to elotrombopag and elotrombopag is predicted to increase the concentration of rifampicin. [Moderate] Theoretical

Oral selenium is predicted to decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after selenium. [Severe] Theoretical

SSRIs (fluvoxamine) are predicted to increase the exposure to elotrombopag. [Moderate] Theoretical

Elotrombopag is predicted to increase the exposure to tenofovir alafenamide. [Moderate] Theoretical

Elotrombopag is predicted to increase the exposure to tenofovir disoproxil. [Moderate] Theoretical

Oral zinc is predicted to decrease the absorption of elotrombopag. Elotrombopag should be taken 2 hours before or 4 hours after zinc. [Severe] Theoretical

Elvitegravir

Antacids moderately decrease the exposure to elvitegravir. Separate administration by at least 4 hours. [Moderate] Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Boventan is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Elvitegravir is predicted to decrease the anticoagulant effect of coumarins. [Moderate] Theoretical

Efavirenz is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Enalapril is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Elvitegravir markedly increases the exposure to grazoprevir. Avoid. [Severe] Study

HIV-protease inhibitors (atazanavir, lopinavir) (boosted with ritonavir) increase the concentration of elvitegravir. Refer to specialist literature. [Moderate] Study

Mometane is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Elvitegravir is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

St John’s Wort is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical

Empagliflozin → see TABLE 14 p. 1378 (antidiabetic drugs), TABLE 8 p. 1376 (hypotension)

Enalapril → see ACE inhibitors

Encorafenib → see TABLE 9 p. 1377 (QT-interval prolongation)

Antiarhythmics (dronedarone) are predicted to moderately increase the exposure to encorafenib. [Moderate] Study → Also see TABLE 9 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to encorafenib. [Severe] Theoretical

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to moderately increase the exposure to encorafenib. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to encorafenib. Avoid or monitor. [Severe] Study → Also see TABLE 9 p. 1377

Aprepitant is predicted to moderately increase the exposure to encorafenib. [Moderate] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to moderately increase the exposure to encorafenib. [Moderate] Study

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Encorafenib (continued)

- **Cobicistat** is predicted to increase the exposure to encorafenib. Avoid or monitor. [Severe] Study

- **Enteral feeds** is predicted to affect the exposure to combined hormonal contraceptives. [Severe] Theoretical

- **Crizotinib** is predicted to moderately increase the exposure to encorafenib. [Moderate] Study → Also see TABLE 9 p. 1377

- **Encorafenib** is predicted to increase the exposure to dolasetravir. [Moderate] Theoretical

- **Enteral feeds** is predicted to decrease the exposure to encorafenib. [Severe] Theoretical

- **Grapefruit juice** is predicted to increase the exposure to encorafenib. Avoid. [Moderate] Study

- **HIV-protease inhibitors** are predicted to increase the exposure to enteral feeds. Avoid or monitor. [Severe] Study → Also see TABLE 9 p. 1377

- **Idelalisib** is predicted to increase the exposure to enteral feeds. Avoid or monitor. [Severe] Study

- **Imatinib** is predicted to moderately increase the exposure to encorafenib. [Moderate] Study

- **Macrolides** (clarithromycin) are predicted to increase the exposure to encorafenib. Avoid or monitor. [Severe] Study → Also see TABLE 9 p. 1377

- **Mitotane** is predicted to decrease the exposure to enteral feeds. [Severe] Theoretical

- **Netupitant** is predicted to moderately increase the exposure to encorafenib. [Moderate] Study

- **Nilotinib** is predicted to moderately increase the exposure to encorafenib. [Moderate] Study → Also see TABLE 9 p. 1377

- **Encorafenib** is predicted to increase the exposure to raltegravir. [Moderate] Theoretical

- **Rifampicin** is predicted to decrease the exposure to encorafenib. [Severe] Theoretical

- **St John's Wort** is predicted to decrease the exposure to enteral feeds. [Severe] Theoretical

- **Enoxaparin** → see low molecular-weight heparins

- **Entacapone**
  - **Iron (oral)** is predicted to decrease the absorption of entacapone. Separate administration by at least 2 hours. [Moderate] Theoretical

- **Entacapone** increases the exposure to levodopa. Monitor side effects and adjust dose. [Moderate] Study

- **Entacapone** is predicted to increase the exposure to methyldopa. [Moderate] Theoretical

- **Entacapone** is predicted to increase the risk of elevated blood pressure when given with monoamine-oxidase A and B inhibitors. Irreversible. Avoid. [Severe] Theoretical

- **Entacapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropics. [Moderate] Theoretical

- **Entacapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). [Moderate] Study

- **Enteral feeds**
  - **Antacids (aluminium hydroxide)** increase the risk of blocked enteral or nasogastric tubes when given with enteral feeds. [Moderate] Study

- **Enteral feeds** decrease the absorption of antiepileptics (phenytoin). [Severe] Study

- **Enteral feeds** (vitamin-K containing) potentially decrease the anticoagulant effect of warfarin. [Severe] Anecdotal

- **Enteral feeds** (vitamin-K containing) potentially decrease the effects of phenindione. [Severe] Theoretical

- **Enteral feeds** decrease the exposure to quinolones (ciprofloxacin). [Moderate] Study

- **Sucralfate** increases the risk of blocked enteral or nasogastric tubes when given with enteral feeds. Separate administration by 1 hour. [Moderate] Study

- **Enteral feeds** decrease the exposure to theophylline. [Moderate] Study

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**Encorafenib**

**Enzalutamide**

**GENERAL INFORMATION**

Caution with concurrent chemotherapy—safety and efficacy not established.

- **Encorafenib** is predicted to markedly decrease the exposure to abemaciclib. Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to abiraterone. Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to aldosterone antagonists (eplerenone). Avoid. [Moderate] Theoretical

- **Encorafenib** is predicted to decrease the exposure to alprazolam. Adjust dose. [Moderate] Theoretical

- **Encorafenib** is predicted to decrease the exposure to antiarrhythmics (disopyramide, dronedarone). Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the efficacy of antiarrhythmics (propafenone). [Moderate] Study

- **Encorafenib** is predicted to decrease the exposure to anticholinesterases, centrally acting (donepezil). [Mild] Study

- **Encorafenib** is predicted to slightly decrease the exposure to antiarrhythmics (brivracetam). [Moderate] Theoretical

- **Encorafenib** is predicted to decrease the exposure to antiarrhythmics (-perampanel). Monitor and adjust dose. [Moderate] Study

- **Encorafenib** is predicted to decrease the exposure to antifungals, azoles (itraconazole). Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to antimalarials (artemether) (with lumefantrine). Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the concentration of antimalarials (piperaquine). Avoid. [Moderate] Theoretical

- **Encorafenib** is predicted to moderately decrease the exposure to apixaban. Use with caution and avoid. [Severe] Study

- **Encorafenib** moderately decreases the exposure to apremilast. Avoid. [Severe] Study

- **Encorafenib** is predicted to markedly decrease the exposure to aprepitant. Avoid. [Moderate] Study

- **Encorafenib** is predicted to moderately decrease the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. [Moderate] Study

- **Encorafenib** is predicted to decrease the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

- **Encorafenib** decreases the exposure to bedaquiline. Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to bictegravir. Avoid. [Moderate] Study

- **Encorafenib** slightly decreases the exposure to bortezomib. Avoid. [Severe] Study

- **Encorafenib** affects the exposure to bosentan. Avoid. [Severe] Study

- **Encorafenib** is predicted to very markedly decrease the exposure to bosutinib. Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to brigitinib. Avoid. [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to cabozantinib. Avoid. [Moderate] Study

- **Encorafenib** is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

- **Encorafenib** is predicted to decrease the exposure to calcium channel blockers (diltiazem, verapamil). [Severe] Study

- **Encorafenib** is predicted to decrease the exposure to cannabis extract. Avoid. [Severe] Theoretical

- **Encorafenib** is predicted to decrease the exposure to cariprazine. Avoid. [Severe] Theoretical

- **Encorafenib** is predicted to decrease the exposure to ceritinib. Avoid. [Severe] Study

- **Encorafenib** decreases the concentration of ciclosporin. [Severe] Study

- **Encorafenib** is predicted to alter the effects of cisplatin. [Moderate] Theoretical

- **Encorafenib** is predicted to decrease the exposure to cinacalcet. Monitor and adjust dose. [Moderate] Study

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Enzalutamide – Enzalutamide

- Enzalutamide decreases the exposure to clomethiazole. Monitor and adjust dose. (Moderate) Study
- Clodopigrol moderately increases the exposure to enzalutamide. Avoid or adjust enzalutamide dose, p. 947. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to clozapine. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to cobicistat. Avoid. (Severe) Theoretical
- Enzalutamide is predicted to markedly decrease the exposure to cobimetinib. Avoid. (Severe) Theoretical
- Enzalutamide is predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to corticosteroids (fluticasone). (Unknown) Theoretical
- Enzalutamide potentially decreases the exposure to coumarins. Avoid or adjust dose and monitor INR. (Severe) Study
- Enzalutamide is predicted to markedly decrease the exposure to crizotinib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to dabrafenib. Avoid. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to dasatinib. Avoid. (Severe) Study
- Enzalutamide is predicted to markedly decrease the exposure to dasabuvir. Avoid. (Severe) Theoretical
- Enzalutamide is predicted to slightly decrease the exposure to delamanid. Avoid. (Moderate) Study
- Enzalutamide decreases the exposure to dolutegravir. Adjust dose. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to doravirine. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to elbasvir. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to eliglustat. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the concentration of elvitegravir. Avoid. (Severe) Theoretical
- Enzalutamide is predicted to decrease the exposure to encorafenib. (Severe) Theoretical
- Enzalutamide is predicted to decrease the effects of ergotamine. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to erlotinib. Avoid or adjust erlotinib dose, p. 979. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to esketamine. Adjust dose. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to etravirine. Avoid. (Severe) Theoretical
- Enzalutamide is predicted to decrease the concentration of everolimus. Avoid or adjust dose. (Severe) Study
- Enzalutamide moderately decreases the exposure to exemestane. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to fesoterodine. Avoid. (Moderate) Study
- Fibrates (gemfibrozil) moderately increase the exposure to enzalutamide. Avoid or adjust enzalutamide dose, p. 947. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to fingolimid. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to fosaprepitant. Avoid. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to gefitinib. Avoid. (Severe) Study
- Enzalutamide is predicted to greatly decrease the concentration of glecaprevir. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to grazoprevir. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Study
- Enzalutamide decreases the concentration of haloperidol. Adjust dose. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to ibritinib. Avoid or adjust ibritinib dose, p. 983. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to idelalisib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to imatinib. Avoid. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to ivabradine. Adjust dose. (Moderate) Theoretical
- Enzalutamide is predicted to moderately to markedly decrease the exposure to ivacaftor. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to ixazomib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to luridason. Avoid. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to macitentan. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to midostaurin. Avoid. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to minodronic. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to mirtazapine. Adjust dose. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to montelukast. (Mild) Study
- Enzalutamide is predicted to markedly decrease the exposure to nalorex. Avoid. (Moderate) Study
- Enzalutamide is predicted to slightly decrease the exposure to nategraline. (Mild) Study
- Enzalutamide is predicted to decrease the exposure to netupitant. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to nevirapine. (Severe) Theoretical
- Enzalutamide is predicted to moderately decrease the exposure to nilotinib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to nitisinone. Adjust dose. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to omacetaxine. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to orapidanetron. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to opioids (alfentanil, fentanyl). (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to opioids (buprenorphine). Monitor and adjust dose. (Moderate) Theoretical
- Enzalutamide decreases the exposure to opioids (methadone). Monitor and adjust dose. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to opioids (oxycodone). Monitor and adjust dose. (Moderate) Study
- Enzalutamide is predicted to moderately decrease the exposure to osimertinib. Avoid. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to osmipemifene. (Moderate) Study
- Enzalutamide is predicted to decrease the exposure to palbociclib. Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to paliperidone. Monitor and adjust dose. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to panobinostat. Avoid. (Moderate) Theoretical
- Enzalutamide is predicted to decrease the exposure to parataprevir (with ritonavir and ombitasvir). Avoid. (Severe) Study
- Enzalutamide is predicted to decrease the exposure to pazopanib. Avoid. (Severe) Theoretical
Enzalutamide (continued)

- Enzalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avaniatl, tadafalati). Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenalati). [Moderate] Theoretical
- Enzalutamide is predicted to moderately to markedly decrease the exposure to pilorensalt. Avoid. [Severe] Study
- Enzalutamide is predicted to moderately to markedly decrease the exposure to pinitalsalt. [Moderate] Study
- Enzalutamide is predicted to decrease the exposure to ponatinsalt. Avoid. [Moderate] Theoretical
- Enzalutamide is predicted to markedly decrease the exposure to avpaqantisalt. Avoid. [Moderate] Study
- Enzalutamide is predicted to decrease the exposure to quetiapiatt. [Moderate] Study
- Enzalutamide is predicted to decrease the exposure to ranolatin. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to rilivprinsalt. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to rispriderone. Adjust dose. [Moderate] Study
- Enzalutamide is predicted to moderately decrease the exposure to repaglinsalt. Monitor blood glucose and adjust dose. [Moderate] Study
- Enzalutamide is predicted to markedly decrease the exposure to rjopibicinl. Avoid. [Severe] Study
- Enzalutamide markedly decreases the exposure to rilipivirin. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to riperidone. Adjust dose. [Moderate] Study
- Enzalutamide is predicted to moderately decrease the exposure to rivoaxobnan. Avoid unless patient can be monitored for signs of thrombosis. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to roflumilastsalt. Avoid. [Moderate] Study
- Enzalutamide is predicted to markedly decrease the exposure to rolpatinet. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to sarafalinsalt. [Moderate] Theoretical
- Enzalutamide is predicted to decrease the exposure to saxaglipint. [Moderate] Study
- Enzalutamide is predicted to decrease the concentration of simvastatin. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to suninib. Avoid or adjust suninib dose, p. 999. [Moderate] Study
- Enzalutamide decreases the concentration of tacrolimus. Monitor and adjust dose. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to taxanes (calbazaaxelax, pacizatxel). Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to taxanes (docetaxel). [Severe] Theoretical
- Enzalutamide is predicted to decrease the concentration of tamsiriolemus. Avoid. [Severe] Study
- Enzalutamide decreases the exposure to tacryclines (doxyclinet). Monitor and adjust dose. [Moderate] Study
- Enzalutamide is predicted to decrease the exposure to tacrolimus. Avoid. [Severe] Theoretical
- Enzalutamide is predicted to decrease the concentration of ticagrelor. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to tivoxain. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to tofavitin. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to tolvaptan. Use with caution or avoid depending on indication. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to toremifene. Adjust dose. [Moderate] Study
- Enzalutamide is predicted to decrease the exposure to trabectedinl. Avoid. [Severe] Theoretical
- Enzalutamide is predicted to markedly decrease the exposure to ulipristalt. Avoid and for 4 weeks after stopping ulipristal. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to vandetanib. Avoid. [Moderate] Study
- Enzalutamide is predicted to moderately decrease the exposure to vepatansalt. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to vemurafenib. Avoid. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vinodines). [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to vinca alkaloids (vinflunine). Avoid. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to vinorelbine. Use with caution or avoid. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to vismodogel. Avoid. [Moderate] Theoretical
- Enzalutamide is predicted to decrease the exposure to vortoxtinet. Monitor and adjust dose. [Moderate] Study
- Enzalutamide is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Study
- Enzalutamide is predicted to decrease the exposure to zopiclon. Adjust dose. [Moderate] Study
- Ephedrine → see sympathomimetics, vasoconstrictor
- Epinrubacin → see anthraclyclines
- Epleronone → see aldosterone antagonists
- Epotin alfa → see TABLE 5 p. 1375 (thromboembolism), TABLE 16 p. 1379 (increased serum potassium)
- Epotin beta → see TABLE 5 p. 1375 (thromboembolism), TABLE 16 p. 1379 (increased serum potassium)
- Epoetin zeta → see TABLE 5 p. 1375 (thromboembolism), TABLE 16 p. 1379 (increased serum potassium)
- Epoprostenol → see TABLE 4 p. 1375 (antiplatelet effects)
- Eprosartan → see angiotensin-II receptor antagonists
- Epftibatide → see TABLE 4 p. 1375 (antiplatelet effects)
- Ergocalciferol → see vitamin D substances

Ergometrine

- Antiarhythmics (dronedaron) are predicted to increase the risk of ergotism when given with ergometrine. [Severe] Theoretical
- Antifungals, azoles (fluconazole, isavucanazole, posaconazole) are predicted to increase the risk of ergotism when given with ergometrine. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergometrine. Avoid. [Severe] Theoretical
- **Ergotamine** is predicted to increase the risk of elevated blood pressure when given with *ergometrine*. Avoid. [Severe] Theoretical
- **Grapefruit juice** is predicted to increase the exposure to *ergotamine*. [Severe] Theoretical
- HIV-protease inhibitors are predicted to increase the risk of ergotism when given with *ergotamine*. Avoid. [Severe] Theoretical
- **Idelalisib** is predicted to increase the risk of ergotism when given with *ergotamine*. Avoid. [Severe] Theoretical
- **Imatinib** is predicted to increase the risk of ergotism when given with *ergotamine*. [Severe] Theoretical
- **Ketamine** is predicted to increase the risk of elevated blood pressure when given with *ergotamine*. [Severe] Theoretical
- **Letermovir** is predicted to increase the concentration of *ergotamine*. Avoid. [Severe] Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the risk of ergotism when given with *ergotamine*. Avoid. [Severe] Theoretical
- **Netupitant** is predicted to increase the risk of ergotism when given with *ergotamine*. [Severe] Theoretical
- **Nilotinib** is predicted to increase the risk of ergotism when given with *ergotamine*. [Severe] Theoretical
- Ergotamine potentially increases the risk of peripheral vasoconstriction when given with sympathomimetics, inotropic (dopamine). Avoid. [Severe] Anecdotal
- **Ergotamine** is predicted to increase the risk of peripheral vasoconstriction when given with sympathomimetics, vasoconstrictor (noradrenaline/norepinephrine). [Severe] Anecdotal

**Ergotamine**

- **Almotriptan** is predicted to increase the risk of vasoconstriction when given with ergotamine. Ergotamine should be taken at least 24 hours before or 6 hours after almotriptan. [Severe] Theoretical
- **Antiarhythmics (dronedarone)** are predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- Antiinflammatory, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- Antiinflammatory, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- Antiinflammatory, azoles (miconazole) are predicted to increase the exposure to ergotamine. Avoid. [Moderate] Theoretical
- Antiretroviral is predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- **Beta blockers, non-selective** are predicted to increase the risk of peripheral vasoconstriction when given with ergotamine. [Severe] Study
- **Beta blockers, selective** are predicted to increase the risk of peripheral vasoconstriction when given with ergotamine. [Severe] Study
- **Bosentan** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- **Ceritinib** is predicted to increase the exposure to ergotamine. Avoid. [Severe] Theoretical
- **Cobicistat** is predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- **Crizotinib** is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- Ergotamine is predicted to increase the risk of ergotism when given with dopamine receptor agonists (bromocriptine, cabergoline). Avoid. [Moderate] Theoretical
- Ergotamine is predicted to increase the risk of ergotism when given with dopamine receptor agonists (pergolide). [Moderate] Theoretical
- **Efavirenz** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- **Eliptiran** increases the risk of vasocostriction when given with ergotamine. Separate administration by 24 hours. [Severe] Study
- **Enzalutamide** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- **Grapefruit juice** is predicted to increase the exposure to ergotamine. [Severe] Theoretical
- HIV-protease inhibitors are predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- **Idelalisib** is predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- **Imatinib** is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- **Letermovir** is predicted to increase the concentration of ergotamine. Avoid. [Severe] Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the risk of ergotism when given with ergotamine. Avoid. [Severe] Theoretical
- **Netupitant** is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- **Nilotinib** is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- **Mirtalbupin** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- **Nilotinib** is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical
- **Palbociclib** is predicted to increase the exposure to ergotamine. Adjust dose. [Moderate] Theoretical
- **Ribociclib (high-dose)** is predicted to increase the exposure to ergotamine. Avoid. [Moderate] Theoretical
- **Rifampin** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- **RizatRIPTAN** is predicted to increase the risk of vasoconstriction when given with ergotamine. Ergotamine should be taken at least 24 hours before or 6 hours after rizatRIPTAN. [Severe] Theoretical
- **Rucaparib** is predicted to increase the exposure to ergotamine. Monitor and adjust dose. [Moderate] Study
- **St John's Wort** is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- **Sumatriptan** increases the risk of vasoconstriction when given with ergotamine. Ergotamine should be taken at least 24 hours before or 6 hours after sumatriptan. [Severe] Study
- **Ticagrelor** is predicted to increase the exposure to ergotamine. Avoid. [Severe] Theoretical
- **Eribulin** see TABLE 15 p. 1378 (myelosuppression), TABLE 12 p. 1378 (peripheral neuropathy), TABLE 9 p. 1377 (Q1-Interval prolongation)

**Erlotinib**

- **FOD & LIFESTYLE** Dose adjustment may be necessary if smoking started or stopped during treatment.
- **Antacids** are predicted to decrease the absorption of erlotinib. Antacids should be taken 4 hours before or 2 hours after erlotinib. [Moderate] Theoretical
- **Antiarhythmics (amiodarone, dronedarone)** are predicted to increase the exposure to erlotinib. [Moderate] Theoretical
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to erlotinib. Avoid or adjust erlotinib dose, p. 97% [Severe] Study
- **Antiinflammatory, azoles (fluconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to erlotinib. [Moderate] Theoretical
- **Antiinflammatory, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to slightly increase the exposure to erlotinib. Use with caution and adjust dose. [Moderate] Study
- **Aprepitant** is predicted to increase the exposure to erlotinib. [Moderate] Theoretical
- **Erlotinib** is predicted to increase the risk of gastrointestinal perforation when given with aspirin (high-dose). [Severe] Theoretical
Erlotinib (continued)

- **Ertapenem** → see carbapenems

**Ertugliflozin** → see tables 14 p. 1378 (antidiabetic drugs), table 8 p. 1376 (hypotension)

**Erythromycin** → see macrolides

**Escitalopram** → see SSRIs

**Esketamine** → see Table 8 p. 1376 (hypotension), table 11 p. 1377 (CNS depressant effects)

**Esketamine** is predicted to increase the risk of seizures when given with *aminophylline*. Avoid. **Severe** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone*) are predicted to decrease the exposure to *esketamine*. Adjust dose. **Moderate** Theoretical

**Antiepileptics** (*carbamazepine*, *eslicarbazepine*, *f***
- HIV-protease inhibitors (ritonavir) are predicted to decrease the efficacy of etravirine. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- Modafinil is predicted to decrease the efficacy of etravirine. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- Nevirapine is predicted to decrease the efficacy of etravirine. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- Rifabutin is predicted to decrease the efficacy of etravirine. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- St John's Wort is predicted to decrease the efficacy of etravirine. MRHA advises avoid for FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- Sugammadex is predicted to decrease the efficacy of etravirine. Use additional contraceptive precautions. [Severe] Theoretical
- Ulipristal is predicted to decrease the efficacy of etravirine. Avoid. [Severe] Theoretical
- Etoposide — see TABLE 15 p. 1378 (myelosuppression)
  - Anti-epileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the efficacy of etravirine. Avoid. [Severe] Theoretical
  - Ciclosporin increases the exposure to etoposide. Monitor and adjust dose. [Severe] Study
  - Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with etoposide. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
  - Netupitant slightly increases the exposure to etoposide. [Moderate] Study
- Etoricoxib — see NSAIDs
- Etravirine
  - Anti-epileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to etravirine. Avoid. [Severe] theoretical
  - Etravirine decreases the exposure to antimalarials (artemether). [Moderate] Study
  - Etravirine is predicted to decrease the exposure to etravirine. Avoid. [Severe] theoretical
  - Bosentan is predicted to decrease the exposure to etravirine. Avoid. [Severe] Study
  - Etravirine is predicted to decrease the exposure to bosutinib. Avoid. [Severe] Theoretical
  - Etravirine is predicted to decrease the exposure to brigatinib. Avoid. [Moderate] Theoretical
  - Etravirine increases the anticoagulant effect of coumarin. [Moderate] Theoretical
  - Etravirine is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
  - Etravirine moderately decreases the exposure to dolutegravir. Avoid unless given with atazanavir, darunavir, or lopinavir (all boosted with ritonavir). [Severe] Study
  - Efavirenz is predicted to decrease the exposure to etravirine. Avoid. [Severe] Study
  - Etravirine is predicted to decrease the exposure to elbasvir. Avoid. [Unknown] Theoretical
  - Enzalutamide is predicted to decrease the exposure to etravirine. Avoid. [Severe] Theoretical
  - Etravirine is predicted to decrease the exposure to etravirine. Avoid. [Severe] Theoretical
  - Etravirine is predicted to decrease the exposure to grazoprevir. Avoid. [High] Theoretical
  - HIV-protease inhibitors (tipranavir) decrease the exposure to etravirine. Avoid. [Severe] Study
  - Etravirine increases the exposure to HIV-protease inhibitors (fosamprenavir boosted with ritonavir). Refer to specialist literature. [Moderate] Study
  - Etravirine is predicted to decrease the exposure to letrozomib. [Moderate] Theoretical
  - Etravirine decreases the exposure to macrolides (clarithromycin) and macrolides (clarithromycin) slightly increase the exposure to etravirine. [Severe] Study
  - Etravirine (with a boosted protease inhibitor) increases the exposure to maraviroc. Avoid or adjust dose. [Moderate] Study
  - Mitotane is predicted to decrease the exposure to etravirine. Avoid. [Severe] Theoretical
  - Nevirapine is predicted to decrease the exposure to etravirine. Avoid. [Severe] Study
  - Etravirine is predicted to decrease the exposure to ombrabant. Avoid. [Severe] Theoretical
  - Etravirine is predicted to decrease the exposure to paritaprevir. Avoid. [Severe] Theoretical
  - Etravirine moderately decreases the exposure to phosphodiesterase type-5 inhibitors. Adjust dose. [Moderate] Study
  - Rifabutin decreases the exposure to etravirine. [Moderate] Study
  - Rilpivirine is predicted to decrease the exposure to etravirine. Avoid. [Severe] Theoretical
  - Etravirine is predicted to decrease the exposure to rilpivirine. Avoid. [Severe] Theoretical
  - St John's Wort is predicted to decrease the exposure to etravirine. Avoid. [Severe] Study
  - Everolimus — see TABLE 15 p. 1378 (myelosuppression)
    - Everolimus potentially increases the risk of angioedema when given with ACE inhibitors. [Severe] Anecdotal
    - Anti-arrhythmics (dronedarone) are predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
    - Anti-epileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
    - Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
    - Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of everolimus. Avoid. [Severe] Study
    - Apalutamide is predicted to decrease the exposure to everolimus. Avoid or monitor. [Moderate] Study
    - Aprepitant is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
    - Bosentan is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
    - Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
    - Certitibib is predicted to increase the exposure to everolimus. [Moderate] Theoretical — Also see TABLE 15 p. 1378
    - Ciclosporin moderately increases the exposure to everolimus. Avoid or adjust dose. [Severe] Study
    - Cobicistat is predicted to increase the concentration of everolimus. Avoid. [Severe] Study
    - Crizotinib is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study — Also see TABLE 15 p. 1378
    - Efavirenz is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
    - Eliglustat is predicted to increase the exposure to everolimus. Adjust dose. [Moderate] Study — Also see TABLE 15 p. 1378
    - Enzalutamide is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
    - Grapefruit juice is predicted to increase the exposure to everolimus. Avoid. [Severe] Theoretical
    - HIV-protease inhibitors are predicted to increase the concentration of everolimus. Avoid. [Severe] Study
    - Idelalisib is predicted to increase the concentration of everolimus. Avoid. [Severe] Study — Also see TABLE 15 p. 1378
    - Imatinib is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study — Also see TABLE 15 p. 1378
    - Lapatinib is predicted to increase the exposure to everolimus. [Moderate] Theoretical
    - Leteromivib is predicted to increase the concentration of everolimus. Monitor and adjust dose. [Severe] Study
    - Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with
Everolimus (continued)
  ▶ Everolimus is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. [Moderate] Theoretical
  ▶ Lumacaftor is predicted to decrease the exposure to everolimus. Avoid. [Severe] Theoretical
  ▶ Macrolides (clarithromycin) are predicted to increase the concentration of everolimus. Avoid. [Severe] Study
  ▶ Macrolides (erythromycin) are predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
  ▶ Mirabegron is predicted to increase the exposure to everolimus. [Mild] Theoretical
  ▶ Mitotane is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study → also see TABLE 15 p. 1378
  ▶ Netupitant is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study
  ▶ Nevirapine is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
  ▶ Nilotinib is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study → also see TABLE 15 p. 1378
  ▶ Palbociclib is predicted to increase the exposure to everolimus. Avoid or adjust dose. [Moderate] Theoretical
  ▶ Ribociclib is predicted to increase the exposure to everolimus. Avoid with caution and adjust dose. [Moderate] Theoretical
  ▶ Rifampicin is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
  ▶ St John’s Wort is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
  ▶ Velpatasvir is predicted to increase the exposure to everolimus. [Severe] Theoretical
  ▶ Venetoclax is predicted to increase the exposure to everolimus. Avoid or adjust dose. [Severe] Study
  ▶ Exemestane
    ▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) moderately decrease the exposure to exemestane. [Moderate] Study
    ▶ Enzalutamide moderately decreases the exposure to exemestane. [Moderate] Study
    ▶ Mitotane moderately decreases the exposure to exemestane. [Moderate] Study
    ▶ Rifampicin moderately decreases the exposure to exemestane. [Moderate] Study
    ▶ St John’s Wort is predicted to decrease the exposure to exemestane. [Moderate] Theoretical
  ▶ Exenatide → see TABLE 14 p. 1378 (antidiabetic drugs)
  ▶ Exenatide increases the concentration of fampiridine. [Severe] Theoretical
  ▶ Fexofenadine is predicted to increase the exposure to azelastine when given with fexofenadine. [Severe] Theoretical
  ▶ Fexofenadine, fexofenadine maleate and fexofenadine fumarate are predicted to increase the exposure to fexofenadine. [Severe] Theoretical
  ▶ Fexofenadine is predicted to decrease the exposure to fexofenadine. [Severe] Theoretical
  ▶ Felbinac → see NSAIDs
  ▶ Felodipine → see calcium channel blockers
  ▶ Fenofibrate → see fibrates
  ▶ Fentanyl → see opioids
  ▶ Ferric carboxymaltose → see iron (injectable)
  ▶ Ferric maltol → see iron (oral)
  ▶ Ferrous fumarate → see iron (oral)
  ▶ Ferrous gluconate → see iron (oral)
  ▶ Fosfoconazole, ketoconazole, voriconazole are predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Fosphenytoin, phenytoin, primidone) are predicted to decrease the exposure to fensoterodine. Avoid. [Moderate] Study
  ▶ Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Cobicistat is predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Severe] Study
  ▶ Critotinib is predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Enzalutamide is predicted to decrease the exposure to fensoterodine. Avoid. [Moderate] Study
  ▶ HIV-protase inhibitors are predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Severe] Study
  ▶ Ivelalisib is predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Severe] Study
  ▶ Imatinib is predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Macrolides (clarithromycin) are predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Macrolides (erythromycin) are predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Mitotane is predicted to decrease the exposure to fensoterodine. Avoid. [Moderate] Study
  ▶ Netupitant is predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Nonsteroidal anti-inflammatory drugs (NSAIDs) see NSAIDs
  ▶ Opioids see opioids
  ▶ Piroxicam, celecoxib, meloxicam are predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4, avoid in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Pimavanserin is predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Severe] Study
  ▶ Prasugrel is predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with moderate inhibitors of CYP3A4, avoid in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Prasugrel is predicted to moderately increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Severe] Study
  ▶ Posaconazole is predicted to increase the exposure to fensoterodine. Adjust fensoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. [Mild] Study
  ▶ Primidone is predicted to decrease the exposure to fensoterodine. Avoid. [Moderate] Study
**Fibrate**

‑ **Antacids** slightly to moderately decrease the exposure to gemfibrozil. **Moderate** Study

‑ Gemfibrozil is predicted to increase the exposure to apalutamide. **Mild** Study

‑ Bezafibrate is predicted to increase the risk of nephrotoxicity when given with ciclosporin. **Severe** Theoretical

‑ Fenofibrate increases the risk of nephrotoxicity when given with ciclosporin. **Severe** Study

‑ Colestipol increases the risk of rhabdomyolysis when given with fenofibrate. **Severe** Anecdotal

‑ Fibrates are predicted to increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. **Severe** Study

‑ Gemfibrozil is predicted to increase the exposure to dabrafenib. **Moderate** Theoretical

‑ Fibrates are predicted to increase the risk of rhabdomyolysis when given with daptomycin. **Severe** Theoretical

‑ Gemfibrozil is predicted to very markedly increase the exposure to dasabuvir. Avoid. **Severe** Study

‑ Gemfibrozil moderately increases the exposure to enzalutamide. Avoid or adjust enzalutamide dose, p. 947. **Severe** Study

‑ Fibrates are predicted to increase the risk of gallstones when given with ezetimibe. **Severe** Theoretical

‑ Fibrates are predicted to increase the risk of hypoglycaemia when given with insulin. **Moderate** Theoretical

‑ Gemfibrozil is predicted to increase the exposure to irinotecan. Avoid. **Moderate** Theoretical

‑ Gemfibrozil is predicted to increase the concentration of lertemovir. **Moderate** Study

‑ Gemfibrozil is predicted to moderately increase the exposure to montelukast. **Moderate** Study

‑ Fibrates are predicted to increase the anticoagulant effect of phenindione. Monitor INR and adjust dose. **Severe** Study

‑ Gemfibrozil increases the exposure to pioglitazone. Monitor blood glucose and adjust dose. **Severe** Study

‑ Gemfibrozil increases the exposure to repaglinide. Avoid. **Severe** Study

‑ Gemfibrozil is predicted to increase the exposure to retinoids (all-transretinoin). Adjust all-transretinoin dose, p. 1262. **Moderate** Theoretical

‑ Gemfibrozil increases the concentration of retinoids (bexarotene). Avoid. **Severe** Study

‑ Gemfibrozil increases the exposure to selexipag. Avoid. **Severe** Study

‑ Ciprofibrate increases the risk of rhabdomyolysis when given with statins (atorvastatin). Avoid or adjust dose. **Severe** Study

‑ Bezafibrate increases the risk of rhabdomyolysis when given with statins (atorvastatin, fluvastatin). **Severe** Study

‑ Fenofibrate increases the risk of rhabdomyolysis when given with statins (atorvastatin, simvastatin). Adjust fenofibrate dose, p. 199. **Severe** Anecdotal

‑ Ciprofibrate increases the risk of rhabdomyolysis when given with statins (fluvastatin). **Severe** Study

‑ Fenofibrate is predicted to increase the risk of rhabdomyolysis when given with statins (fluvastatin). Adjust fenofibrate dose, p. 199. **Severe** Theoretical

‑ Fenofibrate is predicted to increase the risk of rhabdomyolysis when given with statins (pravastatin). Avoid. **Severe** Theoretical

‑ Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with statins (pravastatin). Avoid. **Severe** Study

‑ Fenofibrate increases the risk of rhabdomyolysis when given with statins (rosuvastatin). Adjust fenofibrate and rosuvastatin doses, p. 199, p. 204. **Severe** Anecdotal

‑ Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with statins (rosuvastatin). **Severe** Study

‑ Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with statins (simvastatin). Adjust simvastatin dose, p. 205. **Severe** Study

‑ Gemfibrozil increases the risk of rhabdomyolysis when given with statins. Avoid. **Severe** Anecdotal

‑ Fibrates are predicted to increase the risk of hypoglycaemia when given with sulfonylureas. **Moderate** Theoretical

‑ Gemfibrozil is predicted to increase the concentration of taxanes (paclitaxel). **Severe** Anecdotal

‑ Fibrates are predicted to decrease the efficacy of ursodeoxycholic acid. Avoid. **Severe** Theoretical

### Fidaxomicin

‑ Antiarrhythmics (amiodarone, dronedarone) are predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Antifungals, azoles (itraconazole, ketoconazole) are predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Calcium channel blockers (verapamil) are predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Ciclosporin is predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ HIV protease inhibitors (fopinavir, ritonavir, saquinavir) are predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Lapatinib is predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Macrolides are predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Ranolazine is predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Venlafaxine is predicted to increase the exposure to fidaxomicin. Avoid. **Moderate** Study

‑ Fingolimod → see TABLE 6 p. 1376 (bradycardia), TABLE 9 p. 1377 (QT-interval prolongation)

‑ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fingolimod. **Moderate** Study

‑ Calcium channel blockers (diltiazem, verapamil) are predicted to decrease the exposure to fingolimod. **Moderate** Study

‑ Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fingolimod. Public Health England advises avoid (refer to Green Book). **Severe** Theoretical

‑ Mitotane is predicted to decrease the exposure to fingolimod. **Moderate** Study

‑ Rifampicin is predicted to decrease the exposure to fingolimod. **Moderate** Study

‑ St John’s Wort is predicted to decrease the exposure to fingolimod. Avoid. **Moderate** Theoretical

### Flavoxide

‑ Flavoxide → see TABLE 10 p. 1377 (antimuscarinics)

### Flecainide

‑ Flecainide → see antiarrhythmics

### Fluociclovir

‑ Fluociclovir → see penicillins

### Fluociclovir

‑ Fluociclovir → see antifungals, azoles

### Fluociclovir

‑ Amphotericin increases the risk of toxicity when given with flucytosine. **Severe** Study

‑ Cytarabine decreases the concentration of fluocitoxine. Avoid. **Severe** Study

‑ Zidovudine increases the risk of haematological toxicity when given with fluocytosine. Monitor and adjust dose. **Severe** Theoretical

### Fludarabine

‑ Fludarabine → see TABLE 15 p. 1378 (myeloablation)

‑ Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fludarabine. Public Health England advises avoid (refer to Green Book). **Severe** Theoretical

‑ Fludarabine increases the risk of pulmonary toxicity when given with pentostatin. Avoid. **Severe** Study → Also see TABLE 15 p. 1378

### Fludrocortisone

‑ Fludrocortisone → see corticosteroids

### Fluociclovir

**ROUTE-SPECIFIC INFORMATION**

‑ With intravitreal use in adults: caution with concurrent administration of anticoagulant or antiplatelet drugs (higher incidence of conjunctival haemorrhage).

Interactions do not generally apply to corticosteroids used for topical action unless specified.
Fluorouracil is predicted to increase the risk of toxicity when given with fluorouracil. Avoid. [Moderate] Theoretical

Fluorouracil increases the concentration of antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone). Monitor concentration and adjust dose. [Severe] Anecdotal

Fluorouracil increases the anticoagulant effect of coumarins. [Severe] Anecdotal

Folates (folic acid) are predicted to increase the risk of toxicity when given with fluorouracil. Avoid. [Severe] Theoretical

Folates (folic acid) are predicted to increase the risk of toxicity when given with fluorouracil. Monitor and adjust dose. [Severe] Theoretical

H₂-receptor antagonists (cimetidine) slightly increase the exposure to fluorouracil. [Severe] Study

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fluorouracil. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical

Methotrexate potentially increases the risk of severe skin reaction when given with topical fluorouracil. [Severe] Anecdotal

→ Also see TABLE 15 p. 1378

Metronidazole increases the risk of toxicity when given with fluorouracil. [Severe] Study

Fluoxetine → see SSRIs
Fluphenazine → see phenothiazines
Flurazepam → see Table 11 p. 1377 (CNS depressant effects)
Flupentixol is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical

Also see TABLE 8 p. 1376

Flupentixol decreases the risk of toxicity when given with fluorouracil. [Severe] Study

Flupentixol decreases the effects of levodopa. Avoid or monitor worsening parkinsonian symptoms. [Severe] Theoretical

Fluphenazine decreases the risk of toxicity when given with fluorouracil. [Severe] Study

Fluphenazine is predicted to decrease the concentration of guanfacine. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Fosaprepitant is predicted to increase the concentration of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Efavirenz is predicted to decrease the exposure to fosaprepitant. [Moderate] Theoretical

Enzalutamide is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the anticoagulant effect of coumarins. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Fosaprepitant is predicted to decrease the efficacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Fosaprepitant is predicted to increase the concentration of guanfacine. [Moderate] Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to fosaprepitant. [Moderate] Theoretical

Antifungals, azoles (posaconazole) are predicted to increase the exposure to fosaprepitant. [Moderate] Study

Bosentan is predicted to decrease the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant is predicted to increase the exposure to bosutinib. [Severe] Theoretical

Cobicistat is predicted to increase the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Study

Fosaprepitant is predicted to decrease the anticoagulant effect of coumarins. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Fosaprepitant is predicted to increase the concentration of guanfacine. [Moderate] Theoretical

Fosaprepitant is predicted to slightly increase the exposure to ibrutinib. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant is predicted to increase the exposure to intravenous irinotecan. [Severe] Theoretical

Fosaprepitant is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical

Fosaprepitant is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. [Moderate] Theoretical

Macrolides (clarithromycin) are predicted to increase the exposure to fosaprepitant. [Moderate] Theoretical

Fosaprepitant slightly increases the exposure to midazolam. [Moderate] Study

Midazolam is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Fosaprepitant is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Fosaprepitant is predicted to increase the exposure to pioglitazone. Avoid. [Severe] Theoretical

Rifampicin is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

St John’s Wort is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical

Fosaprepitant decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Fosaprepitant is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical

Foscarnet → see Table 2 p. 1373 (nephrotoxicity)
Foscarnet increases the risk of hypocalcaemia when given with pentamidine. [Severe] Anecdotal

Fosinopril → see ACE inhibitors
Fosphenytoin → see antiepileptics
Frovatriptan → see TABLE 13 p. 1378 (serotonin syndrome)
Frovatriptan – Glecaprevir 1459

- SSRI (fluvoxamine) increase the concentration of frovatriptan.
  - Severe Study → Also see TABLE 13 p. 1378
- Fulvestrant → see TABLE 5 p. 1375 (thromboembolism)
- Furosemide → see loop diuretics
- Fusidic acid
  - ROUTE-SPECIFIC INFORMATION Interactions do not generally apply to topical use unless specified.
  - Fusidic acid increases the risk of rhabdomyolysis when given with statins. Avoid. Severe Anecdotal
- Gabapentin → see antiepileptics
- Galantamine → see anticholinesterases, centrally acting
- Ganciclovir → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity)
  - ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
  - Ganciclovir is predicted to increase the risk of seizures when given with carbapenems (imipenem). Avoid. Severe Anecdotal
  - Ganciclovir is predicted to increase the exposure to didanosine. Moderate Study
- Leflunomide is predicted to increase the exposure to ganciclovir. Moderate Theoretical → Also see TABLE 15 p. 1378
- Mycophenolate is predicted to increase the risk of haematological toxicity when given with ganciclovir. Moderate Theoretical → Also see TABLE 15 p. 1378
- Teriflunomide is predicted to increase the exposure to ganciclovir. Moderate Study
- Gefitinib → see TABLE 15 p. 1378 (myelosuppression)
  - Antacids are predicted to slightly decrease the exposure to gefitinib. Moderate Theoretical
  - Antiarrhythmics (dronedarone) are predicted to increase the exposure to gefitinib. Moderate theoretical
  - Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to gefitinib. Avoid. Severe Study
  - Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to gefitinib. Moderate Theoretical
  - Antihypertensives (diltiazem, verapamil) are predicted to increase the exposure to gefitinib. Severe Anecdotal
- Gefitinib is predicted to increase the exposure to gefitinib. Severe Study
  - Enalapril is predicted to decrease the exposure to gefitinib. Severe Study
  - H₂ receptor antagonists are predicted to slightly to moderately decrease the exposure to gefitinib. Moderate Study
- HIV-protease inhibitors are predicted to increase the exposure to gefitinib. Moderate Study → Also see TABLE 15 p. 1378
- Imitinib is predicted to increase the exposure to gefitinib. Moderate Theoretical → Also see TABLE 15 p. 1378
- Macrolides (clarithromycin) are predicted to increase the exposure to gefitinib. Moderate Study
- Macrolides (erythromycin) are predicted to increase the exposure to gefitinib. Moderate Theoretical
- Mitotane is predicted to decrease the exposure to gefitinib. Avoid. Severe Study → Also see TABLE 15 p. 1378
- Mitomycin is predicted to increase the exposure to gefitinib. Moderate Theoretical
- Nevirapine is predicted to decrease the exposure to gefitinib. Avoid. Severe Theoretical
  - Nilotinib is predicted to increase the exposure to gefitinib. Moderate Theoretical → Also see TABLE 15 p. 1378
- Gefitinib is predicted to increase the risk of bleeding events when given with phenindione. Severe Theoretical
  - Proton pump inhibitors are predicted to decrease the exposure to gefitinib. Severe Theoretical
- Rifampicin is predicted to decrease the exposure to gefitinib. Avoid. Severe Study
- St John's Wort is predicted to decrease the exposure to gefitinib. Avoid. Severe Theoretical
- Gemcitabine → see TABLE 15 p. 1378 (myelosuppression)
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with gemcitabine. Public Health England advises avoid (refer to Green Book). Severe Theoretical
- Gemfibrozil → see fibrates
- Gentamicin → see aminoglycosides

Glecaprevir

- Antiarrhythmics (dronedarone) potentially increase the exposure to glecaprevir. Moderate Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to glecaprevir. Avoid. Severe Study
- Antiepileptics (eslicarbazepine, oxcarbazepine) potentially decrease the exposure to glecaprevir. Severe Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) potentially increase the exposure to glecaprevir. Moderate Theoretical
- Combination hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with glecaprevir. Avoid. Severe Study
- Crizotinib potentially decreases the exposure to glecaprevir. Avoid. Severe Theoretical
- Glecaprevir (with pibrentasvir) increases the exposure to dabigatran. Avoid. Moderate Study
- Glecaprevir (with pibrentasvir) increases the exposure to digoxin. Moderate Theoretical
- Efavirenz is predicted to decrease the exposure to glecaprevir. Avoid. (Severe) Study
- Enalapril is predicted to greatly decrease the concentration of glecaprevir. Avoid. Severe Study
- HIV-protease inhibitors (atazanavir, darunavir, lopinavir) (boosted with ritonavir) increase the exposure to glecaprevir. Avoid. Severe Study
- HIV-protease inhibitors (ritonavir) increase the exposure to glecaprevir. Avoid. Severe Study
- Lumacaftor potentially decreases the exposure to glecaprevir. Avoid. Severe Theoretical
- Mitotane is predicted to greatly decrease the concentration of glecaprevir. Avoid. Severe Study
- Nevirapine is predicted to decrease the exposure to glecaprevir. Avoid. Severe Study
- Rifampicin markedly affects the exposure to glecaprevir. Avoid. Severe Study
- St John's Wort markedly affects the exposure to glecaprevir. Avoid. Severe Study
- Mitotane is predicted to decrease the exposure to glecaprevir. Avoid. Severe Study
- Glecaprevir (with pibrentasvir) markedly increases the exposure to statins (atorvastatin). Avoid. Severe Study
- Glecaprevir (with pibrentasvir) markedly increases the exposure to statins (fluvastatin). Severe Study
- Glecaprevir (with pibrentasvir) increases the exposure to statins (pravastatin). Use with caution and adjust pravastatin dose. Moderate Study
- Glecaprevir (with pibrentasvir) increases the exposure to statins (rosuvastatin). Use with caution and adjust rosuvastatin dose, p. 204. Moderate Study
- Glecaprevir (with pibrentasvir) increases the exposure to statins (simvastatin). Avoid. Moderate Study

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### Grapefruit juice — Grapefruit juice

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Grapefruit juice – Guanethidine

Grapefruit juice is predicted to increase the exposure to regorafenib. Avoid. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to ribociclib. Avoid. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to saxagliptin. [Moderate] Theoretical

Grapefruit juice increases the concentration of sirolimus. [Moderate] Study

Grapefruit juice moderately increases the exposure to SSRIs. (sertraline). Avoid. [Moderate] Study

Grapefruit juice increases the exposure to statins (atorvastatin). Avoid. [Severe] Study

Grapefruit juice increases the exposure to statins (simvastatin). Avoid. [Moderate] Study

Grapefruit juice greatly increases the concentration of temsirolimus. Use with caution or avoid. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to tezacaftor. Avoid. [Severe] Study

Grapefruit juice moderately increases the exposure to ticagrelor. [Moderate] Study

Grapefruit juice increases the exposure to tolvaptan. Avoid. [Moderate] Study

Grapefruit juice is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to venetoclax. Avoid. [Severe] Theoretical

Grass pollen extract

General information

Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline might be ineffective in case of a hypersensitivity reaction) or ACE inhibitors (risk of severe anaphylactoid reactions).

Grazoprevir

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidione) are predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. [Severe] Study

Bosantan is predicted to markedly decrease the exposure to grazoprevir. Avoid. [Severe] Study

Grazoprevir is predicted to markedly decrease the concentration of calcium channel blockers. [Moderate] Theoretical

Ciclosporin greatly increases the exposure to grazoprevir. Avoid. [Severe] Study

Cobicistat is predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. [Severe] Study

Efavirenz is predicted to markedly decrease the exposure to grazoprevir. Avoid. [Severe] Study

Elvitegravir markedly increases the exposure to grazoprevir. Avoid. [Severe] Study

Enzalutamide is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

Estravirine is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

HIV-protease inhibitors are predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. [Severe] Study

Idelalisib is predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. [Severe] Study

Macrolides (clarithromycin) are predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. [Severe] Study

Mitotane is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

Modafinil is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

Nevirapine is predicted to markedly decrease the exposure to grazoprevir. Avoid. [Severe] Study

Rifampicin is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study

St John’s Wort is predicted to markedly decrease the exposure to grazoprevir. Avoid. [Severe] Study

Grazoprevir is predicted to increase the exposure to statins (atorvastatin). Adjust atorvastatin dose, p. 202. [Moderate] Study

Grazoprevir is predicted to increase the exposure to statins (fluvastatin). Adjust fluvastatin dose, p. 203. [Unknown] Theoretical

Grazoprevir increases the exposure to statins (rosuvastatin). Adjust rosuvastatin dose, p. 204. [Moderate] Study

Grazoprevir is predicted to increase the exposure to statins (simvastatin). Adjust simvastatin dose, p. 205. [Unknown] Theoretical

Grazoprevir is predicted to increase the concentration of simtubin. Use with caution and adjust dose. [Moderate] Theoretical

Grazoprevir increases the exposure to tacrolimus. [Moderate] Study

Griseofulvin

ROUTE-SPECIFIC INFORMATION

Interactions do not generally apply to topical use unless specified.

Alcohol (beverage) potentially causes a disulfiram-like reaction when given with griseofulvin. [Moderate] Anecdotal

Antiepileptics (phenobarbital, primidione) decrease the effects of griseofulvin. [Moderate] Study

Griseofulvin potentially decreases the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Griseofulvin potentially decreases the anticoagulant effect of coumarins. [Moderate] Anecdotal

Griseofulvin potentially decreases the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Griseofulvin potentially decreases the efficacy of oral levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Griseofulvin potentially decreases the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Guanethidine → see TABLE 8 p. 1376 (Hypotension)

Amfetamines (dexamfetamine) decrease the effects of guanethidine. [Severe] Study

Benperidol is predicted to decrease the effects of guanethidine. [Moderate] Theoretical → Also see TABLE 8 p. 1376

 Droperidol is predicted to decrease the effects of guanethidine. Monitor and adjust dose. [Moderate] Theoretical → Also see TABLE 8 p. 1376

 Haloperidol is predicted to decrease the antihypertensive effects of guanethidine. Monitor and adjust dose. [Moderate] Theoretical → Also see TABLE 8 p. 1376

Monoamine-oxidase A and B inhibitors, irreversible are predicted to decrease the antihypertensive effects of guanethidine. Avoid and for 14 days after stopping the MAOI. [Severe] Theoretical → Also see TABLE 8 p. 1376

Phenothiazines are predicted to decrease the antihypertensive effects of guanethidine. [Moderate] Theoretical → Also see TABLE 8 p. 1376

Guanethidine is predicted to increase the effects of sympathomimetics, inotropic (dopamine). [Severe] Theoretical

Guanethidine is predicted to increase the effects of sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). [Moderate] Study

Guanethidine increases the effects of sympathomimetics, vasoconstrictor (metaraminol). [Severe] Anecdotal

Guanethidine increases the effects of sympathomimetics, vasoconstrictor (phenylephrine). [Severe] Study

Tricyclic antidepressants are predicted to decrease the antihypertensive effects of guanethidine. [Moderate] Study → Also see TABLE 8 p. 1376
Guanfacine → see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)

- Antiarrhythmics (dronedarone) are predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Guanfacine increases the concentration of antiepileptics (valproate). Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Bosentan is predicted to decrease the concentration of guanfacine. Adjust dose. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical → Also see TABLE 8 p. 1376
- Chloramphenicol is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Cimetidine is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Crizotinib is predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Efavirenz is predicted to decrease the concentration of guanfacine. Adjust dose. [Moderate] Theoretical
- Enalapril is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
- Fosaprepitant is predicted to increase the concentration of guanfacine. [Moderate] Theoretical
- Grapefruit juice is predicted to increase the exposure to guanfacine. Avoid. [Moderate] Theoretical
- HIV-protease inhibitors are predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
- Idelalisib is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
- Imatinib is predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
- Macrolides (erythromycin) are predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Guanfacine is predicted to increase the concentration of ranitidine. [Moderate] Theoretical
- Mitotane is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
- Netupitant is predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Nilotinib is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Rifampicin is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- Guselkumab → see monoclonal antibodies

**H₂ receptor antagonists**

- Cimetidine decreases the clearance of albendazole. [Moderate] Study
- Cimetidine increases the concentration of aminophylline. Adjust dose. [Severe] Study
- Cimetidine slightly increases the exposure to anthracyclines (epirubicin). Avoid. [Moderate] Study
- Cimetidine increases the exposure to antiarrhythmics (amiodarone). [Moderate] Study
- Cimetidine slightly increases the exposure to antiarrhythmics (flecainide). Monitor and adjust dose. [Mild] Study
- Cimetidine increases the exposure to antiarrhythmics (lidocaine). Monitor and adjust dose. [Moderate] Study
- Cimetidine is predicted to increase the exposure to antiepileptics (propafenone). Monitor and adjust dose. [Moderate] Theoretical
- Cimetidine transiently increases the concentration of antiepileptics (carbamazepine). Monitor concentration and adjust dose. [Moderate] Study
- Cimetidine increases the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. [Severe] Study
- H₂ receptor antagonists are predicted to decrease the absorption of antifungals, azoles (itraconazole). Administer itraconazole capsules with an acidic beverage. [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the absorption of antifungals, azoles (ketoconazole). Administer ketoconazole with an acidic beverage. [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the exposure to antifungals, azoles (posaconazole). Avoid use of posaconazole oral suspension. [Moderate] Study
- Cimetidine decreases the clearance of antimalarials (chloroquine). [Moderate] Study
- Cimetidine slightly increases the exposure to antimalarials (quinine). [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the absorption of bosutinib. [Moderate] Theoretical
- Cimetidine slightly increases the exposure to calcium channel blockers (diltiazem, nimodipine). Monitor and adjust dose. [Moderate] Study
- Cimetidine is predicted to slightly increase the exposure to calcium channel blockers (verapamil). [Moderate] Study
- Cimetidine increases the exposure to calcium channel blockers (nifedipine), Monitor and adjust dose. [Severe] Study
- Cimetidine increases the exposure to calcium channel blockers (lindalipine). [Moderate] Theoretical
- Cimetidine is predicted to slightly increase the exposure to capcetabine. [Severe] Theoretical
- H₂ receptor antagonists are predicted to decrease the absorption of ceritinib. [Moderate] Theoretical
- Cimetidine increases the concentration of ciclosporin. [Mild] Study
- Cimetidine increases the concentration of coumarins. [Severe] Study
- Cimetidine increases the exposure to dopamine receptor agonists (pramipexole). Adjust dose. [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the absorption of dipyridamole (immediate release tablets). [Moderate] Theoretical
- Cimetidine is predicted to increase the exposure to erlotinib. Erlotinib should be taken 2 hours before or 10 hours after H₂ receptor antagonists. [Moderate] Study
- Cimetidine increases the concentration of fampridine. Avoid. [Severe] Theoretical
- Cimetidine slightly increases the exposure to fluorouracil. [Severe] Study
- H₂ receptor antagonists are predicted to slightly to moderately decrease the exposure to gefitinib. [Moderate] Study
- H₂ receptor antagonists decrease the exposure to HIV-protease inhibitors (atazanavir). Monitor and adjust dose. [Moderate] Study
- Cimetidine is predicted to decrease the clearance of hydroxychloroquine. [Moderate] Theoretical
- H₂ receptor antagonists are predicted to decrease the absorption of lapatinib. Avoid. [Moderate] Theoretical
- H₂ receptor antagonists are predicted to decrease the exposure to ledipasvir. Adjust dose. See ledipasvir with sofosbuvir p. 628. [Moderate] Study
- **Leflunomide** is predicted to increase the exposure to H₂ receptor antagonists (cimetidine, famotidine). [Moderate] Theoretical
- H₂ receptor antagonists (cimetidine, ranitidine) are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. [Moderate] Theoretical
- Cimetidine slightly increases the exposure to macrolides (erythromycin). [Moderate] Study
- Cimetidine increases the concentration of mebendazole. [Moderate] Study
- Cimetidine increases the exposure to mirtazapine. Monitor and adjust dose. [Moderate] Study
- Cimetidine increases the exposure to moclobemide. Adjust moclomemide dose, p. 362. [Mild] Study
- H₂ receptor antagonists are predicted to decrease the absorption of nilotinib. H₂ receptor antagonists should be taken 10 hours before or 2 hours after nilotinib. [Mild] Theoretical
- Cimetidine increases the concentration of opioids (alfentanil). Use with caution and adjust dose. [Severe] Study
- Cimetidine increases the exposure to opioids (fentanyl). [Moderate] Study
  - H₂ receptor antagonists are predicted to decrease the exposure to pazopanib. H₂ receptor antagonists should be taken 10 hours before or 2 hours after pazopanib. [Moderate] Theoretical
- Cimetidine increases the exposure to phenindione. [Severe] Anecdotal
- Cimetidine moderately increases the exposure to praziquantel. [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the exposure to rifampicin. H₂ receptor antagonists should be taken 12 hours before or 4 hours after rifampicin. [Severe] Study
- Cimetidine slightly increases the exposure to roflumilast. [Moderate] Study
- H₂ receptor antagonists potentially decrease the exposure to sofosbuvir. Adjust dose, see ledipasvir with sofosbuvir p. 628, sofosbuvir with velpatasvir p. 629, and sofosbuvir with velpatasvir and voxilaprevir p. 630. [Moderate] Study
- Cimetidine slightly increases the exposure to SSRIs (citalopram, escitalopram). Adjust dose. [Moderate] Study
- Cimetidine slightly increases the exposure to SSRIs (paroxetine, sertraline). [Moderate] Study
- Cimetidine is predicted to increase the risk of toxicity when given with tegafur. [Severe] Theoretical
- Teriflunomide is predicted to increase the exposure to H₂ receptor antagonists (cimetidine, famotidine). [Moderate] Study
- Cimetidine increases the concentration of theophylline. Adjust dose. [Severe] Study
- Cimetidine increases the exposure to tricyclic antidepressants. [Moderate] Study
- H₂ receptor antagonists are predicted to decrease the concentration of velpasvir. Adjust dose, see sofosbuvir with velpatasvir p. 629. [Moderate] Study
- Cimetidine slightly increases the exposure to venlafaxine. [Mild] Study
- Cimetidine slightly increases the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Mild] Study

### Haloperidol

See Table 8 p. 1376 (hypotension), Table 9 p. 1377 (QT-interval prolongation), Table 11 p. 1377 (CNS depressant effects), Table 10 p. 1377 (antimuscarinic).

#### Food and Lifestyle

Dose adjustment might be necessary if smoking started or stopped during treatment.

- **Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) decrease the concentration of haloperidol. Adjust dose. [Moderate] Study
  - Also see Table 11 p. 1377
- **Haloperidol** potentially increases the risk of overheating and dehydration when given with antiepileptics (zonisamide). Avoid in children. [Severe] Theoretical
- **Antifungals, azoles (itraconazole)** increase the concentration of haloperidol. [Moderate] Study
- **Haloperidol** is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical
  - Also see Table 8 p. 1376
  - Also see Table 9 p. 1377
  - Also see Table 10 p. 1377

- **Enzalutamide** decreases the concentration of haloperidol. Adjust dose. [Moderate] Study
- **Haloperidol** potentially opposes the effects of glyceral phenylbutyrate. [Moderate] Theoretical
- **Haloperidol** is predicted to decrease the antihypertensive effects of guanethidine. Monitor and adjust dose. [Moderate] Theoretical
  - Also see Table 8 p. 1376
- **HIV-protease inhibitors (ritonavir)** are predicted to increase the exposure to haloperidol. [Severe] Theoretical
- **Haloperidol** decreases the effects of levodopa. [Severe] Study
  - Also see Table 8 p. 1376
- **Mitotane** decreases the concentration of haloperidol. Adjust dose. [Moderate] Study
- **Rifampicin** decreases the concentration of haloperidol. Adjust dose. [Moderate] Study
- **Haloperidol** potentially decreases the effects of sodium phenylbutyrate. [Moderate] Anecdotal
- **SSRIs** (fluoxetine) increase the concentration of haloperidol. Adjust dose. [Moderate] Anecdotal
- **SSRIs** (fluoxetine) increase the concentration of haloperidol. Adjust dose. [Moderate] Anecdotal
- **Venlafaxine** slightly increases the exposure to haloperidol. [Severe] Study
  - Also see Table 9 p. 1377
  - Also see Table 11 p. 1377

#### Heparin (unfractionated)

See Table 16 p. 1379 (increased serum potassium), Table 3 p. 1375 (anticoagulant effects).

- **Ranolazine** increases the risk of bleeding events when given with heparin (unfractionated). [Severe] Theoretical

#### Hepatitis B immunoglobulin

See immunoglobulins

**HIV-protease inhibitors** — see Table 9 p. 1377 (QT-interval prolongation)

- atazanavir - darunavir - fosamprenavir - lopinavir - ritonavir - saquinavir - tipranavir

Caution on concurrent use of atazanavir, lopinavir with ritonavir, and ritonavir with drugs that prolong the PR interval.

Concurrent use of saquinavir with drugs that prolong the PR interval is contra-indicated.

Caution on concurrent use of tipranavir with drugs that increase risk of bleeding.

**Tipranavir** slightly decreases the exposure to abacavir. Avoid. [Severe] Study

**HIV-protease inhibitors** are predicted to increase the exposure to abacavir. Adjust or avoid abacavir dose, p. 967. [Severe] Study

**HIV-protease inhibitors** (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to alfatinib. Separate administration by 1 hour. [Moderate] Study

**Ritonavir** is predicted to decrease the exposure to agomelatine. [Moderate] Theoretical

**Ritonavir** decreases the exposure to abiraterone. [Moderate] Study

**HIV-protease inhibitors** are predicted to markedly increase the exposure to aldosterone antagonists (spironolactone). Avoid. [Severe] Study

**HIV-protease inhibitors** (ritonavir, saquinavir) are predicted to increase the exposure to aliskiren. [Moderate] Theoretical

**HIV-protease inhibitors** increase the exposure to almotriptan. [Mild] Study

**HIV-protease inhibitors** are predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. [Moderate] Study

**HIV-protease inhibitors** are predicted to increase the exposure to alpha blockers (doxazosin). [Moderate] Study

**HIV-protease inhibitors** moderately increase the exposure to alprazolam. Avoid. [Mild] Study

**HIV-protease inhibitors** (ritonavir, tipranavir) are predicted to increase the exposure to amifetamine. [Severe] Theoretical

**Ritonavir** decreases the exposure to aminophylline. Adjust dose. [Moderate] Study

**Ritonavir** is predicted to decrease the exposure to anaesthetics, local (ropivacaine). [Mild] Theoretical

**Antacids** are predicted to decrease the absorption of atazanavir. Atazanavir should be taken 2 hours before or 1 hour after antacids. [Severe] Theoretical
HIV-protease inhibitors (continued)

- **Antacids** are predicted to decrease the absorption of tipranavir. Separate administration by 2 hours. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to antiretrovirals (amprenavir). Avoid. **Severe** Theoretical → Also see TABLE 9 p. 1377

- HIV-protease inhibitors are predicted to increase the exposure to antiretrovirals (disopyramide). **Severe** Theoretical → Also see TABLE 9 p. 1377

- HIV-protease inhibitors very markedly increase the exposure to antiretrovirals (dronedarone). Avoid. **Severe** Study → Also see TABLE 9 p. 1377

- Ritonavir is predicted to increase the exposure to antiretrovirals (flecainide). Avoid or monitor side effects. **Severe** Theoretical

- HIV-protease inhibitors are predicted to increase the exposure to antiretrovirals (lidoceaine). Avoid. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to antiretrovirals (propafenone). Monitor and adjust dose. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to antiretrovirals (rifampicin) and antiretrovirals (rifapentine). **Severe** Theoretical

- HIV-protease inhibitors are predicted to affect the exposure to antiretrovirals (fosphenytoin, phenytoin) and antiepileptics (phenobarbital, primidone) decrease the concentration of HIV-protease inhibitors. **Severe** Theoretical

- Ritonavir slightly decreases the exposure to antiepileptics (lamotrigine). **Severe** Study

- HIV-protease inhibitors are predicted to very slightly increase the exposure to antiepileptics (perampanel). **Mild** Study

- HIV-protease inhibitors are predicted to affect the concentration of antiepileptics (phenobarbital, primidone) and antiepileptics (phenobarbital, primidone) are predicted to decrease the concentration of HIV-protease inhibitors. **Severe** Theoretical

- Ritonavir is predicted to decrease the concentration of antiepileptics (valproate). **Severe** Anadotal

- Antifungals, azoles (fluconazole) slightly increase the exposure to antiretrovirals (tipranavir). Avoid or adjust dose. **Moderate** Study

- Antifungals, azoles (micazosine) are predicted to increase the concentration of HIV-protease inhibitors. Use with caution and adjust dose. **Moderate** Theoretical

- Antifungals, azoles (posaconazole) are predicted to increase the exposure to HIV-protease inhibitors. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (itraconazole). Avoid or monitor side effects. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (fluconazole). Use with caution and adjust dose. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (ketoconazole). Use with caution and adjust dose. **Moderate** Study

- Antifungals, azoles (voriconazole) potentially affect the exposure to HIV-protease inhibitors. **Severe** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (voriconazole) and antifungals, azoles (voriconazole) potentially affect the exposure to antifungals, azoles (ketoconazole). Use with caution and adjust dose. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (itraconazole). Avoid. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (ketoconazole). Use with caution and adjust dose. **Moderate** Study

- HIV-protease inhibitors are predicted to affect the exposure to antifungals, azoles (voriconazole) and antifungals, azoles (voriconazole) potentially affect the exposure to HIV-protease inhibitors. **Severe** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors are predicted to increase the exposure to antifungals, azoles (itraconazole). Avoid. **Moderate** Study

- HIV-protease inhibitors are predicted to affect the exposure to antimalarials (quinine). **Severe** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors are predicted to increase the exposure to apalutamide. **Mild** Study → Also see TABLE 9 p. 1377

- Ritonavir is predicted to increase the exposure to apixaban. **Avoid.** **Severe** Theoretical

- HIV-protease inhibitors are predicted to markedly increase the exposure to aprepitant. **Moderate** Study

- HIV-protease inhibitors are predicted to slightly increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to aripiprazole. **Avoid.** **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to axitinib. Avoid or adjust dose. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to bedaquiline. Avoid prolonged use. **Avoid.** **Mild** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to bictegravir. Use with caution or avoid. **Moderate** Theoretical

- HIV-protease inhibitors slightly increase the exposure to bortezomib. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to bosentan. **Severe** Study

- HIV-protease inhibitors are predicted to markedly increase the exposure to bosutinib. Avoid or adjust dose. **Severe** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors are predicted to increase the exposure to brigatinib. Adjust brigatinib dose, p. 971. **Severe** Study

- Ritonavir is predicted to decrease the exposure to bupropion. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to bupirone. Adjust bupirone dose, p. 342. **Severe** Study

- HIV-protease inhibitors slightly increase the exposure to cabozantinib. **Moderate** Study → Also see TABLE 9 p. 1377

- Ritonavir is predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. **Moderate** Study

- HIV-protease inhibitors are predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). **Severe** Study

- HIV-protease inhibitors are predicted to markedly increase the exposure to calcium channel blockers (lercanidipine). Avoid. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to cannabis extract. Use with caution and adjust dose. **Moderate** Theoretical

- HIV-protease inhibitors are predicted to moderately increase the exposure to cariprazine. Avoid. **Severe** Study

- HIV-protease inhibitors are predicted to increase the exposure to ceritinib. Avoid or adjust dose. p. 973. **Severe** Study → Also see TABLE 9 p. 1377

- HIV-protease inhibitors increase the concentration of ciclosporin. **Severe** Study

- HIV-protease inhibitors are predicted to moderately increase the exposure to clofarabine. Adjust clofarabine dose, p. 232. **Moderate** Study

- HIV-protease inhibitors are predicted to moderately increase the exposure to ciraparib. **Moderate** Study

- HIV-protease inhibitors are predicted to moderately increase the exposure to clofarabine. **Moderate** Study

- HIV-protease inhibitors are predicted to moderate increase the exposure to coibemel. **Moderate** Study

- HIV-protease inhibitors are predicted to markedly increase the exposure to coibemel. **Moderate** Study

- HIV-protease inhibitors are predicted to affect the exposure to cotropamine. **Avoid.** **Moderate** Study
HIV-protease inhibitors are predicted to increase the exposure to colchicine. Avoid potent inhibitors of CYP3A4 or adjust colchicine dose, p. 1120. (Severe) Study

Atazanavir (unboosted) increases the exposure to combined hormonal contraceptives. Adjust dose. (Severe) Study

Ritonavir is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to corticosteroids (beclometasone) (risk with beclometasone is likely to be lower than with other corticosteroids). Moderate Theoretical

HIV-protease inhibitors are predicted to increase the exposure to corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. (Severe) Study

HIV-protease inhibitors are predicted to affect the anticoagulant effect of coumarins. (Moderate) Study

HIV-protease inhibitors are predicted to moderately increase the exposure to crizotinib. Avoid. Moderate Theoretical

HIV-protease inhibitors are predicted to increase the exposure to dabrafenib. Use with caution or avoid. Moderate Study

HIV-protease inhibitors are predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. (Severe) Study

Dasabuvir (with ombrutdin, paritaprevir, and ritonavir) decreases the concentration of darunavir. Avoid or adjust dose. (Moderate) Study

HIV-protease inhibitors are predicted to markedly increase the exposure to dasatinib. Avoid or adjust dose—consult product literature. (Severe) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to delamanid. (Severe) Study → Also see TABLE 9 p. 1377

Ritonavir is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Ritonavir is predicted to increase the exposure to diazepam. Avoid. (Moderate) Theoretical

Didanosine (buffered) decreases the exposure to atazanavir. Didanosine should be taken 2 hours after atazanavir, p. 648, p. 656. (Severe) Study

Didanosine (buffered) is predicted to decrease the exposure to darunavir (boosted with ritonavir). Didanosine should be taken 1 hour before or 2 hours after darunavir. (Moderate) Theoretical

Tipranavir decreases the exposure to didanosine. Separate administration by 2 hours. (Moderate) Study

Ritonavir increases the concentration of digoxin. Adjust dose and monitor concentration. (Severe) Study

Fosamprenavir (boosted with ritonavir) slightly decreases the exposure to dolutegravir. Avoid if resistant to HIV-integrase inhibitors. (Severe) Study

Tipranavir moderately decreases the exposure to dolutegravir. Refer to specialist literature. (Severe) Study

HIV-protease inhibitors increase the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study

HIV-protease inhibitors increase the exposure to dopamine receptor agonists (bromocriptine). (Severe) Study

HIV-protease inhibitors are predicted to increase the concentration of dopamine receptor agonists (cabergoline). (Moderate) Anecdotal

HIV-protease inhibitors are predicted to increase the exposure to doravirine. (Mild) Study

Ritonavir is predicted to decrease the exposure to duloxetine. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical

HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to slightly increase the exposure to edoxaban. Severe Theoretical

Efavirenz decreases the exposure to HIV-protease inhibitors. Refer to specialist literature. (Severe) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to markedly increase the exposure to eletriptan. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Study

HIV-protease inhibitors (atazanavir, lopinavir) (boosted with ritonavir) increase the concentration of elvitegravir. Refer to specialist literature. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to encorafenib. Avoid or monitor. (Severe) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the risk of ergotism when given with ergotamine. Avoid. (Severe) Theoretical

HIV-protease inhibitors are predicted to increase the risk of ergotism when given with ergotamine. Avoid. (Severe) Theoretical

HIV-protease inhibitors are predicted to slightly increase the exposure to erlotinib. Use with caution and adjust dose. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to esктematine. Adjust dose. (Moderate) Study

Ritonavir is predicted to decrease the efficacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Etravirine increases the exposure to fosaprepavir (boosted with ritonavir). Refer to specialist literature. (Moderate) Study

Tipranavir decreases the exposure to etravirine. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the concentration of everolimus. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to moderately increase the exposure to fesoterodine. Adjust fesoterodine dose with potent inhibitors of CYP3A4; avoid in hepatic and renal impairment, p. 777. (Severe) Study

HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to fidaxomicin. Avoid. (Moderate) Study

Ritonavir is predicted to increase the exposure to flurazepam. Avoid. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to fosaprepitant. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to gefitinib. (Moderate) Study

HIV-protease inhibitors (atazanavir, darunavir, lopinavir) (boosted with ritonavir) increase the exposure to glecaprevir. Avoid. (Severe) Study

Ritonavir increases the exposure to glecaprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to grazoprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to grazoprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to markedly increase the exposure to grazoprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to markedly increase the exposure to grazoprevir. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to grazoprevir. Avoid. (Severe) Study

Ritonavir is predicted to increase the exposure to haloperidol. (Severe) Theoretical

Ritonavir is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

HIV-protease inhibitors are predicted to very markedly increase the exposure to ibritinib. Avoid potent inhibitors of CYP3A4 or adjust ibritinib dose, p. 983. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to imatinib. (Moderate) Study

HIV-protease inhibitors are predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

Ritonavir is predicted to decrease the exposure to iron chelators (deferasirox). Monitor serum ferritin and adjust dose. (Moderate) Theoretical

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HIV-protease inhibitors (continued)

- **HIV-protease inhibitors** are predicted to increase the exposure to *inabradine*. Avoid. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *ivaclacafor*. Adjust ivaclacafor, p. 293 or lumacafor with ivaclacafor p. 294 or tezacafor with ivaclacafor p. 295 dose with potent inhibitors of CYP3A4. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *lapatinib*. Avoid. **(Moderate)** Study → Also see TABLE 9 p. 1377
- **Tipranavir (boosted with ritonavir)** is predicted to decrease the exposure to *ledipasvir*. Avoid. **(Severe)** Theoretical
- **HIV-protease inhibitors** (atazanavir, ritonavir) are predicted to increase the concentration of *intermeneron*. **(Moderate)** Study
- **Ritonavir** is predicted to decrease the concentration of *intermeneron*. **(Moderate)** Study
- **Ritonavir** is predicted to decrease the efficacy of *levonordestrol*. For FSRH guidance, see Contraceptives, interactions p. 794. **(Theoretical)**
- **HIV-protease inhibitors** are predicted to markedly increase the exposure to *lopinavir, ritonavir.* **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *lurasidone*. Avoid. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *lomipadate*. Avoid. **(Severe)** Study
- **Atazanavir** is predicted to increase the exposure to macrolides (clarithromycin). Adjust dose in renal impairment. **(Severe)** Study
- **Ritonavir** increases the exposure to macrolides (clarithromycin). Adjust dose in renal impairment. **(Severe)** Study
- **Tipranavir (boosted with ritonavir)** increases the exposure to macrolides (clarithromycin) and macrolides (clarithromycin) increase the exposure to tipranavir (boosted with ritonavir). Monitor; adjust dose in renal impairment. **(Severe)** Study
- **HIV-protease inhibitors** (darunavir, fosamprenavir, lopinavir) (boosted with ritonavir) are predicted to increase the exposure to macrolides (clarithromycin). Adjust dose in renal impairment. **(Severe)** Study
- **HIV-protease inhibitors** (atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, tipranavir) are predicted to increase the exposure to macrolides (clarithromycin). **(Severe)** Theoretical
- **Darunavir (boosted with ritonavir)** markedly increases the exposure to *maraviroc*. Refer to specialist literature. **(Severe)** Study
- **Maraviroc** potentially decreases the exposure to fosamprenavir and fosamprenavir potentially decreases the exposure to *maraviroc*. Avoid. **(Severe)** Study
- **HIV-protease inhibitors** (atazanavir, saquinavir) moderately to markedly increase the exposure to *maraviroc*. Refer to specialist literature. **(Severe)** Study
- **Ritonavir (boosted with ritonavir)** moderately increases the exposure to *maraviroc*. Refer to specialist literature. **(Severe)** Study
- **Ritonavir** is predicted to decrease the exposure to *melatonin*. **(Moderate)** Theoretical
- **Ritonavir** is predicted to increase the clearance of *mexiteline*. Monitor and adjust dose. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to very markedly increase the exposure to *midostaurin*. Avoid or monitor for toxicity. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *mirabegron*. Adjust mirabegron dose in hepatic and renal impairment, p. 781. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *mirtazapine*. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *modafinil*. **(Theoretical)**
- **HIV-protease inhibitors** (lopinavir, ritonavir, saquinavir) are predicted to increase the risk of neutropenia when given with monoclonal antibodies (brentuximab vedotin). Monitor and adjust dose. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to monoclonal antibodies (trastuzumab emtansine). Avoid. **(Severe)** Theoretical
- **HIV-protease inhibitors** are predicted to markedly increase the exposure to *naltrexol*. Avoid. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *netupitant*. Avoid or adjust. **(Moderate)** Study
- **Nevirapine** decreases the exposure to HIV-protease inhibitors. For FSRH guidance, see Contraceptives, interactions p. 794. **(Severe)** Theoretical
- **HIV-protease inhibitors** are predicted to moderately increase the exposure to *nilotinib*. Avoid. **(Severe)** Study → Also see TABLE 9 p. 1377
- **HIV-protease inhibitors** (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to *nintedanib*. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *nitisineone*. Adjust dose. **(Moderate)** Theoretical
- **Ritonavir** is predicted to decrease the efficacy of *norgestrel*. For FSRH guidance, see Contraceptives, interactions p. 794. **(Severe)** Theoretical
- **Ritonavir** is predicted to decrease the exposure to *olanzapine*. Monitor and adjust dose. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *olaparib*. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1006. **(Moderate)** Study
- **Ombitasvir** (in fixed-dose combination with dasabuvir) decreases the concentration of *darunavir*. Avoid or adjust dose. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. **(Severe)** Study
- **HIV-protease inhibitors** (boosted with ritonavir) are predicted to decrease the exposure to opioids (methadone). **(Moderate)** Study → Also see TABLE 9 p. 1377
- **Ritonavir** is predicted to decrease the concentration of *opioids (morphine)*. **(Moderate)** Theoretical
- **Ritonavir** increases the risk of CNS toxicity when given with opioids (pethidine). **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *oxepifene*. Avoid in poor CYP2C9 metabolisers. **(Moderate)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *palbociclib*. Avoid or adjust palbociclib dose, p. 992. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *panobinostat*. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. **(Moderate)** Study → Also see TABLE 9 p. 1377
- **Atazanavir (boosted with ritonavir)** markedly increases the exposure to *paritaprevir*. Avoid or give unboosted. **(Moderate)** Study
- **Darunavir (boosted with ritonavir)** slightly decreases the exposure to *paritaprevir*. Avoid or give unboosted. **(Moderate)** Study
- **HIV-protease inhibitors** (fosamprenavir, tipranavir) (boosted with ritonavir) are predicted to increase the exposure to *paritaprevir*. Avoid. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *panobinostat*. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. **(Moderate)** Study → Also see TABLE 9 p. 1377
- **Atazanavir (boosted with ritonavir)** markedly increases the exposure to *paritaprevir*. Avoid or give unboosted. **(Moderate)** Study
- **Darunavir (boosted with ritonavir)** slightly decreases the exposure to *paritaprevir*. Avoid or give unboosted. **(Moderate)** Study
- **HIV-protease inhibitors** (fosamprenavir, tipranavir) (boosted with ritonavir) are predicted to increase the exposure to *paritaprevir*. Avoid. **(Severe)** Study
- **Lopinavir (boosted with ritonavir)** moderately to markedly increases the exposure to *paritaprevir*. Avoid. **(Severe)** Study
- **Saquinavir** is predicted to increase the exposure to *paritaprevir* (in fixed-dose combination). Avoid. **(Severe)** Study
- **HIV-protease inhibitors** are predicted to increase the exposure to *pazopanib*. Avoid or adjust pazopanib dose, p. 993. **(Moderate)** Study → Also see TABLE 9 p. 1377
- **HIV-protease inhibitors** are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. **(Severe)** Study → Also see TABLE 9 p. 1377
HIV-protease inhibitors are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. (Severe) Study → Also see TABLE 9 p. 1377.

HIV-protease inhibitors are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). Use with caution or avoid. (Severe) Study

HIV-protease inhibitors (atazanavir, lopinavir) (boosted with ritonavir) increase the exposure to pibrentasvir. Avoid. (Severe) Study

Tipranavir potentially increases the exposure to pibrentasvir. (Severe) Theoretical

Saquinavir is predicted to increase the exposure to pibrentasvir. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to pimozide. Avoid. (Severe) Study → Also see TABLE 9 p. 1377

Ritonavir is predicted to decrease the exposure to pimozide. (Moderate) Theoretical

HIV-protease inhibitors are predicted to slightly increase the exposure to praziquantel. (Weak) Study

Proton pump inhibitors decrease the exposure to atazanavir. Avoid or adjust dose. (Severe) Study

Proton pump inhibitors increase the exposure to saquinavir. Avoid. (Severe) Study

Tipranavir decreases the exposure to proton pump inhibitors. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to quetiapine. Avoid. (Severe) Study

Atazanavir increases the exposure to raltegravir (high-dose). Avoid. (Moderate) Study

Darunavir increases the risk of rash when given with raltegravir. (Moderate) Study

Fosamprenavir (boosted with ritonavir) decreases the exposure to raltegravir and raltegravir decreases the exposure to fosamprenavir (boosted with ritonavir). Avoid. (Severe) Study

Tipranavir (boosted with ritonavir) is predicted to decrease the exposure to raltegravir (high-dose). Avoid. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to ranolazine. Avoid. (Severe) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to reboxetine. Avoid. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to regorafenib. Avoid. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to regapline. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to regorafenib (alternate). Adjust altiretinoin dose, p. 1262. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. (Moderate) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir) (boosted with ritonavir) increase the exposure to rifabutin. Monitor and adjust dose. (Severe) Study

Ritonavir markedly increases the exposure to rifabutin. Avoid or adjust dose. (Severe) Study

Rifampicin is predicted to moderately to markedly decrease the exposure to HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir). Avoid. (Severe) Study

Rifampicin slightly decreases the exposure to ritonavir. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to tipranavir. Avoid. (Severe) Study

Ritonavir is predicted to increase the exposure to riociguat. Avoid. (Moderate) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to risedronate. Adjust dose. (Moderate) Study → Also see TABLE 9 p. 1377

Ritonavir moderately increases the exposure to rivaroxaban. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to rivolumibin. Adjust dose and monitor side effects. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to saxagliptin. (Moderate) Study

HIV-protease inhibitors are predicted to increase the concentration of sirolimus. Avoid. (Severe) Study

Tipranavir is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical

HIV-protease inhibitors are predicted to increase the exposure to soflufenac. Adjust soflufenac p. 779 or tamsuloxin with soflufenac p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study

HIV-protease inhibitors are predicted to moderately increase the exposure to SSRIs (dapoxetine). Avoid potent inhibitors of CYP3A4 or adjust dapoxetine dose, p. 821. (Severe) Study

St John’s Wort is predicted to decrease the exposure to HIV-protease inhibitors. Avoid. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to statins (atorvastatin). Avoid or adjust dose and monitor rhabdomyolysis. (Severe) Study

HIV-protease inhibitors slightly to moderately increase the exposure to statins (rosuvastatin). Avoid or adjust dose. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to statins (simvastatin). Avoid. (Severe) Study

HIV-protease inhibitors are predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. (Moderate) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to taxanes (cabazitaxel). Avoid. (Severe) Study

HIV-protease inhibitors are predicted to moderately increase the exposure to taxanes (docetaxel). Avoid or adjust dose. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to taxanes (paclitaxel). (Severe) Theoretical

HIV-protease inhibitors are predicted to increase the concentration of temsirolimus. Avoid. (Severe) Theoretical

HIV-protease inhibitors (atazanavir, darunavir, lopinavir) increase the exposure to tenofovir alafenamide. Avoid or adjust dose. (Moderate) Study

Tipranavir is predicted to decrease the exposure to tenofovir alafenamide. Avoid. (Moderate) Theoretical

HIV-protease inhibitors (atazanavir, darunavir, lopinavir) are predicted to increase the risk of renal impairment when given with tenofovir disoproxil. (Severe) Anecdotal

HIV-protease inhibitors are predicted to increase the exposure to tezacaftor. Avoid or adjust dose of p. 295 with potent inhibitors of CYP3A4. (Severe) Study

Ritonavir is predicted to decrease the exposure to theophylline. Adjust dose. (Moderate) Study

Ritonavir decreases the concentration of thyroid hormones (levothyroxine). MHRA advises monitor TSH for at least one month after starting or stopping ritonavir. (Moderate) Anecdotal

HIV-protease inhibitors are predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Ritonavir moderately decreases the exposure to tizanidine. (Mild) Study

HIV-protease inhibitors are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 105. (Moderate) Study

HIV-protease inhibitors are predicted to increase the exposure to tolerodine. Avoid. (Severe) Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with potent inhibitors of CYP3A4, p. 666. (Severe) Study

HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the exposure to topotecan. (Severe) Study

HIV-protease inhibitors are predicted to increase the exposure to toremifene. (Moderate) Theoretical → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to trabectedin. Avoid or adjust dose. (Severe) Theoretical
HIV-protease inhibitors (continued)

▶ HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the concentration of trametinib. (Moderate) Theoretical Study

▶ HIV-protease inhibitors are predicted to moderately increase the exposure to trazodone. Avoid or adjust dose. (Moderate) Study

▶ HIV-protease inhibitors (ritonavir, tipranavir) are predicted to increase the exposure to tricyclic antidepressants. (Moderate) Theoretical Study

▶ HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

▶ Ritonavir decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

Tipranavir is predicted to increase the exposure to velpatasvir. (Severe) Theoretical

▶ HIV-protease inhibitors are predicted to increase the exposure to vemurafenib. (Severe) Theoretical Also see TABLE 9 p. 1377

▶ HIV-protease inhibitors are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Severe) Study

▶ HIV-protease inhibitors are predicted to increase the exposure to vinca alkaloids. (Severe) Theoretical Also see TABLE 9 p. 1377

▶ HIV-protease inhibitors are predicted to increase the exposure to vitamin D substances (paricalcitol). (Moderate) Study

▶ Atazanavir (boosted with ritonavir) increases the concentration of voriconazole. Avoid. (Severe) Study

▶ Lopinavir (boosted with ritonavir) is predicted to increase the concentration of voriconazole. Avoid. (Severe) Theoretical

▶ Tipranavir (boosted with ritonavir) is predicted to increase the concentration of voriconazole. (Severe) Theoretical

▶ Tipranavir slightly decreases the exposure to zidovudine.

Avoid. (Moderate) Study

▶ HIV-protease inhibitors are predicted to increase the exposure to zopiclone. Adjust dose. (Moderate) Theoretical

Hormone replacement therapy

▶ Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Hormone replacement therapy is predicted to alter the exposure to antiepileptics (lamotrigine). (Moderate) Theoretical

▶ Aprepitant is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Bosantan is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Hormone replacement therapy decreases the clearance of dopamine receptor agonists (ropinirole). Monitor and adjust dose. (Moderate) Study

▶ Evirenz is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Fosaprepitant is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ HIV-protease inhibitors (ritonavir) are predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Hormone replacement therapy is predicted to increase the risk of venous thromboembolism when given with lenalidomide. (Severe) Theoretical

▶ Modafinil is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Hormone replacement therapy is predicted to increase the exposure to monoamine-oxidase B inhibitors (selegiline). Avoid. (Moderate) Study

▶ Nevirapine is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ NSAI.D. (etoricoxib) slightly increase the exposure to hormone replacement therapy. (Moderate) Study

▶ Hormone replacement therapy potentially opposes the effects of espomiphene. Avoid. (Severe) Theoretical

▶ Hormone replacement therapy is predicted to increase the risk of venous thromboembolism when given with pomalidomide. (Severe) Theoretical

▶ Hormone replacement therapy potentially opposes the effects of raloxifene. Avoid. (Severe) Theoretical

▶ Rifabutin is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ Rifampicin is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

▶ St John's Wort is predicted to decrease the efficacy of hormone replacement therapy. (Moderate) Theoretical

▶ Hormone replacement therapy is predicted to increase the risk of venous thromboembolism when given with thalidomide. (Severe) Theoretical

▶ Oral hormone replacement therapy is predicted to decrease the effects of thyroid hormones. (Moderate) Theoretical

Hydralazine see see TABLE 8 p. 1376 (hypotension)

▶ Diazoxide increases the risk of severe hypotension when given with hydralazine. (Severe) Study Also see TABLE 8 p. 1376

▶ Hydrochlorothiazide see thiazide diuretics

▶ Hydrocortisone see corticosteroids

▶ Hydroflumethiazide see thiazide diuretics

▶ Hydromorphone see opioids

▶ Hydroxy-carbamazepine see TABLE 15 p. 1378 (myelosuppression)

▶ Hydroxy-carbamazepine increases the risk of toxicity when given with vigabatrin. Avoid. (Severe) Study

▶ Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with hydroxy-carbamazepine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

▶ Hydroxy-carbamazepine increases the risk of toxicity when given with stavudine. Avoid. (Severe) Study

▶ Hydroxychloroquine

▶ Hydroxychloroquine is predicted to decrease the effects of agalasise. (Moderate) Theoretical

▶ Antacids decrease the absorption of hydroxychloroquine. Separate administration by at least 4 hours. (Moderate) Study

▶ Calcium salts (calcium carbonate) decrease the absorption of hydroxychloroquine. Separate administration by at least 4 hours. (Moderate) Study

▶ Hydroxychloroquine is predicted to decrease the efficacy of oral cholera vaccine. (Moderate) Theoretical

▶ H1 receptor antagonists (cimetidine) are predicted to decrease the clearance of hydroxychloroquine. (Moderate) Theoretical

▶ Lanthanum is predicted to decrease the absorption of hydroxychloroquine. Separate administration by at least 2 hours. (Moderate) Theoretical

▶ Hydroxychloroquine is predicted to decrease the exposure to famotidine. Avoid simultaneous administration. (Severe) Theoretical

▶ Hydroxychloroquine is predicted to increase the risk of haematological toxicity when given with penicillamine. Avoid. (Severe) Theoretical

▶ Hydroxychloroquine is predicted to decrease efficacy rabies vaccine. (Moderate) Theoretical

▶ Hydroxychloroquine is predicted to decrease efficacy of oral cholera vaccine. (Moderate) Theoretical

▶ Hydroxychloroquine is predicted to decrease efficacy of oral cholera vaccine. (Moderate) Theoretical

▶ Hydrazine see antihistamines, sedating

▶ Hypoglycaemic agents see TABLE 10 p. 1377 (antimuscarinics)

▶ Ibrutinib see TABLE 15 p. 1378 (myelosuppression), TABLE 4 p. 1375 (antiplatelet effects)

FOOD AND LIFESTYLE Avoid food or drink containing bitter (Seville) oranges as they are predicted to increase the exposure to ibrutinib.

▶ Antiarrhythmics (amiodarone) are predicted to increase the exposure to ibrutinib. Adjust ibrutinib dose, p. 983. (Severe) Theoretical

▶ Antiarrhythmics (dronedarone) are predicted to increase the exposure to ibrutinib. Adjust ibrutinib dose with moderate inhibitors of CYP3A4, p. 983. (Severe) Study

▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ibrutinib. Avoid or adjust ibrutinib dose, p. 983. (Severe) Study

▶ Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ibrutinib. Adjust
Idelalisib is predicted to increase the exposure to antiarrhythmics (amiodarone). Avoid. (Moderate) Theoretical
Idelalisib is predicted to very markedly increase the exposure to antiarrhythmics (dronedarone). Avoid. (Severe) Study
Idelalisib is predicted to increase the exposure to antiarrhythmics (propafenone). Monitor and adjust dose. (Severe) Study
Idelalisib is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. (Moderate) Study
Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to idelalisib. Avoid. (Severe) Study
Idelalisib is predicted to very slightly increase the exposure to antiepileptics (perampanel). (Mild) Study
Idelalisib is predicted to increase the exposure to antifungals, azoles (isavuconazole). Avoid or monitor side effects. (Severe) Study
Idelalisib is predicted to increase the exposure to antihistamines, non-sedating (micolazine). Avoid. (Severe) Study
Idelalisib is predicted to increase the exposure to antihistamines, non-sedating (rupatadine). Avoid. (Moderate) Study
Idelalisib is predicted to increase the concentration of antimalarials (piperazine). (Severe) Theoretical
Idelalisib is predicted to increase the exposure to apalutamide. (Mild) Study
Idelalisib is predicted to markedly increase the exposure to aprapentin. (Moderate) Study
Idelalisib is predicted to slightly increase the exposure to aripiprazole. Adjust aripiprazole dose. p. 975. (Moderate) Study
Idelalisib is predicted to increase the exposure to atraxinib. Adjust arixtratinib dose or avoid. (Moderate) Study → Also see TABLE 15 p. 1378
Idelalisib is predicted to increase the exposure to bedaquiline. Avoid prolonged use. (Mild) Study
Idelalisib is predicted to increase the exposure to beta, agonists (salmeterol). Avoid. (Severe) Study
Idelalisib slightly increases the exposure to bortezomib. (Moderate) Study → Also see TABLE 15 p. 1378
Idelalisib is predicted to decrease the exposure to bosutinib. Avoid or adjust dose. (Severe) Study → Also see TABLE 15 p. 1378
Idelalisib is predicted to increase the exposure to brigitanib. Adjust brigitanib dose, p. 971. (Severe) Study
Idelalisib is predicted to increase the exposure to buspirone. Adjust buspirone dose, p. 340. (Severe) Study
Idelalisib slightly increases the exposure to cabozantinib. (Moderate) Study → Also see TABLE 15 p. 1378
Idelalisib is predicted to increase the exposure to calcium channel blockers (amiodipine, felodipine, lacidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. (Moderate) Study
Idelalisib is predicted to increase the exposure to calcium channel blockers (diltiazem, verapamil). (Severe) Study
Idelalisib is predicted to markedly increase the exposure to calcium channel blockers (lercanidipine). Avoid. (Severe) Study
Idelalisib is predicted to increase the exposure to cannabis extract. Use with caution and adjust dose. (Moderate) Theoretical
Idelalisib is predicted to moderately increase the exposure to cariprazine. Avoid. (Severe) Study
Idelalisib is predicted to increase the exposure to certinib. Avoid or adjust certinib dose, p. 973. (Severe) Study → Also see TABLE 15 p. 1378
Idelalisib increases the concentration of ciclosporin. (Severe) Study
Idelalisib is predicted to moderately increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
Idelalisib is predicted to moderately increase the exposure to cinacalcet. Adjust dose. (Moderate) Study
Idelalisib is predicted to markedly increase the exposure to cobimetinib. Avoid or monitor for toxicity. (Severe) Study
Idelalisib is predicted to increase the exposure to colchicine. Avoid potential inhibitors of CYP3A4 or adjust colchicine dose, p. 1120. (Severe) Study
Idelalisib (continued)

> Idelalisib is predicted to increase the exposure to corticosteroids (beclometasone) (risk with beclometasone is likely to be lower than with other corticosteroids). (Moderate) Theoretical

> Idelalisib is predicted to increase the exposure to corticosteroids (betamethasone, budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects. (Severe) Study

> Idelalisib is predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. (Severe) Study

> Idelalisib is predicted to markedly to very markedly increase the exposure to dasatinib. Avoid or adjust dose—consult product literature. (Severe) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to very slightly increase the exposure to delamanid. (Severe) Study

> Idelalisib increases the risk of QT-prolongation when given with domperidone. Avoid. (Severe) Study

> Idelalisib increases the exposure to dopamine receptor agonists (bromocriptine). (Severe) Study

> Idelalisib is predicted to increase the concentration of dopamine receptor agonists (cabergoline). (Moderate) Anecdotal

> Idelalisib is predicted to increase the exposure to doravirine. (Moderate) Study

> Idelalisib is predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. (Moderate) Theoretical

> Idelalisib increases the exposure to ergotamine. Avoid. (Severe) Study

> Enzalutamide is predicted to decrease the exposure to idelalisib. Avoid. (Severe) Study

> Idelalisib is predicted to increase the risk of ergotism when given with ergotamine. Avoid. (Severe) Study

> Idelalisib is predicted to increase the risk of ergotism when given with ergotamine. Avoid. (Severe) Theoretical

> Idelalisib is predicted to slightly increase the exposure to erlotinib. Use with caution and adjust dose. (Moderate) Study

> Idelalisib is predicted to increase the exposure to esteketamine. (Moderate) Study

> Idelalisib is predicted to increase the concentration of everolimus. Avoid. (Severe) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to moderately increase the exposure to fosprofant. (Moderate) Theoretical

> Idelalisib is predicted to increase the exposure to gefitinib. (Moderate) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to moderately to markedly increase the exposure to grazoprevir. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Study

> Idelalisib is predicted to increase the exposure to ibutrintinib dose, p. 983. (Severe) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to imatinib. (Moderate) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to ivabradine. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study

> Idelalisib is predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study

> Idelalisib is predicted to markedly to very markedly increase the exposure to lomitapide. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to luridazine. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to macitentan. (Moderate) Study

> Idelalisib markedly increases the exposure to maraviroc. Adjust dose. (Severe) Theoretical

> Idelalisib is predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Severe) Study

> Idelalisib is predicted to very markedly increase the exposure to midostaurin. Avoid or monitor for toxicity. (Severe) Study

> Idelalisib is predicted to increase the exposure to mirabegron. Adjust mirabegron dose in hepatic and renal impairment, p. 781. (Moderate) Study

> Idelalisib is predicted to increase the exposure to mirtazapine. (Moderate) Study

> Mitotane is predicted to decrease the exposure to idelalisib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to modafinil. (Mild) Theoretical

> Idelalisib is predicted to increase the exposure to monoclonal antibodies (trastuzumab emtansine). Avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378

> Idelalisib is predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to netupitant. (Moderate) Study

> Nevirapine is predicted to decrease the exposure to idelalisib. Avoid. (Moderate) Theoretical

> Idelalisib is predicted to moderately increase the exposure to nilotinib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to nitrosimine. Adjust dose. (Moderate) Theoretical

> Idelalisib is predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. (Severe) Study

> Idelalisib is predicted to increase the exposure to opioids (methadone). (Severe) Theoretical

> Idelalisib is predicted to increase the exposure to ospeimifen. Avoid in poor CYP2C9 metabolisers. (Moderate) Study

> Idelalisib is predicted to increase the exposure to oxbutynin. (Mild) Study

> Idelalisib is predicted to increase the exposure to palbociclib. Avoid or adjust palbociclib dose, p. 992. (Severe) Study

> Idelalisib is predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. (Moderate) Study → Also see TABLE 15 p. 1378

> Paritaprevir is predicted to increase the exposure to idelalisib. Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to pazopanib. Avoid or adjust pazopanib dose, p. 993. (Moderate) Study → Also see TABLE 15 p. 1378

> Idelalisib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avancan, vardenafin). Avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (siludafin). Avoid potent inhibitors of CYP3A4 or adjust siludafin dose, p. 811. (Severe) Study

> Idelalisib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). Use with caution or avoid. (Severe) Study

> Idelalisib is predicted to increase the exposure to pimozide. Avoid. (Severe) Study
Idelalisib is predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study

Idelalisib is predicted to moderately increase the exposure to praziquantel. [Severe] Study

Idelalisib is predicted to increase the exposure to quetiapine. Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to ranolazine. Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to reboxetine. Avoid. [Moderate] Study

Idelalisib is predicted to increase the exposure to regorafenib. Avoid. [Moderate] Study → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the exposure to repaglinide. [Moderate] Study

Idelalisib is predicted to increase the exposure to retinoids (alitretinoin). Adjust alitretinoin dose, p. 1262. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 991. [Moderate] Study

Rifampin is predicted to decrease the exposure to idelalisib. Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to risperidone. Adjust dose. [Moderate] Study

Idelalisib is predicted to increase the exposure to ruxolitinib. Adjust dose and monitor side effects. [Moderate] Study → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the exposure to saxagliptin. [Moderate] Study

Idelalisib is predicted to increase the concentration of sirolimus. Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or ramulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. [Severe] Study

Idelalisib is predicted to moderately increase the exposure to SSRIs (dapoxetine). Avoid potent inhibitors of CYP3A4 or adjust dapoxetine dose, p. 821. [Severe] Study

St John’s Wort is predicted to decrease the exposure to idelalisib. Avoid. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to statins (atorvastatin). Avoid or adjust dose and monitor rhabdomyolysis. [Severe] Study

Idelalisib is predicted to increase the exposure to statins (simvastatin). Avoid. [Severe] Study

Idelalisib is predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the concentration of tacrolimus. Monitor and adjust dose. [Severe] Study

Idelalisib is predicted to increase the exposure to taxanes (cabazitaxel). Avoid. [Severe] Study → Also see TABLE 15 p. 1378

Idelalisib is predicted to moderately increase the exposure to taxanes (docetaxel). Avoid or adjust dose. [Severe] Study → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the exposure to taxanes (paclitaxel). [Severe] Theoretical → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the concentration of temsirolimus. Avoid. [Severe] Theoretical → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 292 dose with potent inhibitors of CYP3A4. [Severe] Study

Idelalisib is predicted to markedly increase the exposure to ticagrelor. Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. [Moderate] Study

Idelalisib is predicted to increase the exposure to tolfatan. Manufacturer advises caution or adjust tolfatan dose with potent inhibitors of CYP3A4, p. 669. [Severe] Study

Idelalisib is predicted to increase the exposure to toremifene. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to trabectedin. Avoid or adjust dose. [Severe] Theoretical → Also see TABLE 15 p. 1378

Idelalisib is predicted to moderately increase the exposure to trazodone. Avoid or adjust dose. [Moderate] Study

Idelalisib is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. [Severe] Study

Idelalisib is predicted to increase the exposure to vemurafenib. [Severe] Theoretical

Idelalisib is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study

Idelalisib is predicted to increase the exposure to venlafaxine. [Moderate] Study

Idelalisib is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical → Also see TABLE 15 p. 1378

Idelalisib is predicted to increase the exposure to vitamin D substances (paricalcitol). [Moderate] Study

Idelalisib is predicted to increase the exposure to zopiclone. Adjust dose. [Moderate] Theoretical

Ifosfamide → see alkylating agents

Iloprost → see TABLE 4 p. 1375 (antiplatelet effects)

Imatinib → see TABLE 15 p. 1378 (myelosuppression)

Imatinib is predicted to increase the exposure to abemaciclib. [Moderate] Study

Imatinib is predicted to increase the exposure to aldosterone antagonists (eplerenone). Adjust eplerenone dose, p. 193. [Severe] Study

Imatinib is predicted to increase the exposure to alpha blockers (tamsulosin). [Moderate] Theoretical

Imatinib is predicted to increase the exposure to alprazolam. [Severe] Study

Imatinib is predicted to increase the exposure to antiarrhythmics (dronedrone). [Severe] Theoretical

Imatinib is predicted to increase the exposure to antiarrhythmics (propafenone). Monitor and adjust dose.

Imatinib is predicted to increase the exposure to antihistamines, non-sedating (mizolastine). [Severe] Theoretical

Imatinib is predicted to increase the exposure to antihistamines, non-sedating (fupatadine). Avoid. [Moderate] Study

Imatinib is predicted to increase the concentration of antimarialars (piperacarone). [Severe] Theoretical

Aprepitant is predicted to increase the exposure to imatinib. [Moderate] Theoretical

Asparaginase is predicted to increase the risk of hepatotoxicity when given with imatinib. [Severe] Theoretical → Also see TABLE 15 p. 1378

Imatinib is predicted to increase the exposure to axitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Imatinib is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [HIV] Theoretical

Bosentan is predicted to decrease the exposure to imatinib. [Moderate] Study

Imatinib is predicted to increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Theoretical → Also see TABLE 15 p. 1378

Imatinib is predicted to increase the exposure to buspirone. Use with caution and adjust dose. [Moderate] Study

Imatinib is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to imatinib. [Moderate] Theoretical

Imatinib is predicted to increase the exposure to calcium channel blockers (amiodipine, felodipine, laclidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study
Imatinib (continued)

- **Imatinib** is predicted to increase the exposure to **cariprazine**. Avoid. **Severe** Study
- **Imatinib** is predicted to increase the exposure to **ceritinib**. **Moderate** Theoretical  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the concentration of **cilostazol**. **Severe** Study
- **Cobicistat** is predicted to increase the exposure to **imatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **cobimetinib**. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **colchicine**. Adjust **colchicine** dose with moderate inhibitors of CYP3A4, p. 1200. **Severe** Study
- **Imatinib** is predicted to increase the exposure to the corticosteroids (methylprednisolone). Monitor and adjust dose. **Moderate** Study
- **Imatinib** is predicted to increase the risk of bleeding events when given with **coumarins**. **Severe** Theoretical
- **Crizotinib** is predicted to increase the risk of hepatotoxicity when given with **imatinib**. **Severe** Theoretical  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to slightly increase the exposure to **darifenacin**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **dasatinib**. **Severe** Study  
  Also see **TABLE 15** p. 1378
- **Imatinib** increases the risk of QT-prolongation when given with **domperidone**. Avoid. **Severe** Study
- **Imatinib** is predicted to increase the exposure to **dopamine receptor agonists** (**bromocriptine**). **Severe** Theoretical
- **Imatinib** is predicted to increase the concentration of **dopamine receptor agonists** (**cabergoline**). **Moderate** Aneodal
- **Imatinib** is predicted to moderately increase the exposure to **dutasteride**. **Mild** Study
- **Efavirenz** is predicted to decrease the exposure to **imatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **erlotinib**. Avoid or adjust dose—consult product literature. **Severe** Study
- **Imatinib** is predicted to moderately increase the exposure to **encorafenib**. **Moderate** Study
- **Enzalutamide** is predicted to decrease the exposure to **imatinib**. Avoid. **Moderate** Study
- **Imatinib** is predicted to increase the risk of ergotism when given with **ergometrine**. **Severe** Theoretical
- **Imatinib** is predicted to increase the risk of ergotism when given with **ergotamine**. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **erlotinib**. **Moderate** Theoretical
- **Imatinib** is predicted to increase the concentration of **everolimus**. Avoid or adjust dose. **Moderate** Study  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **fesoterodine**. Adjust **fesoterodine** dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. **Mild** Study
- **Imatinib** is predicted to increase the exposure to **gefitinib**. **Moderate** Theoretical  
  Also see **TABLE 15** p. 1378
- **Grapefruit juice** is predicted to increase the exposure to **imatinib**. **Moderate** Theoretical
- **Imatinib** is predicted to increase the concentration of **guanfacine**. Adjust **guanfacine** dose, p. 352. **Moderate** Theoretical
- **HIV-protease inhibitors** are predicted to increase the exposure to **imatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **ibrutinib**. Adjust **ibrutinib** dose with moderate inhibitors of CYP3A4, p. 983. **Severe** Study  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **ibrutinib**. **Moderate** Study  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **ivabradine**. Adjust **ivabradine** dose, p. 211. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **ivacaftor**. Adjust **ivacaftor** dose, p. 293 or **tezacaftor** with **ivacaftor** p. 295 dose with moderate inhibitors of CYP3A4. **Severe** Study
- **Imatinib** is predicted to increase the exposure to **lapatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **lomitapide**. Avoid. **Moderate** Theoretical
- **Imatinib** is predicted to increase the exposure to **lurasidone**. Adjust **lurasidone** dose, p. 396. **Moderate** Study
- **Macrolides (clarithromycin)** are predicted to increase the exposure to **imatinib**. **Moderate** Study
- **Macrolides (erythromycin)** are predicted to increase the exposure to **imatinib**. **Moderate** Theoretical
- **Imatinib** is predicted to increase the exposure to **midazolam**. Monitor side effects and adjust dose. **Severe** Study
- **Imatinib** is predicted to increase the exposure to **midostaurin**. **Moderate** Theoretical
- **Mirtazapine** is predicted to decrease the exposure to **imatinib**. Avoid. **Moderate** Study  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **naloxegol**. Adjust **naloxegol** dose and monitor side effects, p. 65. **Moderate** Study
- **Netupitant** is predicted to increase the exposure to **imatinib**. **Moderate** Theoretical
- **Nevirapine** is predicted to decrease the exposure to **imatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **olaparib**. Avoid moderate inhibitors of CYP3A4 or adjust **olaparib** dose, p. 1005. **Moderate** Theoretical  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **opioids** (**alfentanil, buprenorphine, fentanyl, oxycodone**). Monitor and adjust dose. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **opioids** (**methadone, sufentanil**). **Moderate** Theoretical
- **Imatinib** is predicted to increase the exposure to **oxybutynin**. **Mild** Theoretical
- **Imatinib** increases the risk of hepatotoxicity when given with **paracetamol**. **Severe** Aneodal
- **Imatinib** is predicted to increase the exposure to **pazopanib**. **Moderate** Theoretical  
  Also see **TABLE 15** p. 1378
- **Pegaspargase** is predicted to increase the risk of hepatotoxicity when given with **imatinib**. **Severe** Theoretical  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the risk of bleeding events when given with **phenindione**. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors** (**avanafil**). Adjust **avanafil** dose, p. 812. **Moderate** Theoretical
- **Imatinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors** (**sildenafil**). Monitor or adjust **sildenafil** dose with moderate inhibitors of CYP3A4, p. 812. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors** (**tadalafil**). **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors** (**vardenafil**). Adjust dose. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **pimozide**. Avoid. **Severe** Theoretical
- **Imatinib** is predicted to increase the exposure to **quetiapine**. Avoid. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **ranolazine**. **Severe** Study
- **Imatinib** is predicted to increase the exposure to **riboxicillic**. **Moderate** Study
- **Rifampicin** is predicted to decrease the exposure to **imatinib**. Avoid. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **roxolitinib**. **Moderate** Theoretical  
  Also see **TABLE 15** p. 1378
- **Imatinib** is predicted to increase the exposure to **saxagliptin**. **Mild** Study
- **Imatinib** increases the concentration of **sirolimus**. Monitor and adjust dose. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **SSRIs (dapoxetine)**. Adjust **dapoxetine** dose with moderate inhibitors of CYP3A4, p. 821. **Moderate** Theoretical
- **St John’s Wort** is predicted to decrease the exposure to **imatinib**. **Moderate** Study
- **Imatinib** is predicted to increase the exposure to **statins** (**atorvastatin**). Monitor and adjust dose. **Severe** Study

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**TABLE 15** p. 1378

**BNF 78**
Imatinib – Iron (oral) 1473

- Iron (oral) is used to treat iron deficiency anemia. It can also be used for other conditions as directed by your healthcare provider.

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study

- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

- Aprepitant is predicted to increase the exposure to intravenous irinotecan. (Severe) Theoretical

- Cobimetinib is predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

- Enzalutamide is predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study

- Fibrates (gemfibrozil) are predicted to increase the exposure to irinotecan. Avoid. (Moderate) Theoretical

- Fosaprepitant is predicted to increase the exposure to irinotecan. Avoid. (Moderate) Theoretical

- HIV-protease inhibitors are predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

- Idelalisib is predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study → Also see TABLE 15 p. 1378

- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with irinotecan. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

- Macrolides (clarithromycin) are predicted to increase the risk of toxicity when given with irinotecan. Avoid. (Moderate) Study

- Mitotane is predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study → Also see TABLE 15 p. 1378

- Netupitant is predicted to increase the exposure to irinotecan. (Moderate) Study

- Irinotecan is predicted to decrease the effects of neuromuscular blocking drugs, non-depolarising. (Moderate) Theoretical

- Piriton is predicted to decrease the exposure to irinotecan. (Mild) Theoretical

- Rifampicin is predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study

- Rolipram is predicted to increase the exposure to irinotecan. Avoid or monitor. (Moderate) Study

- St John’s Wort slightly decreases the exposure to irinotecan. Avoid. (Severe) Study

- Irinotecan is predicted to increase the risk of prolonged neuromuscular blockade when given with suxamethonium. (Moderate) Theoretical

- Iron (injectable)
  - Ferric carboxymaltose • iron dextran • iron isomaltoside 1000 • iron sucrose

- Chloramphenicol decreases the efficacy of intravenous iron (injectable). (Moderate) Anecdotal

- Iron (oral)
  - Ferric maltol • ferrous fumarate • ferrous gluconate • ferrous sulfate • sodium ferederate

- Antacids decrease the absorption of iron (oral). Iron (oral) should be taken 1 hour before or 2 hours after antacids. (Moderate) Study

- Iron (oral) decreases the exposure to bicitravir. Bicitravir should be taken 2 hours before iron (oral). (Moderate) Study

- Iron (oral) is predicted to decrease the absorption of oral biphosphonates (ibandronic acid). Avoid iron (oral) for at least 6 hours before or 1 hour after ibandronic acid. (Moderate) Theoretical

- Iron (oral) decreases the absorption of biphosphonates (risendronate). Separate administration by at least 2 hours. (Moderate) Study

- Iron (oral) decreases the absorption of biphosphonates (sodium clodronate). Avoid iron (oral) for 4 hours before or 1 hour after sodium clodronate. (Moderate) Study

- Calcium salts (calcium carbonate) decrease the absorption of iron (oral). Calcium carbonate should be taken 1 hour before or 2 hours after iron (oral). (Moderate) Study

- Iron (oral) is predicted to decrease the exposure to carbipoda. (Moderate) Theoretical

- Imatinib is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. (Severe) Study

- Irinotecan is predicted to increase the exposure to sunitinib. (Moderate) Theoretical → Also see TABLE 15 p. 1378

- Irinotecan is predicted to increase the concentration of temsirolimus. (Moderate) Theoretical → Also see TABLE 15 p. 1378

- Irinotecan is predicted to increase the exposure to taxanes (cabazitaxel). (Moderate) Theoretical → Also see TABLE 15 p. 1378

- Irinotecan is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

- Irinotecan is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4. (Severe) Study

- Irinotecan is predicted to increase the exposure to trazodone. (Moderate) Theoretical

- Irinotecan is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

- Irinotecan is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Severe) Study

- Irinotecan is predicted to increase the exposure to vinca alkaloids. (Severe) Theoretical → Also see TABLE 15 p. 1378

- Irinotecan is predicted to increase the exposure to zopiclone. Adjust dose. (Moderate) Study

- Immidapril → see ACE inhibitors

- Imipenem → see carbapenems

- Imipramine → see tricyclic antidepressants

- Immunoglobulins
  - Anti-β (Rh) immunoglobulin • antithymocyte immunoglobulin (rabbit) • hepatitis B immunoglobulin • normal immunoglobulin • rabbies immunoglobulin • tetanus immunoglobulin • varicella-zoster immunoglobulin

- Immunoglobulins are predicted to alter the effects of monoclonal antibodies (dinituximab). Avoid. (Severe) Theoretical

- Indacaterol → see β agonists

- Indapamide → see thiazide diuretics

- Indometacin → see NSAIDs

- Indoramin → see alpha blockers

- Influnexab → see monoclonal antibodies

- Influenza vaccine (live) → see live vaccines

- Inotersen → see TABLE 4 p. 1375 (antiplatelet effects)

- Inotuzumab ozogamicin → see monoclonal antibodies

- Insulins → see TABLE 14 p. 1378 (antidiabetic drugs)

- Fibrates are predicted to increase the risk of hypoglycaemia when given with insulins. (Moderate) Theoretical

- Interferon alfa → see interferons

- Interferon beta → see interferons

- Interferons → see TABLE 15 p. 1378 (myelosuppression)

- Interferon alfa - interferon beta - peginterferon alfa

- Interferons are predicted to slightly increase the exposure to aminophylline. Adjust dose. (Moderate) Theoretical

- Interferon alfa is predicted to increase the risk of peripheral neuropathy when given with telbivudine. Avoid. (Severe) Theoretical

- Peginterferon alfa increases the risk of peripheral neuropathy when given with telbivudine. Avoid. (Severe) Study

- Interferons slightly increase the exposure to theophylline. Adjust dose. (Moderate) Study

- Ipilimumab → see monoclonal antibodies

- Ipratropium → see TABLE 10 p. 1377 (antisialcarcinics)

- Beta, agonists are predicted to increase the risk of glaucoma when given with ipratropium. (Moderate) Anecdotal

- Irbesartan → see angiotensin-II receptor antagonists

- Irinotecan → see TABLE 15 p. 1378 (myelosuppression)
Iron (oral) — Ivabradine

Iron (oral) (continued)

Iron (oral) decreases the efficacy of iron (oral).
- **Chloramphenicol** decreases the efficacy of iron (oral).
  - **Moderate** Theoretical

Iron (oral) decreases the absorption of dolutegravir.
- **Dolutegravir** should be taken 2 hours before or 6 hours after iron (oral).
  - **Moderate** Study

Iron (oral) is predicted to decrease the absorption of eltrobrogol. Eltrobrogol should be taken 2 hours before or 4 hours after iron (oral).
- **Severe** Theoretical

Iron (oral) is predicted to decrease the absorption of entacapone. Separate administration by at least 2 hours.
- **Moderate** Theoretical

Iron (oral) decreases the absorption of levodopa.
- **Moderate** Study

Iron (oral) decreases the effects of methyldopa.
- **Moderate** Study

Iron (oral) is predicted to decrease the absorption of penicillamine. Separate administration by at least 2 hours.
- **Mild** Study

Iron (oral) decreases the exposure to quinolones. Separate administration by at least 2 hours.
- **Moderate** Study

Iron (oral) decreases the absorption of tetracyclines. Tetracyclines should be taken 2 to 3 hours after iron (oral).
- **Moderate** Study

Iron (oral) decreases the absorption of thyroid hormones (levothyroxine). Separate administration by at least 4 hours.
- **Moderate** Study

Trientine potentially decreases the absorption of iron (oral).
- **Moderate** Theoretical

Zinc is predicted to decrease the efficacy of iron (oral) and iron (oral) is predicted to decrease the efficacy of zinc.
- **Moderate** Study

Iron chelators
desferrioxan, desferrioxamine, desferroxamine.

> **Deferasirox** is predicted to increase the exposure to aminophylline. Avoid, **Moderate** Theoretical

Antacids (aluminium hydroxide) are predicted to decrease the exposure to deferasirox. Avoid, **Moderate** Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to deferasirox. Monitor serum ferritin and adjust dose.
- **Moderate** Theoretical

Ascorbic acid is predicted to increase the risk of cardiovascular side-effects when given with desferrioxamine. **Severe** Theoretical

Aspirin (high-dose) is predicted to increase the risk of gastrointestinal bleeds when given with deferasirox. **Severe** Theoretical

Bisphosphonates are predicted to increase the risk of gastrointestinal bleeding when given with deferasirox. **Severe** Theoretical

Deferasirox is predicted to increase the exposure to clozapine.
- Avoid, **Moderate** Theoretical

Corticosteroids are predicted to increase the risk of gastrointestinal bleeding when given with deferasirox. **Severe** Theoretical

HIV- protease inhibitors (ritonavir) are predicted to decrease the exposure to deferasirox. Monitor serum ferritin and adjust dose.
- **Moderate** Theoretical

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with desferrioxamine.
- Avoid, **Severe** Theoretical

NSAIDs are predicted to increase the risk of gastrointestinal bleeding when given with deferasirox.
- **Severe** Theoretical

Deferasirox moderately increases the exposure to repaglinide.
- Avoid, **Moderate** Study

Rifampicin is predicted to decrease the exposure to deferasirox. Monitor serum ferritin and adjust dose.
- **Moderate** Study

Deferasirox is predicted to increase the exposure to selexipag. Adjust dose.
- **Moderate** Study

Deferasirox increases the exposure to theophylline. Avoid.
- **Moderate** Study

Deferasirox is predicted to increase the exposure to tizanidine.
- **Moderate** Theoretical

Iron dextran → see iron (injectable)

Iron isomaltoside 1000 → see iron (injectable)

Iron sucrose → see iron (injectable)

Isavuconazole → see antifungals, azoles

Isocarboxazid → see monoamine-oxidase A and B inhibitors, irreversible

Isoflurane → see volatile halogenated anaesthetics

Isomethaphene → see sympathomimetics, vasconstrictor

Isoniazid → see TABLE 1. p. 1375 (hepatotoxicity), TABLE 12 p. 1378 (peripheral neuropathy)

FOOD AND LIFESTYLE
Avoid tyramine-rich foods (such as mature cheeses, salami, pickled herring, Bovril®, Oxo®, Marmite® or any similar meat or yeast extract or fermented soya bean extract, and some beers, lagers or wines) or histamine-rich foods (such as very mature cheese or fish from the scromboid family (e.g. tuna, mackerel, salmon)), as tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating reported.

> Isoniazid is predicted to affect the clearance of aminophylline.
- **Severe** Theoretical

Isoniazid markedly increases the concentration of antiepileptics (carbamazepine) and antiepileptics (carbamazepine) increase the risk of hepatotoxicity when given with isoniazid. Monitor concentration and adjust dose.
- **Severe** Study → Also see TABLE 1 p. 1375

Isoniazid increases the concentration of antiepileptics (fosphenytoin, phenytoin). **Moderate** Study → Also see TABLE 12 p. 1378

Cycloserine increases the risk of CNS toxicity when given with isoniazid. Monitor and adjust dose.
- **Moderate** Study

Isoniazid is predicted to increase the risk of peripheral neuropathy when given with didanosine.
- **Severe** Theoretical → Also see TABLE 1 p. 1375 → Also see TABLE 12 p. 1378

Isoniazid increases the risk of optic neuropathy when given with ethambutol.
- **Severe** Anecdotal

Isoniazid decreases the effects of levodopa.
- **Moderate** Study

Isoniazid is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. **Unknown** Theoretical → Also see TABLE 1 p. 1375

Isoniazid is predicted to increase the risk of peripheral neuropathy when given with stavudine.
- **Severe** Theoretical → Also see TABLE 12 p. 1378

Isoniazid is predicted to affect the clearance of theophylline.
- **Severe** Anecdotal

Isoniazid potentially increases the risk of nephrotoxicity when given with volatile halogenated anaesthetics (methoxyflurane).
- Avoid, **Severe** Theoretical

Isosorbide dinitrate → see nitrates

Isosorbide mononitrate → see nitrates

Isotretinoin → see retinoids

Itracnozole → see antifungals, azoles

Ivabradine → see TABLE 6 p. 1376 (bradycardia), TABLE 9 p. 1377 (QT-interval prolongation)

> Antiarrhythmics (dronedarone) are predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. **Severe** Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ivabradine. Adjust dose.
- **Moderate** Theoretical

Antifungals, azoles (Fluconazole, Isavuconazole, Posaconazole) are predicted to increase the exposure to ivabradine. Adjust ivabradine dose, p. 211. **Severe** Theoretical

Antifungals, azoles (Itraconazole, Ketoconazole, Voriconazole) are predicted to increase the exposure to ivabradine.
- Avoid, **Severe** Study

Aprepitant is predicted to increase the exposure to ivabradine.
- Adjust ivabradine dose, p. 211. **Severe** Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ivabradine.
- Avoid, **Moderate** Study → Also see TABLE 6 p. 1376

Cobicistat is predicted to increase the exposure to ivabradine.
- Avoid, **Severe** Study

Crizotinib is predicted to increase the exposure to ivabradine.
- Adjust ivabradine dose, p. 211. **Severe** Theoretical → Also see TABLE 6 p. 1376
Ivacaftor

**FOOD AND LIFESTYLE** Avoid bitter (Seville) oranges as they are predicted to increase the exposure to ivacaftor.

**Antirrhynthmics (dronedaron)** are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Study](#)

**Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to moderately to markedly decrease the exposure to ivacaftor. Avoid. [Study](#)

**Antifungals, azoles (itraconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. [Study](#)

**Apalutamide** is predicted to decrease the exposure to ivacaftor. Avoid with monitor. [Moderate](#)

**Aprepitant** is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Study](#)

**Bosentan** is predicted to decrease the exposure to ivacaftor. [Study](#)

**Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Moderate](#)

**Cobicistat** is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. [Study](#)

**Ivacaftor** is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. [Severe](#)

**Netupitant** is predicted to increase the exposure to ivacaftor. Adjust ivacaftor p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. [Severe](#)

**St John's Wort** is predicted to decrease the exposure to ivacaftor. [Severe](#)

**Mitotane** is predicted to decrease the exposure to ivacaftor. Adjust dose. [Severe](#)

**Mitotane** increases the exposure to ivacaftor. Adjust dose. [Severe](#)

**Ivermectin** potentially increases the anticoagulant effect of coumarins. [Severe](#)

**Levamisole** increases the exposure to ivermectin. [Moderate](#)

**Ivazoxim**

**Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to ivazoxim. Avoid. [Severe](#)

**Levamisole** increases the exposure to ivazoxim. [Moderate](#)

**St John's Wort** is predicted to decrease the exposure to ivazoxim. [Severe](#)

**Ivazoxim**

**Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to ivazoxim. Avoid. [Severe](#)

**Levamisole** increases the exposure to ivazoxim. [Moderate](#)

**St John's Wort** is predicted to decrease the exposure to ivazoxim. [Severe](#)

**Ivazoxim**

**Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to ivazoxim. Avoid. [Severe](#)

**Levamisole** increases the exposure to ivazoxim. [Moderate](#)

**St John's Wort** is predicted to decrease the exposure to ivazoxim. [Severe](#)

**Ivazoxim**

**Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to ivazoxim. Avoid. [Severe](#)

**Levamisole** increases the exposure to ivazoxim. [Moderate](#)

**St John's Wort** is predicted to decrease the exposure to ivazoxim. [Severe](#)
Lamivudine – Laronidase

Lamivudine (continued)

- Zidovudine increases the risk of toxicity when given with lamivudine. Severe Anecdotal

Lamotrigine → see antiepileptics

Lanreotide

- Beta blockers, non-selective are predicted to increase the risk of bradycardia when given with lanreotide. (Moderate) Theoretical
- Beta blockers, selective are predicted to increase the risk of bradycardia when given with lanreotide. (Moderate) Theoretical
- Lanreotide is predicted to decrease the absorption of oral ciclosporin. Adjust dose. (Severe) Theoretical

Lansoprazole → see proton pump inhibitors

Lanthanum

- Lanthanum is predicted to decrease the absorption of antifungals, azoles (ketoconazole). Separate administration by at least 2 hours. (Moderate) Theoretical
- Lanthanum is predicted to decrease the absorption of antimalarials (chloroquine). Separate administration by at least 2 hours. (Moderate) Theoretical
- Lanthanum is predicted to decrease the absorption of hydroxychloroquine. Separate administration by at least 2 hours. (Moderate) Theoretical
- Lanthanum moderately decreases the exposure to quinolones. Quinolones should be taken 2 hours before or 4 hours after lanthanum. (Moderate) Study
- Lanthanum is predicted to decrease the absorption of tetracyclines. Separate administration by 2 hours. (Moderate) Theoretical
- Lanthanum decreases the absorption of thyroid hormones. Separate administration by 2 hours. (Moderate) Study
- Lanthanum is predicted to decrease the absorption to apatinib. Separate administration by 12 hours. (Moderate) Study
- Lanthanum is predicted to increase the exposure to aliskiren. (Anecdotal) Theoretical
- Lanthanum is predicted to decrease the absorption of rilpamib. Separate administration by 12 hours. (Moderate) Theoretical
- Lanthanum is predicted to increase the absorption of antihistamines, non-sedating (fexofenadine).
- Antacids are predicted to decrease the absorption of lapatinib. Avoid. (Moderate) Theoretical
- Antiarhythmics (dronedarone) are predicted to increase the exposure to lapatinib. (Moderate) Study → Also see TABLE 9 p. 1377
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the absorption to lapatinib. Avoid. (Severe) Study
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to lapatinib. (Moderate) Study → Also see TABLE 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study → Also see TABLE 9 p. 1377
- Lapatinib is predicted to increase the exposure to aripiprazol. (Anecdotal) Theoretical
- Aprepitant is predicted to increase the exposure to lapatinib. (Moderate) Study
- Lapatinib is predicted to increase the exposure to beta blockers, non-selective (nadolol). (Moderate) Study
- Lapatinib is predicted to increase the exposure to bictegravir. Use with caution or avoid. (Severe) Theoretical
- Bosentan is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to lapatinib. (Moderate) Study
- Lapatinib is predicted to increase the exposure to ceritinib. (Moderate) Theoretical → Also see TABLE 9 p. 1377
- Cobicistat is predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study
- Lapatinib is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose, p. 1220. (Moderate) Theoretical
- Lapatinib is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical
- Crizotinib is predicted to increase the exposure to lapatinib. (Moderate) Study → Also see TABLE 9 p. 1377
- Lapatinib is predicted to increase the exposure to dabigatran. (Severe) Theoretical
- Lapatinib is predicted to increase the exposure to digoxin. (Moderate) Theoretical
- Lapatinib is predicted to slightly increase the exposure to edoxaban. (Severe) Theoretical
- Efavirenz is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study → Also see TABLE 9 p. 1377
- Enzalutamide is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Lapatinib is predicted to increase the exposure to erlotinib. (Moderate) Theoretical
- Lapatinib is predicted to increase the exposure to everolimus. (Moderate) Theoretical
- Lapatinib is predicted to increase the exposure to fidaxomimon. Avoid. (Moderate) Study
- Grapefruit juice is predicted to increase the exposure to lapatinib. Avoid. (Moderate) Theoretical
- H1-receptor antagonists are predicted to decrease the absorption of lapatinib. Avoid. (Moderate) Theoretical
- HIV-protease inhibitors are predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study → Also see TABLE 9 p. 1377
- Idelalisib is predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study
- Imatinib is predicted to increase the exposure to lapatinib. (Anecdotal) Study
- Lapatinib is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical
- Lapatinib is predicted to increase the exposure to loperamide. (Moderate) Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study → Also see TABLE 9 p. 1377
- Macrolides (erythromycin) are predicted to increase the exposure to lapatinib. Avoid. (Moderate) Study
- Mitotane is predicted to increase the exposure to lapatinib. Avoid. (Severe) Study
- Netupitant is predicted to increase the exposure to lapatinib. (Moderate) Study
- Nevirapine is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Nilotinib is predicted to increase the exposure to lapatinib. (Moderate) Study → Also see TABLE 9 p. 1377
- Lapatinib is predicted to increase the exposure to nintedanib. (Anecdotal) Study
- Lapatinib is predicted to increase the exposure to panobinostat. Adjust dose. (Moderate) Theoretical → Also see TABLE 9 p. 1377
- Lapatinib is predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical
- Lapatinib is predicted to increase the exposure to pitavastatin. (Moderate) Theoretical
- Pitolisant is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Theoretical
- Rifampicin is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Laronidase
- Aliskiren is predicted to increase the exposure to topotecan. (Severe) Study
- Laronidase is predicted to increase the exposure to trametinib. (Moderate) Theoretical
- Laronidase is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. (Severe) Theoretical
- Hydroxychloroquine are predicted to decrease the exposure to laronidase. Avoid simultaneous administration. (Severe) Theoretical

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Ledipasvir

- **Acids** are predicted to decrease the exposure to ledipasvir.
- Separate administration by 4 hours. ([Moderate] Theoretical)
- **Ledipasvir** is predicted to increase the risk of severe bradycardia or heart block when given with antiarrhythmics (amiodarone).
  - Refer to specialist literature. ([Severe] Anecdotal)
- Antiepileptics (**carbamazepine**) are predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Study)
- Antiepileptics (**fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone**) are predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Theoretical)
- **Calcium salts** (calcium carbonate) are predicted to decrease the exposure to ledipasvir. Separate administration by 4 hours. ([Moderate] Theoretical)
- **Ledipasvir** is predicted to increase the exposure to dabigatran. ([Moderate] Theoretical)
- **H₂ receptor antagonists** are predicted to decrease the exposure to ledipasvir. Adjust dose, see ledipasvir with sofosbuvir p. 628. ([Moderate] Study)
- HIV-protease inhibitors (**tipranavir** boosted with ritonavir) are predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Theoretical)
- Proton pump inhibitors are predicted to decrease the exposure to ledipasvir. Adjust dose, see ledipasvir with sofosbuvir p. 628. ([Moderate] Theoretical)
- Rifabutin is predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Theoretical)
- Rifampicin is predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Study)
- **St John’s Wort** is predicted to decrease the exposure to ledipasvir. Avoid. ([Severe] Study)
- **Ledipasvir** is predicted to increase the exposure to statins (atorvastatin, fluvastatin, pravastatin, simvastatin). Monitor and adjust dose. ([Moderate] Theoretical)
- **Ledipasvir** is predicted to increase the exposure to statins (rosuvastatin). Avoid. ([Severe] Theoretical)
- **Ledipasvir** (with sofosbuvir) slightly increases the exposure to tenofovir disoproxil. ([Moderate] Study)

**PHARMACOLOGY**

**Leflunomide**

- Is predicted to increase the exposure to adefovir. ([Moderate] Theoretical)
- **Leflunomide** is predicted to decrease the exposure to alogelamine. ([Moderate] Theoretical)
- **Leflunomide** decreases the exposure to aminophylline. Adjust dose. ([Moderate] Study)
- **Leflunomide** is predicted to decrease the exposure to antihistamines, non-sedating (fexofenadine). ([Moderate] Study)
- **Leflunomide** is predicted to increase the exposure to anthracyclines (daunorubicin, doxorubicin, mitoxantrone). ([Moderate] Theoretical) → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to anxiolytics (buspirone). ([Moderate] Theoretical) → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to barbiturines. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to bosentan. ([Moderate] Study)
- **Leflunomide** is predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. ([Moderate] Study)
- **Leflunomide** is predicted to increase the exposure to cephalexin (cefaclor). ([Moderate] Theoretical)
- **Leflunomide** is predicted to decrease the exposure to clozapine. ([Moderate] Theoretical) → Also see TABLE 15 p. 1378
- **Leflunomide** increases the antiplatelet effect of coumarins. ([Severe] Anecdotal)
- **Leflunomide** is predicted to decrease the exposure to duloxetine. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to ganciclovir. ([Moderate] Theoretical) → Also see TABLE 15 p. 1378

- **Leflunomide** is predicted to increase the exposure to H₂ receptor antagonists (cimetidine, famotidine). ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the concentration of interferon. ([Moderate] Study)
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with leflunomide. Public Health England advises avoid (refer to Green Book). ([Severe] Theoretical)
- **Leflunomide** is predicted to increase the exposure to loop diuretics (**fuosimide**). ([Moderate] Theoretical)
- **Leflunomide** is predicted to decrease the exposure to melatonin. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to methotrexate. ([Moderate] Theoretical) → Also see TABLE 11 p. 1375 → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the clearance of mefloquine. Monitor and adjust dose. ([Moderate] Study)
- **Leflunomide** is predicted to increase the exposure to montelukast. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to nateglinide. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to NSAIDs (indometacin, ketoprofen). ([Moderate] Theoretical)
- **Leflunomide** is predicted to decrease the exposure to omeprazole. Monitor and adjust dose. ([Moderate] Study) → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to oseltamivir. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to penicillins (beta-lactam). ([Moderate] Study)
- **Leflunomide** is predicted to increase the exposure to pioglitazone. ([Moderate] Study)
- **Leflunomide** is predicted to decrease the exposure to piritidrone. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to quinolones (ciprofloxacin). ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to repaglinide. ([Moderate] Study)
- **Leflunomide** is predicted to increase the exposure to rifampicin. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to selexipag. Adjust dose. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to statins (atorvastatin, fluvastatin, pravastatin, simvastatin). ([Moderate] Study) → Also see TABLE 1 p. 1375
- **Leflunomide** is predicted to increase the exposure to statins (rosuvastatin). Adjust dose. ([Moderate] Study) → Also see TABLE 1 p. 1375
- **Leflunomide** is predicted to increase the exposure to sufiaslazine. ([Moderate] Study) → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to sulfonylureas (glibenclamide). ([Moderate] Study)
- **Leflunomide** is predicted to increase the concentration of taxanes (paclitaxel). ([Severe] Anecdotal) → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to tolenovir alafenamide. ([Moderate] Theoretical)
- **Leflunomide** is predicted to increase the exposure to tolenovir disoproxil. ([Moderate] Theoretical)
- **Leflunomide** is predicted to decrease the exposure to theophylline. Adjust dose. ([Moderate] Study)
- **Leflunomide** moderately decreases the exposure to tizanidine. ([Mild] Study)
- **Leflunomide** is predicted to increase the exposure to topotecan. ([Moderate] Study) → Also see TABLE 15 p. 1378
- **Leflunomide** is predicted to increase the exposure to zidovudine. ([Moderate] Theoretical) → Also see TABLE 15 p. 1378

**Lenalidomide**

- See TABLE 1 p. 1375 (hepatotoxicity), TABLE 15 p. 1378
- **Myelosuppression**, **(TABLE 5) p. 1375 (thromboembolism)**
- **Combined hormonal contraceptives** are predicted to increase the risk of venous thromboembolism when given with lenalidomide. Avoid. ([Severe] Theoretical)
### Interactions

**Lenalidomide** (continued)

- **Hormone replacement therapy** is predicted to increase the risk of venous thromboembolism when given with lenalidomide.  
  (Severe) Theoretical

**Levatinib** → see TABLE 9 (QT-interval prolongation)

**Lercanidipine** → see calcium channel blockers

**Letermovir**

- **Letermovir** is predicted to increase the concentration of antiretrovirals (amiodarone).  
  (Moderate) Theoretical

- **Antiepileptics (carbamazepine, phenobarbital, primidone)** are predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Letermovir** is predicted to decrease the concentration of antiepileptics (fosphenytoin, phenytoin) and antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Letermovir** slightly decreases the exposure to antifungals, azoles (voriconazole).  
  (Moderate) Study

- **Letermovir** is predicted to increase the concentration of antihistamines, non-sedating (fexofenadine).  
  (Moderate) Theoretical

- **Letermovir** is predicted to increase the concentration of bosentan.  
  (Moderate) Theoretical

- **Letermovir** increases the exposure to ciclosporin and ciclosporin increases the exposure to leterminov.  
  Monitor and adjust leterminov dose, p. 639.  
  (Severe) Study

- **Letermovir** is predicted to decrease the concentration of coumarins (warfarin).  
  Monitor and adjust dose.  
  (Moderate) Theoretical

- **Efavirenz** is predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Eflornithine** is predicted to increase the concentration of theophylline.  
  (Moderate) Theoretical

- **Erlotinib** is predicted to decrease the concentration of leterminov.  
  (Moderate) Study

- **Etoposide** is predicted to increase the concentration of ergotamine.  
  Avoid, (Severe) Theoretical

- **Etravirine** is predicted to decrease the exposure to leterminov.  
  (Moderate) Theoretical

- **Letermovir** is predicted to increase the concentration of levodopa.  
  Monitor and adjust dose.  
  (Severe) Study

- **Fibrates** are predicted to increase the concentration of levodopa.  
  Avoid, (Severe) Theoretical

- **Macrolides** (clarithromycin, erythromycin) are predicted to increase the concentration of levodopa.  
  (Moderate) Study

- **Letermovir** slightly to moderately increases the exposure to levodopa.  
  Monitor and adjust dose.  
  (Moderate) Study

- **Modafinil** is predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Letermovir** is predicted to increase the exposure to opioids (alfentanil, fentanyl).  
  Monitor and adjust dose.  
  (Moderate) Study

- **Letermovir** is predicted to increase the concentration of pimozide.  
  Avoid, (Severe) Theoretical

- **Letermovir** is predicted to increase the concentration of repaglinide.  
  Avoid, (Moderate) Theoretical

- **Rifaximin** is predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Rifampicin** is predicted to affect the concentration of leterminov.  
  (Severe) Theoretical

- **Letermovir** moderately increases the exposure to sirolimus.  
  Monitor and adjust dose.  
  (Severe) Study

- **St John’s Wort** is predicted to decrease the concentration of leterminov.  
  (Moderate) Theoretical

- **Letermovir** moderately increases the exposure to statins (atorvastatin).  
  (Severe) Study

- **Letermovir** is predicted to increase the exposure to statins (fluvastatin).  
  Monitor and adjust dose.  
  (Moderate) Theoretical

- **Letermovir** is predicted to increase the exposure to statins (pravastatin).  
  Avoid or adjust dose.  
  (Moderate) Theoretical

- **Letermovir** is predicted to increase the exposure to statins (resovastatin, simvastatin).  
  Avoid, (Severe) Study

- **Letermovir** is predicted to increase the concentration of sulfonyleureas (glibenclamide).  
  (Moderate) Theoretical

- **Letermovir** moderately increases the exposure to tacrolimus.  
  Monitor and adjust dose.  
  (Severe) Study

- **Teriflunomide** is predicted to increase the concentration of leterminov.  
  (Moderate) Study

**Levamisole**

- **Albendazole** slightly decreases the exposure to levamisole.  
  Levamisole moderately decreases the exposure to albendazole.  
  (Moderate) Study

- **Alcohol (beverage)** potentially causes a disulfiram-like reaction when given with levamisole.  
  (Moderate) Study

- **Levamisole increases the exposure to ivermectin.**  
  (Moderate) Study

**Levetiracetam** → see antiepileptics

**Levoduonol** → see beta blockers, non-selective

**Levobupivacaine** → see anaesthetics, local

**Levocetirizine** → see antihistamines, non-sedating

**Levodopa** → see TABLE 8 p. 1376 (hypotension)

**General information** Drugs with antimuscarinic effects might reduce the absorption of levodopa, see TABLE 10 p. 1377.

- **Amisulpride** is predicted to decrease the effects of levodopa.  
  Avoid, (Severe) Theoretical

- **Antiepileptics (fosphenytoin, phenytoin)** decrease the effects of levodopa.  
  (Moderate) Study

- **Atorvastatin** decreases the effects of levodopa.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Asetrapine** is predicted to decrease the effects of levodopa.  
  Adjust dose.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Baclofen** is predicted to increase the risk of side-effects when given with levodopa.  
  (Severe) Anaesthetic → Also see TABLE 8 p. 1376

- **Benperidol** is predicted to decrease the effects of levodopa.  
  (Severe) Study → Also see TABLE 8 p. 1376

- **Buproprion** increases the risk of side-effects when given with levodopa.  
  (Moderate) Study

- **Clonazepam** is predicted to decrease the effects of levodopa.  
  (Severe) Theoretical

- **Fluoxetine** decreases the effects of levodopa.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Entacapone** increases the exposure to levodopa.  
  Monitor side effects and adjust dose.  
  (Moderate) Study

- **Flupentixol** decreases the effects of levodopa, Avoid or monitor worsening parkinsonian symptoms.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Haloperidol** decreases the effects of levodopa.  
  (Severe) Study → Also see TABLE 8 p. 1376

- **Iron (oral)** decreases the absorption of levodopa.  
  (Moderate) Study

- **Isoniazid** decreases the effects of levodopa.  
  (Moderate) Study

- **Levodopa** is predicted to increase the risk of elevated blood pressure when given with linezolid.  
  Avoid, (Severe) Theoretical

- **Loxapine** is predicted to decrease the effects of levodopa.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Lurasidone** is predicted to decrease the effects of levodopa.  
  (Severe) Theoretical → Also see TABLE 8 p. 1376

- **Memantine** is predicted to increase the effects of levodopa.  
  (Moderate) Theoretical

- **Metoclopramide** decreases the effects of levodopa.  
  Avoid, (Moderate) Study

- **Levodopa increases the risk of side-effects when given with moclobemide.**  
  (Moderate) Study

- **Levodopa** increases the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, irreversible.  
  Avoid and for 14 days after stopping the MAOIs.  
  (Severe) Study → Also see TABLE 8 p. 1376

- **Monoamine-oxidase B inhibitors** are predicted to increase the effects of levodopa.  
  Adjust dose.  
  (Mild) Study → Also see TABLE 8 p. 1376

**TABLE 9**

p. 1377 (QT-interval prolongation)
Levodopa decreases the effects of levodopa. Avoid or monitor worsening Parkinsonian symptoms. [Severe] Anecdotal → Also see TABLE 8 p. 1376

Opicapone increases the exposure to levodopa. Adjust dose. [Moderate] Study

Paliperidone is predicted to decrease the effects of levodopa. [Severe] Theoretical → Also see TABLE 8 p. 1376

Phenothiazines decrease the effects of levodopa. Avoid or monitor worsening Parkinsonian symptoms. [Severe] Study → Also see TABLE 8 p. 1376

Pimozide decreases the effects of levodopa. [Severe] Theoretical → Also see TABLE 8 p. 1376

Quetiapine decreases the effects of levodopa. [Severe] Anecdotal → Also see TABLE 8 p. 1376

Risperidone is predicted to decrease the effects of levodopa. Avoid or adjust dose. [Severe] Anecdotal → Also see TABLE 8 p. 1376

Sulpiride is predicted to decrease the effects of levodopa. Avoid. [Severe] Theoretical → Also see TABLE 8 p. 1376

Tetrazenazine is predicted to decrease the effects of levodopa. Use with caution or avoid. [Moderate] Theoretical

Tocapline increases the exposure to levodopa. Monitor and adjust dose. [Moderate] Study

Tryptophan greatly decreases the concentration of levodopa. [Moderate] Study

Zuclopenthixol is predicted to decrease the effects of levodopa. Avoid or monitor worsening Parkinsonian symptoms. [Severe] Theoretical → Also see TABLE 8 p. 1376

Levodopa

Lisdexamfetamine

Reboxetine

Monoamine-oxidase B inhibitors

St John’s Wort is predicted to decrease the efficacy of levodopa. MRHA advises avoid. For FSRH guidance, see Table 8 p. 1376

Sugammadex is predicted to decrease the exposure to levodopa. Use additional contraceptive precautions. [Severe] Theoretical

Ulipristal is predicted to decrease the efficacy of levonorgestrel. Avoid. [Severe] Theoretical

Levethyroxine → see thyroid hormones

Lidocaine → see antiarrhythmics

Linaclotide → see TABLE 14 p. 1378 (antidiabetic drugs)

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to linaclotide. [Moderate] Study

Enzalutamide is predicted to decrease the exposure to linaclotide. [Moderate] Study

Linaclotide is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. [Moderate] Theoretical

Mitotane is predicted to decrease the exposure to linaclotide. [Moderate] Study

Rifampicin is predicted to decrease the exposure to linaclotide. [Moderate] Study

Linezolid → see TABLE 15 p. 1378 (myelosuppression), TABLE 13 p. 1378 (serotonin syndrome)

**FOOD AND LIFESTYLE** Patients taking linezolid should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, salami, pickled herring, Bovril®, Oxo®, Marmite® or any similar meat or yeast extract or fermented soya bean extract, and some beers, lagers or wines).

**Beta, agonists** are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical

Bupropion is predicted to increase the risk of intraoperative hypertension when given with linezolid. [Severe] Anecdotal → Also see TABLE 13 p. 1378

Buspirone is predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical → Also see TABLE 13 p. 1378

Levodopa is predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical

Macrolides (clarithromycin) increase the exposure to linezolid. [Moderate] Anecdotal

Methylphenidate is predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical

Moclobemide is predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping moclobemide. [Severe] Theoretical → Also see TABLE 13 p. 1378

Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping moclobemide. [Severe] Theoretical → Also see TABLE 13 p. 1378

Monoamine-oxidase B inhibitors (rasagiline, selegiline) are predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping rasagiline. [Severe] Theoretical → Also see TABLE 13 p. 1378

Monoamine-oxidase B inhibitors (safinamide) are predicted to increase the risk of side-effects when given with linezolid. Avoid and for 1 week after stopping safinamide. [Severe] Theoretical → Also see TABLE 13 p. 1378

Reboxetine is predicted to increase the risk of a hypertensive crisis when given with linezolid. Avoid. [Severe] Theoretical

Rifampicin slightly decreases the exposure to linezolid. [Moderate] Study

Sympathomimetics, inotropic are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical

Sympathomimetics, vasoconstrictor (adrenaline/epinephrine, ephedrine, isometheptene, noradrenaline/norepinephrine, phenylephrine) are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Theoretical

Sympathomimetics, vasoconstrictor (pseudoephedrine) increase the risk of elevated blood pressure when given with linezolid. Avoid. [Severe] Study

Liothyronine → see thyroid hormones

Liraglutide → see TABLE 14 p. 1378 (antidiabetic drugs)

Lisdexamfetamine → see amphetamines

Lisinopril → see ACE inhibitors
Lithium → see TABLE 13 p. 1378 (serotonin syndrome), TABLE 9 p. 1377 (QT-interval prolongation)

- **ACE inhibitors** are predicted to increase the concentration of lithium. Monitor and adjust dose. [Severe] Anecdotal
- **Acetazolamide** alters the concentration of lithium. [Severe] Anecdotal
- Aldosterone antagonists (eplerenone) potentially increase the concentration of lithium. Avoid. [Moderate] Theoretical
- Aldosterone antagonists (spironolactone) potentially increase the concentration of lithium. [Moderate] Study of
- **Aminophylline** is predicted to decrease the concentration of lithium. [Moderate] Theoretical
- Angiotensin-II receptor antagonists potentially increase the concentration of lithium. Monitor concentration and adjust dose. [Severe] Anecdotal
- Antiepileptics (carbamazepine, oxcarbazepine) are predicted to increase the risk of neurotoxicity when given with lithium. [Severe] Anecdotal
- **Calcitonin (salmon)** decreases the concentration of lithium. Monitor concentration and adjust dose. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the risk of neurotoxicity when given with lithium. [Severe] Anecdotal
- **Loop diuretics** increase the concentration of lithium. Monitor and adjust dose. [Severe] Study
- Methyldopa increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal
- **Mexiteline** potentially affects the exposure to lithium. Avoid. [Unknown] Theoretical
- NSAIDs increase the concentration of lithium. Monitor and adjust dose. [Severe] Study
- Phenothiazines potentially increase the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → also see TABLE 9 p. 1377
- Potassium-sparing diuretics (triatriperen) potentially increase the clearance of lithium. [Moderate] Study
- **Quetiapine** potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal
- **Risperidone** potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → also see TABLE 9 p. 1377
- **Sodium bicarbonate** decreases the concentration of lithium. [Severe] Anecdotal
- **Sulphide** potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → also see TABLE 9 p. 1377
- **Theophylline** is predicted to decrease the concentration of lithium. Monitor concentration and adjust dose. [Moderate] Anecdotal
- Thiadiazide diuretics increase the concentration of lithium. Avoid or monitor concentration. [Severe] Anecdotal → also see TABLE 13 p. 1378 → also see TABLE 9 p. 1377
- Zuclopenthixol potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → also see TABLE 9 p. 1377

**Live vaccines**

- Bacillus Calmette-Guérin vaccine - influenza vaccine (live) - measles, mumps and rubella vaccine, live - rotavirus vaccine - typhoid vaccine, oral - varicella-zoster vaccine - yellow fever vaccine, live

**General information**

Oral typhoid vaccine is inactivated by concurrent administration of antibacterials or antimalarials; antibacterials should be avoided for 5 days before and after oral typhoid vaccination; mefloquine should be avoided for at least 12 hours before or after oral typhoid vaccination; for other antimalarials oral typhoid vaccine vaccination should be completed at least 3 days before the first dose of the antimalarial (except proguanil hydrochloride with atovaquone, which can be given concurrently).

- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with abatacept. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with alkylating agents. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with amsacrine. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with anthracyclines. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with azathioprine (high-dose). Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with baricitinib. Avoid. [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with belatacept. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with bevacizumab. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with clofarabine. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with cyclophosphamide. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with cladribine. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with dactinomycin. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with dimethyl fumarate. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with etanercept. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with everolimus. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with everolimus. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical

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Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fenogliptin. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fludarabine. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with fluorouracil. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with gemcitabine. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with hydroxychloroquine. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with irinotecan. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with lomitapide. Avoid. (Refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with lomefloxacin. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with mercaptopurine (high-dose). Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with methotrexate (high-dose). Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with mitomycin. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with monoclonal antibodies. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with pemetrexed. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with platino compounds. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with procarbazine. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with raltitrexed. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with sirolimus. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with streptozocin. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tacrolium. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with taxanes (docetaxel, paclitaxel). Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tegafur. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with temsirolimus. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tegafur. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tioguanine. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tocilizumab. Public Health England advises avoid (refer to Green Book).  
Live vaccines potentially increase the risk of generalised infection (possibly life-threatening) when given with tofacitinib. Avoid. (Severe) Theoretical  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with trebolectin. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with trastuzumab. Public Health England advises avoid (refer to Green Book).  
Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with vinca alkaloids. Public Health England advises avoid (refer to Green Book).  
Lixisenatide  see TABLE 1 p. 1378 (antidiabetic drugs)  
Separation of administration Some orally administered drugs should be taken at least 1 hour before, or 4 hours after, lixisenatide injection.  

calories Lofepzamine see triyclic antidepressant  
Lofexidine see TABLE 8 p. 1376 (hypotension), TABLE 9 p. 1377 (QT interval prolongation), TABLE 11 p. 1377 (CN depressant effects)  
Lomitapide see TABLE 1 p. 1375 (hepatotoxicity)  
Food and lifestyle Bitter (Seville) orange is predicted to increase the exposure to lomitapide; separate administration by 12 hours.  
Alprazolam is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
Antiarhythmic (amiodarone) are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
Antineoplastics (carbamazepine, fosphenytoin, phenobarbital, phenytin, primidone) are predicted to decrease the exposure to lomitapide. Monitor and adjust dose. (Moderate) Theoretical also see TABLE 1 p. 1375  
Antifungals, azoles ( clotrimazole) are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to lomitapide. Avoid. (Severe) Study also see TABLE 1 p. 1375  
Apalutamide is predicted to decrease the exposure to lomitapide. Avoid or monitor. (Moderate) Study
Lomitapide (continued)  
- **Aprepitant** is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Bicalutamide** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Calcium channel blockers (amlodipine, lacidipine)** are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Ciclosporin** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Clocostazol** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Cobicistat** is predicted to markedly increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Ciclosporin** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Ciclosporin** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to lomitapide. Avoid. (Severe) Study  
- **Oral combined hormonal contraceptives** slightly increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Lomitapide** increases the exposure to coumarins (warfarin). Monitor INR and adjust dose. (Severe) Study  
- **Crizotinib** is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Enzalutamide** is predicted to decrease the exposure to lomitapide. Monitor and adjust dose. (Moderate) Theoretical  
- **Everolimus** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Fosaprepitant** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Grapefruit juice** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **H₂ receptor antagonists (cimetidine, ranitidine)** are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **HIV-protease inhibitors** are predicted to markedly increase the exposure to lomitapide. Avoid. (Severe) Study  
- **Idelalisib** is predicted to markedly increase the exposure to lomitapide. Avoid. (Severe) Study  
- **Imatinib** is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Isoniazid** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Unknown) Theoretical → Also see TABLE 1 p. 1375  
- **Ivacaftor** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Lapatinib** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Linagliptin** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Macrolides (azithromycin)** are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Macrolides (clarithromycin)** are predicted to markedly increase the exposure to lomitapide. Avoid. (Severe) Study  
- **Macrolides (erythromycin)** are predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Mecobalamin** is predicted to decrease the exposure to lomitapide. Monitor and adjust dose. (Moderate) Theoretical  
- **Netupitant** is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Nilotinib** is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical  
- **Pazopanib** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Peppermint oil** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Propiverine** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Ranolazine** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Rifampicin** is predicted to decrease the exposure to lomitapide. Monitor and adjust dose. (Moderate) Theoretical  
- **SSRIs (fluvoxamine)** are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Unknown) Theoretical  
- **SSRIs (fluoxetine)** are predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Lomitapide increases the exposure to statins (atorvastatin).** Adjust lomitapide dose or separate administration by 12 hours. p. 207. (MID) Study → Also see TABLE 1 p. 1375  
- **Lomitapide increases the exposure to statins (simvastatin).** Monitor and adjust simvastatin dose. p. 205. (Moderate) Study → Also see TABLE 1 p. 1375  
- **Tacrolimus** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Ticagrelor** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Tolvaptan** is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical  
- **Lomustine** → see alkylating agents  
- **Loop diuretics** → see TABLE 18 p. 1379 (hypotension), TABLE 8 p. 1376 (hypotension), TABLE 19 p. 1379 (ototoxicity), TABLE 17 p. 1379 (reduced serum potassium)  
  - lumisetron - furosemide - torasemide  
- **Aliksiren** slightly decreases the exposure to furosemide. (Moderate) Study → Also see TABLE 8 p. 1376  
- **Loop diuretics** increase the risk of nephrotoxicity when given with **aminoglycosides**. Avoid. (Moderate) Study → Also see TABLE 19 p. 1379  
- **Antiepileptics (fosphenytoin, phenytoin)** decrease the effects of furosemide. (Moderate) Study  
- **Intravenous furosemide** potentially increases the risk of sweating, variable blood pressure, and tachycardia when given after **chloral hydrate**. (Moderate) Anecdotal  
- **Dasabuvir** (with ombitasvir, paritaprevir, and ritonavir) increases the concentration of furosemide. Adjust dose. (Moderate) Study  
- **Leflunomide** is predicted to increase the exposure to furosemide. (Moderate) Theoretical  
- **Loop diuretics** increase the concentration of lithium. Monitor and adjust dose. (Severe) Study  
- **Paritaprevir** (with ritonavir and ombitasvir) is predicted to increase the exposure to furosemide. Adjust dose. (Moderate) Theoretical  
- **Reboxetine** is predicted to increase the risk of hypokalaemia when given with **loop diuretics**. (Moderate) Theoretical  
- **Teriflunomide** is predicted to increase the exposure to furosemide. (Moderate) Study  
- **Loperamide**  
  - **Antiarhythmics (dronedarone)** are predicted to increase the exposure to loperamide. (Severe) Theoretical  
  - **Ceritinib** is predicted to increase the exposure to loperamide. (Moderate) Theoretical  
  - **Loperamide greatly increases the absorption of oral desmopressin** (and possibly sublingual). (Moderate) Study  
  - **Eligulstat** is predicted to increase the exposure to loperamide. Adjust dose. (Moderate) Study  
  - **Lapatinib** is predicted to increase the exposure to loperamide. (Moderate) Theoretical  
  - **Mirabegron** is predicted to increase the exposure to loperamide. (MID) Theoretical  
  - **Opicapone** is predicted to increase the exposure to loperamide. Avoid. (Moderate) Study  
  - **Paritaprevir** (with ritonavir and ombitasvir) is predicted to increase the exposure to loperamide. (Moderate) Study  
  - **Pibrentasvir** (with glecaprevir) is predicted to increase the exposure to loperamide. (MID) Theoretical  
  - **Velpatasvir** is predicted to increase the exposure to loperamide. (Severe) Theoretical  
- **Lopinavir** → see HIV-protease inhibitors  
- **Loprazolam** → see TABLE 11 p. 1377 (CNS depressant effects)  
- **Loratadine** → see antihistamines, non-sedating
Lorazepam — Macitentan 1483

**Lorazepam** see Table 11 p. 1377 (CNS depressant effects)

- **Rifampicin** increases the clearance of lorazepam. [Moderate] Study

**Lormetazepam** see Table 11 p. 1377 (CNS depressant effects)

- **Lumacaftor** increases the clearance of lormetazepam. [Moderate] Study

**Low molecular-weight heparins** see Table 16 p. 1379 (increased serum potassium), Table 3 p. 1375 (anticoagulant effects)

- **Dalteparin** - enoxaparin - tinzaparin

- **Ranibizumab** increases the risk of bleeding events when given with low molecular-weight heparins. [Severe] Theoretical

**Loxapine** see Table 8 p. 1376 (hypotension), Table 11 p. 1377 (CNS depressant effects), Table 10 p. 1377 (antimuscarinics)

- **Combined hormonal contraceptives** are predicted to increase the exposure to loxapine. Avoid. [Unknown] Theoretical

- **Loratadine** is predicted to decrease the effects of **levodopa**.

- **Midazolam** is predicted to decrease the exposure to **lumacaftor**. [Moderate] Theoretical — also see Table 8 p. 1376

- **Mexiteline** is predicted to increase the exposure to lopinavir. Avoid. [Unknown] Theoretical

- **Quinolones (ciprofloxacin)** are predicted to increase the exposure to lopinavir. Avoid. [Unknown] Theoretical

- **Sulfisoxazole (fluvanoxamine)** are predicted to increase the exposure to lopinavir. Avoid. [Unknown] Theoretical

**Lumacaftor**

- **Lumacaftor** is predicted to decrease the exposure to antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone). Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to antifungals, azoles (fluconazole). Adjust dose, [Minor] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to antifungals, azoles (itraconazole, ketoconazole, posaconazole, voriconazole). Avoid or monitor efficacy. [Moderate] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to ciclosporin. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the efficacy of combined hormonal contraceptives. Use additional contraceptive precautions. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to corticosteroids (methylprednisolone). Adjust dose. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to everolimus. Avoid. [Severe] Theoretical

- **Lumacaftor** potentially decreases the exposure to glicaprevir. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the efficacy of levonorgestrel. Use additional contraceptive precautions. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to macrolides (clarithromycin, erythromycin). [Moderate] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to midazolam. Avoid. [Severe] Theoretical

- **Lumacaftor** potentially decreases the exposure to pibrentasvir. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to rifabutin. Adjust dose, [Moderate] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to sirolimus. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to tacrolimus. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the exposure to temsirolimus. Avoid. [Severe] Theoretical

- **Lumacaftor** is predicted to decrease the efficacy of ulipristal. Use additional contraceptive precautions. [Severe] Theoretical

**Lumefantrine** see antimalarials

**Lurasidone** see Table 8 p. 1376 (hypotension), Table 11 p. 1377 (CNS depressant effects)

- **Antiarrhythmics (dronedarone)** are predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to lurasidone. Avoid. [Moderate] Study — also see Table 11 p. 1377

- **Antifungals, azoles (fluconazole, itraconazole)** are predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to lurasidone. Avoid. [Severe] Study

- **Apalutamide** is predicted to decrease the exposure to lurasidone. Avoid or monitor. [Moderate] Study

- **Aprepitant** is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Bosentan** is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. [Moderate] Theoretical

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study — also see Table 8 p. 1376

- **Cobicistat** is predicted to increase the exposure to lurasidone. Avoid. [Severe] Study

- **Crizotinib** is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Efavirenz** is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. [Moderate] Theoretical

- **Enzalutamide** is predicted to decrease the exposure to lurasidone. Avoid. [Severe] Study

- **Grapefruit juice** is predicted to increase the exposure to lurasidone. Avoid. [Severe] Theoretical

- **HIV protease inhibitors** are predicted to increase the exposure to lurasidone. Avoid. [Severe] Study

- **Idelalisib** is predicted to increase the exposure to lurasidone. Avoid. [Severe] Study

- **Imatinib** is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Lurasidone** is predicted to decrease the effects of levodopa. [Severe] Theoretical — also see Table 8 p. 1376

- **Macrolides (clarithromycin)** are predicted to increase the exposure to lurasidone. Avoid. [Severe] Study

- **Macrolides (erythromycin)** are predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Mitotane** is predicted to decrease the exposure to lurasidone. Avoid. [Moderate] Study

- **Netupitant** is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Nevirapine** is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. [Moderate] Theoretical

- **Nilotinib** is predicted to increase the exposure to lurasidone. Adjust lurasidone dose, p. 398. [Moderate] Study

- **Rifampicin** is predicted to decrease the exposure to lurasidone. Avoid. [Severe] Study

- **St John’s Wort** is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. [Moderate] Theoretical

**Lymecycline** see tetracyclines

**Macitentan**

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to macitentan. Avoid. [Severe] Study

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to macitentan. [Moderate] Study

- **Cobicistat** is predicted to increase the exposure to macitentan. [Moderate] Study

- **Enalaprilam** is predicted to decrease the exposure to macitentan. Avoid. [Severe] Study

- **HIV protease inhibitors** are predicted to increase the exposure to macitentan. [Moderate] Study

- **Itraconazole** is predicted to increase the exposure to macitentan. [Moderate] Study

- **Loratadine** is predicted to decrease the exposure to macitentan. Avoid. [Severe] Study

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Macrolides → see TABLE 9 p. 1377 (QT-interval prolongation)

azithromycin ▶ clarithromycin ▶ erythromycin

▶ Interactions do not generally apply to topical use of azithromycin unless specified.

Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

▶ Clarithromycin is predicted to increase the exposure to abemaciclib. Avoid or adjust abemaciclib dose. p. 967. [Severe] Study

Erythromycin is predicted to increase the exposure to abemaciclib. [Moderate] Study

▶ Macrolides are predicted to increase the exposure to afatinib. Separate administration by 12 hours. [Moderate] Study

Clarithromycin is predicted to markedly increase the exposure to aldososterone antagonists (eplerenone). Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to aldososterone antagonists (eplerenone). Adjust eplerenone dose, p. 133. [Severe] Study

Azithromycin is predicted to increase the exposure to aliskiren. [Moderate] Theoretical

▶ Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to aliskiren. [Moderate] Study

Clarithromycin increases the exposure to amlodipine. [Moderate] Theoretical

▶ Clarithromycin is predicted to moderately increase the exposure to alpha blockers (alfuzosin, tamsulosin). Use with caution or avoid. [Moderate] Study

Clarithromycin is predicted to increase the exposure to alpha blockers (doxazosin). [Moderate] Study

▶ Erythromycin is predicted to increase the exposure to alpha blockers (tamsulosin). [Moderate] Theoretical

Clarithromycin moderately increases the exposure to alfuzosin. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to alfuzosin. [Severe] Study

Azithromycin is predicted to increase the exposure to amlodipine. [Severe] Study

▶ Azithromycin is predicted to increase the exposure to amlodipine. [Severe] Study

Clarithromycin is predicted to increase the exposure to amlodipine. Adjust dose. [Moderate] Theoretical

▶ Amlodipine is predicted to increase the exposure to erythromycin. Adjust dose. [Severe] Study

Clarithromycin very markedly increases the exposure to antihistamines (dronedarone). Avoid. [Severe] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to moderately increase the exposure to antihistamines (dronedarone). Avoid. [Severe] Theoretical → Also see TABLE 9 p. 1377

Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to antihistamines (lidocaine). [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to antihistamines (propafenone). Monitor and adjust dose. [Severe] Study

Erythromycin is predicted to increase the exposure to antihistamines (propafenone). Monitor and adjust dose. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. [Moderate] Study

Clarithromycin slightly increases the concentration of antiepileptics (carbamazepine). Monitor concentration and adjust dose. [Severe] Study

Erythromycin markedly increases the concentration of antiepileptics (carbamazepine). Monitor concentration and adjust dose. [Severe] Study

▶ Clarithromycin is predicted to markedly increase the exposure to antiepileptics (perampanel). [Mild] Study

Clarithromycin is predicted to increase the exposure to antifungals, azoles (isavuconazole). Avoid or monitor side effects. [Severe] Study

Erythromycin is predicted to increase the exposure to antifungals, azoles (isavuconazole). [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to antibiotics, azoles (itraconazole). Avoid. [Severe] Theoretical

Clarithromycin is predicted to increase the exposure to anitihistamines, non-sedating (mizolastine). Avoid. [Severe] Study

Erythromycin is predicted to increase the exposure to anitihistamines, non-sedating (mizolastine). [Severe] Theoretical

Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to antihistamines, non-sedating (rupatadine). Avoid. [Moderate] Study

Macrolides (clarithromycin, erythromycin) are predicted to increase the concentration of antimalarials (piperazine). [Severe] Theoretical

Clarithromycin is predicted to increase the exposure to apalutamide. [Mild] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to apixaban. [Moderate] Theoretical

Clarithromycin is predicted to markedly increase the exposure to aprepitant. [Moderate] Study

Erythromycin is predicted to increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. [Moderate] Study

Clarithromycin is predicted to increase the exposure to axitinib. Avoid or adjust dose. [Moderate] Study

Erythromycin is predicted to increase the exposure to axitinib. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Study → Also see TABLE 9 p. 1377

Erythromycin is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 9 p. 1377

Macrolides are predicted to increase the exposure to beta blockers, non-selective (nadolol). [Moderate] Study

Clarithromycin is predicted to increase the exposure to beta blockers, non-selective (nadolol). Avoid. [Severe] Study

Macrolides are predicted to increase the exposure to bicitravir. Use with caution or avoid. [Moderate] Theoretical

Clarithromycin slightly increases the exposure to bortezomib. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to bosentan. [Moderate] Theoretical

Clarithromycin is predicted to markedly increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377

Clarithromycin is predicted to increase the exposure to brigitinib. Adjust brigitinib dose, p. 971. [Severe] Study

Clarithromycin is predicted to increase the exposure to buspirone. Adjust buspirone dose, p. 342. [Severe] Study

Erythromycin is predicted to increase the exposure to buspirone. Use with caution and adjust dose. [Moderate] Study

Clarithromycin slightly increases the exposure to cabozantinib. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to cabozantinib. [Mild] Theoretical → Also see TABLE 9 p. 1377

Erythromycin is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

▶ Erythromycin is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

Clarithromycin is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Avoid. [Severe] Study
Erythromycin is predicted to increase the exposure to calcium channel blockers (verapamil). Study

Clarithromycin is predicted to increase the exposure to cannabis extract. Use with caution and adjust dose. Moderate

Clarithromycin is predicted to moderately increase the exposure to caripazine. Avoid. Study

Erythromycin is predicted to increase the exposure to caripazine. Avoid. Study

Clarithromycin is predicted to increase the exposure to clarithromycin. Avoid or adjust dose. Moderate

Erythromycin is predicted to increase the exposure to clarithromycin. Avoid or adjust dose. Moderate

Clarithromycin increases the concentration of ciclosporin. Study

Erythromycin is predicted to increase the concentration of ciclosporin. Study

Clarithromycin is predicted to moderately increase the exposure to clobetasol. Adjust clobetasol dose. Moderate

Erythromycin slightly increases the exposure to clobetasol. Adjust clobetasol dose. Moderate

Clarithromycin is predicted to moderately increase the exposure to cromakalim. Adjust dose. Moderate

Erythromycin potentially increases the risk of toxicity when given with clonazepam. Severe Anecdotal

Clarithromycin is predicted to markedly increase the exposure to coformycin. Avoid or monitor. Severe

Azithromycin is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose. Severe

Clarithromycin is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose. Severe

Erythromycin is predicted to increase the exposure to corticosteroids (beclomethasone) (risk with beclomethasone is likely to be lower than with other corticosteroids). Moderate

Clarithromycin is predicted to increase the exposure to corticosteroids (budesonide, ciclesonide, deflazacort, dexamethasone, fludrocortisone, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, triamcinolone). Avoid or monitor side effects.

Clarithromycin is predicted to increase the exposure to prednisolone. Monitor and adjust dose. Moderate

Erythromycin is predicted to moderately increase the exposure to cortisol (hydrocortisone). Severe

Clarithromycin is predicted to moderately increase the exposure to cortisone. Avoid or adjust dose—consult product literature. Moderate

Clarithromycin is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. Moderate

Erythromycin is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. Moderate

Macrolides (erythromycin, clarithromycin) increase the anticoagulant effect of coumarin. Monitor INR and adjust dose. Severe Anecdotal

Clarithromycin is predicted to moderately increase the exposure to crizotinib. Avoid. Moderate Study → Also see TABLE 9 p. 1377

Macrolides are predicted to increase the exposure to dabigatran. Moderate Theoretical

Clarithromycin is predicted to increase the exposure to dabrafenib. Use with caution or avoid. Moderate

Clarithromycin is predicted to markedly to very markedly increase the exposure to darifenacin. Avoid. Study

Erythromycin is predicted to slightly increase the exposure to darifenacin. Moderate

Clarithromycin is predicted to markedly increase the exposure to dasatinib. Avoid or adjust dose—consult product literature. Study → Also see TABLE 9 p. 1377

Erythromycin is predicted to increase the exposure to dasatinib. Severe Study → Also see TABLE 9 p. 1377

Clarithromycin very slightly increases the exposure to delamamine. Severe Study → Also see TABLE 9 p. 1377

Macrolides increase the concentration of digoxin. Severe

Macrolides (clarithromycin, erythromycin) increase the risk of QT-prolongation when given with domperidone. Avoid. Severe

Clarithromycin increases the exposure to dopamine receptor agonists (bromocriptine). Severe

Erythromycin is predicted to increase the exposure to dopamine receptor agonists (bromocriptine). Severe

Macrolides (clarithromycin, erythromycin) are predicted to increase the concentration of dopamine receptor agonists (cabergoline). Avoid. Severe

Clarithromycin is predicted to increase the exposure to doravirine. Midi Study

Clarithromycin is predicted to increase the exposure to dutasteride. Monitor side effects and adjust dose. Moderate

Erythromycin is predicted to moderately increase the exposure to dutasteride. Midi

Erythromycin slightly increases the exposure to edoxaban. Adjust edoxaban dose. Midi

Macrolides (azithromycin, clarithromycin) are predicted to slightly increase the exposure to edoxaban. Severe

Efavirenz decreases the exposure to clarithromycin. Moderate

Clarithromycin is predicted to markedly increase the exposure to elatinan. Avoid. Study

Erythromycin moderately increases the exposure to elatinan. Avoid. Moderate Study

Clarithromycin is predicted to increase the exposure to enzalutam. Avoid or monitor. Severe Study → Also see TABLE 9 p. 1377

Clarithromycin is predicted to moderately increase the exposure to enzalutam. Avoid or monitor. Moderate Study → Also see TABLE 9 p. 1377

Clarithromycin is predicted to increase the risk of ergotism when given with ergometrine. Avoid. Severe

Erythromycin is predicted to increase the risk of ergotism when given with ergometrine. Severe

Clarithromycin is predicted to increase the risk of ergotism when given with ergotamine. Avoid. Severe

Erythromycin is predicted to increase the risk of ergotism when given with ergotamine. Severe

Erythromycin is predicted to slightly increase the exposure to ergotamine. Use with caution and adjust dose. Moderate

Clarithromycin is predicted to increase the exposure to erlotinib. Avoid or monitor. Severe Study → Also see TABLE 9 p. 1377

Clarithromycin is predicted to moderately increase the exposure to erlotinib. Avoid or monitor. Severe Study

Clarithromycin is predicted to increase the exposure to erlotinib. Avoid or monitor. Severe Study

Clarithromycin is predicted to moderately increase the exposure to erlotinib. Avoid or monitor. Severe Study

Clarithromycin is predicted to increase the exposure to erlotinib. Avoid or monitor. Severe Study

Etravirine decreases the exposure to clarithromycin and clarithromycin slightly increases the exposure to etravirine. Severe

Clarithromycin is predicted to increase the concentration of everolimus. Avoid. Severe

Erythromycin is predicted to increase the concentration of everolimus. Avoid or adjust dose. Moderate

Clarithromycin is predicted to moderately increase the exposure to fosaprepitant. Avoid. Moderate

Clarithromycin is predicted to increase the exposure to gefitinib. Moderate

Clarithromycin is predicted to increase the exposure to gefitinib. Moderate

Erythromycin is predicted to increase the exposure to gefitinib. Moderate

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Macrolides – Macrolides 1485
Macrolides (continued)

- Clarithromycin is predicted to moderately to markedly increase the exposure to **grazoprevir**. Avoid. [Severe] Study
- Clarithromycin is predicted to increase the exposure to **guanfacine**. Adjust guanfacine dose, p. 352. [Moderate] Study
- Erythromycin is predicted to increase the concentration of **guanfacine**. Adjust guanfacine dose, p. 352. [Moderate] Theoretical
- H₂ receptor antagonists (cimetidine) slightly increase the exposure to **erythromycin**. [Moderate] Study
- HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, tipranavir) are predicted to increase the exposure to clarithromycin. Adjust dose in renal impairment. [Severe] Study
- HIV-protease inhibitors (ritonavir) increase the exposure to clarithromycin. Adjust dose in renal impairment. [Severe] Study
- HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, tipranavir) are predicted to increase the exposure to clarithromycin. [Severe] Study
- Clarithromycin is predicted to increase the exposure to HIV-protease inhibitors (saquinavir) and HIV-protease inhibitors (saquinavir) increase the exposure to clarithromycin. Avoid. [Severe] Study ⇒ Also see TABLE 9 p. 1377
- Erythromycin is predicted to increase the exposure to HIV-protease inhibitors (saquinavir). Avoid. [Severe] Theoretical ⇒ Also see TABLE 9 p. 1377
- Clarithromycin is predicted to very markedly increase the exposure to **ibrutinib**. Avoid. [Severe] Study
- Erythromycin is predicted to increase the exposure to **ibrutinib**. Adjust ibrutinib dose, p. 983. [Severe] Study
- Clarithromycin is predicted to increase the exposure to **ivabradine**. Adjust ibrutinib dose with moderate inhibitors of CYP3A4. **Severe** Study
- Clarithromycin is predicted to increase the exposure to **imatinib**. [Moderate] Theoretical
- Clarithromycin is predicted to increase the risk of toxicity when given with **irinotecan**. Avoid. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to **ivabradine**. Avoid. [Severe] Study
- Erythromycin is predicted to increase the exposure to **ivabradine**. Adjust ibrutinib dose with moderate inhibitors of CYP3A4 or adjust ibrutinib dose, p. 983. [Severe] Study
- Clarithromycin is predicted to increase the exposure to **ivacaftor**. Adjust ivacaftor, p. 293 or lumacaftor with ivacaftor p. 294 or tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. **Severe** Study
- Erythromycin is predicted to increase the exposure to ivacaftor. Adjust ivacaftor, p. 293 or tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study
- Clarithromycin is predicted to increase the exposure to **lapiatinib**. Avoid. [Moderate] Study ⇒ Also see TABLE 9 p. 1377
- Erythromycin is predicted to increase the exposure to **lapiatinib**. Avoid. [Moderate] Study
- Clarithromycin is predicted to increase the concentration of **lertromivir**. [Moderate] Study
- Clarithromycin increases the exposure to **linezolid**. [Moderate] Aneodal
- Azithromycin is predicted to increase the exposure to **lomitapide**. Separate administration by 12 hours. [Moderate] Theoretical
- Clarithromycin is predicted to markedly increase the exposure to **lomitapide**. Avoid. [Severe] Study
- Erythromycin is predicted to increase the exposure to **lomitapide**. Avoid. [Moderate] Theoretical
- Lumacaftor is predicted to decrease the exposure to macrolides (clarithromycin, erythromycin). [Moderate] Theoretical
- Clarithromycin is predicted to increase the exposure to **lurasidone**. Adjust lurasidone dose, p. 398. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to **macitentan**. [Moderate] Study
- Clarithromycin is predicted to markedly increase the exposure to **maraviroc**. Adjust dose. [Severe] Study
- Clarithromycin is predicted to markedly to very markedly increase the exposure to **midazolam**. Avoid or adjust dose. [Severe] Study
- Erythromycin is predicted to increase the exposure to **midazolam**. Monitor side effects and adjust dose. [Severe] Study
- Clarithromycin is predicted to very markedly increase the exposure to **midostaurin**. Avoid or monitor for toxicity. [Severe] Study
- Clarithromycin is predicted to increase the exposure to midostaurin. [Moderate] Theoretical
- Clarithromycin is predicted to increase the exposure to **mirabegron**. Adjust mirabegron dose in hepatic and renal impairment, p. 781. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to **mirzapapine**. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to monolocular antibodies (trastuzumab emtansine). Avoid. [Severe] Theoretical
- Clarithromycin is predicted to markedly increase the exposure to **naloxegol**. Avoid. [Severe] Study
- Erythromycin is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to **netupitant**. [Moderate] Study
- Nevirapine decreases the exposure to clarithromycin. [Moderate] Study
- Clarithromycin is predicted to moderately increase the exposure to **nilotinib**. Avoid. [Severe] Study ⇒ Also see TABLE 9 p. 1377
- Erythromycin is predicted to increase the exposure to nilotinib. [Moderate] Theoretical ⇒ Also see TABLE 9 p. 1377
- Clarithromycin is predicted to markedly increase the exposure to **nintedanib**. [Moderate] Study
- Erythromycin and **mirabegron** are predicted to increase the exposure to **nitidine**. [Moderate] Study
- Macrolides are predicted to increase the exposure to **nitidine**. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to **nitisinone**. Adjust dose. [Moderate] Theoretical
- Clarithromycin is predicted to increase the exposure to **olaparib**. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. [Moderate] Study
- Erythromycin is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. [Moderate] Theoretical
- Erythromycin is predicted to increase the exposure to opioids (alpetan, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. [Moderate] Study
- Clarithromycin is predicted to increase the exposure to opioids (alpetan, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. [Severe] Study
- Clarithromycin is predicted to increase the concentration of opioids (methadone). [Severe] Theoretical ⇒ Also see TABLE 9 p. 1377
- Erythromycin is predicted to increase the exposure to opioids (methadone, sufentanil). [Moderate] Theoretical ⇒ Also see TABLE 9 p. 1377
- Clarithromycin is predicted to increase the exposure to **esopenine**. Avoid in poor CYP2C9 metabolisers. [Moderate] Study
- Clarithromycin is predicted to markedly increase the exposure to **oxybutynin**. [High] Study
- Erythromycin is predicted to increase the exposure to oxybutynin. [High] Theoretical
- Clarithromycin is predicted to increase the exposure to **palbociclib**. Avoid or adjust palbociclib dose, p. 992. [Severe] Study
- Clarithromycin is predicted to increase the exposure to **panobinostat**. Adjust panobinostat dose; in hepatic
Macrolides

Erythromycin

Clarithromycin

Macrolides

impairment avoid, p. 936. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Macrolides (azithromycin, erythromycin) are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to paritaprevir. Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to paritaprevir. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to pazopanib. Avoid or adjust pazopanib dose, p. 993. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to pazopanib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avananfl). Adjust avananfl dose, p. 812. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avananfl, vardenafili). Avoid. [Severe] Study → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avananfl, sildenafil). Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avananfl, tadalafil). Monitor or adjust tadalafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). [Severe] Theoretical

▶ Erythromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). [Severe] Theoretical

▶ Erythromycin is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (vardenafili). Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to pibrentasvir. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to pimozone. Avoid. [Severe] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to pimozone. Avoid. [Severe] Theoretical → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study

▶ Clarithromycin is predicted to moderately increase the exposure to praziquantel. [Mild] Study

▶ Clarithromycin is predicted to increase the exposure to quetiapine. Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to quetiapine. Avoid. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to ranolazine. Avoid. [Severe] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to ranolazine. [Severe] Study → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to reboxetine. Avoid. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to regorafenib. Avoid. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to repaglinide. [Moderate] Study

▶ Clarithromycin is predicted to increase the exposure to retinoids (altretinoin). Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Azithromycin increases the risk of neutropenia when given with rifabutin. [Severe] Study

▶ Clarithromycin increases the risk of uveitis when given with rifabutin. Adjust dose. [Severe] Study

▶ Erythromycin is predicted to increase the risk of uveitis when given with rifabutin. Adjust dose. [Severe] Theoretical

▶ Rifampicin decreases the concentration of clarithromycin. [Severe] Study

▶ Clarithromycin is predicted to increase the exposure to risperidone. Adjust dose. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to ruxolitinib. Adjust dose and monitor side effects. [Moderate] Study

▶ Erythromycin is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to saxagliptin. [Moderate] Study

▶ Erythromycin is predicted to increase the exposure to saxagliptin. [Mild] Study

▶ Clarithromycin is predicted to increase the concentration of sirolimus. Avoid. [Severe] Study

▶ Clarithromycin increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study

▶ Clarithromycin is predicted to moderately increase the exposure to SSRIs (dapsone). Avoid potent inhibitors of CYP3A4 or adjust dapsone dose, p. 821. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to SSRIs (dapsone). Adjust dapsone dose with moderate inhibitors of CYP3A4, p. 821. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to statins (atorvastatin). Avoid or adjust dose and monitor (rhabdomyolysis, [Severe] Study

▶ Erythromycin is predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. [Severe] Study

▶ Clarithromycin moderately increases the exposure to statins (pravastatin). [Severe] Study

▶ Erythromycin is predicted to increase the exposure to statins (pravastatin). [Severe] Study

▶ Clarithromycin is predicted to increase the exposure to statins (simvastatin). Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. [Severe] Study

▶ Clarithromycin is predicted to slightly increase the exposure to sulfonylureas. [Moderate] Theoretical

▶ Clarithromycin is predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 9 p. 1377

▶ Erythromycin is predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

▶ Clarithromycin is predicted to increase the exposure to sunitinib. [Severe] Theoretical

▶ Clarithromycin is predicted to increase the concentration of tacrolimus. Monitor and adjust dose. [Severe] Study

▶ Erythromycin is predicted to increase the concentration of tacrolimus. [Severe] Study

▶ Clarithromycin is predicted to increase the exposure to taxanes (cabazitaxel). Avoid. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to taxanes (cabazitaxel). [Moderate] Theoretical

▶ Clarithromycin is predicted to moderately increase the exposure to taxanes (docetaxel). Avoid or adjust dose. [Severe] Study

▶ Clarithromycin is predicted to increase the exposure to taxanes (paclitaxel). [Severe] Theoretical

▶ Clarithromycin is predicted to increase the concentration of temsirolimus. Avoid. [Severe] Theoretical

▶ Erythromycin is predicted to increase the concentration of temsirolimus. [Moderate] Theoretical

▶ Clarithromycin is predicted to increase the exposure to tezacafor. Adjust tezacafor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. [Severe] Study

▶ Erythromycin is predicted to increase the exposure to tezacafor. Adjust tezacafor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study

▶ Erythromycin decreases the clearance of theophylline and theophylline potentially decreases the clearance of erthyromycin. Adjust dose. [Severe] Study
Macrolides (continued)

- Macrolides (azithromycin, clarithromycin) are predicted to increase the exposure to theophylline. Adjust dose. (Moderate Anecdotal)
- Azithromycin is predicted to increase the exposure to ticagrelor. Use with caution or avoid. (Severe Study)
- Clarithromycin is predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe Study)
- Clarithromycin is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose. p. 105. (Moderate Study)
- Erythromycin given with a potent CYP3A4 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate Study)
- Clarithromycin is predicted to increase the exposure to tolerodine. Avoid. (Severe Study) → Also see TABLE 9 p. 1377
- Erythromycin is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with high inhibitors of CYP3A4, p. 669. (Severe Study)
- Erythromycin is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 669. (Moderate Study)
- Macrolides are predicted to increase the exposure to topotecan. (Severe Study)
- Clarithromycin is predicted to increase the exposure to toremifene. (Moderate) Theoretical → Also see TABLE 9 p. 1377
- Clarithromycin is predicted to increase the exposure to troleandomycin. Avoid or adjust dose. (Severe Theoretical)
- Macrolides are predicted to increase the concentration of trametinib. (Theoretical Methodological)
- Clarithromycin is predicted to moderately increase the exposure to trazodone. Avoid or adjust dose. (Severe Study)
- Erythromycin is predicted to increase the exposure to trazodone. (Severe) Theoretical
- Clarithromycin is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe Study)
- Erythromycin is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate Study)
- Clarithromycin is predicted to increase the exposure to vemurafenib. (Severe) Theoretical → Also see TABLE 9 p. 1377
- Macrolides (clarithromycin, erythromycin) are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Moderate Study)
- Clarithromycin is predicted to increase the exposure to venlafaxine. (Moderate Study) → Also see TABLE 9 p. 1377
- Clarithromycin is predicted to increase the exposure to venlafaxine. (Moderate) Study → Also see TABLE 9 p. 1377
- Clarithromycin is predicted to increase the exposure to vitamin D substances (paricalcitol). (Moderate Study)
- Clarithromycin decreases the absorption of zidovudine. Separate administration by at least 2 hours. (Moderate Study)
- Clarithromycin is predicted to increase the exposure to zopiclone. Adjust dose. (Moderate Theoretical)
- Erythromycin is predicted to increase the exposure to zopiclone. Adjust dose. (Moderate Study)

- Magnesium
  - Oral magnesium decreases the absorption of bisphosphonates (alendronic acid). Alendronic acid should be taken at least 30 minutes before magnesium. (Moderate Study)
  - Oral magnesium is predicted to decrease the absorption of oral bisphosphonates (ibandronic acid). Avoid magnesium for at least 6 hours before or 1 hour after ibandronic acid. (Moderate Theoretical)
  - Oral magnesium decreases the absorption of bisphosphonates (risendronate). Separate administration by at least 2 hours. (Moderate Study)
  - Oral magnesium decreases the absorption of bisphosphonates (sodium clodronate). Avoid magnesium for 2 hours before or 1 hour after sodium clodronate. (Moderate Study)
  - Intravenous magnesium potentially increases the risk of hypotension when given with calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, verapamil) (in pregnant women). (Severe) Anecdotal
  - Intravenous magnesium increases the effects of neuromuscular blocking drugs, non-depolarising. (Moderate Study)
  - Intravenous magnesium is predicted to increase the effects of suxamethonium. (Moderate Study)
  - Magnesium carbonate → see antacids
  - Magnesium trisilicate → see antacids

- Maraviroc
  - Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to maraviroc. Adjust dose. (Severe Study)
  - Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to maraviroc. Adjust dose. (Severe Study)
  - Apalutamide is predicted to decrease the exposure to maraviroc. Avoid. (Moderate Study)
  - Aprepitant is predicted to increase the exposure to maraviroc. (Moderate Study)
  - Bosentan is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe Study)
  - Bicalutamide is predicted to decrease the exposure to maraviroc. (Severe Study)
  - Cobicistat markedly increases the exposure to maraviroc. Refer to specialist literature. (Severe Study)
  - Efavirenz decreases the exposure to maraviroc. Refer to specialist literature. (Severe) Theoretical
  - Enalaprilat is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe Study)
  - Etravirine (with a boosted protease inhibitor) increases the exposure to maraviroc. Avoid or adjust dose. (Moderate Study)
  - HIV-protease inhibitors (atazanavir, saquinavir) moderately to markedly increase the exposure to maraviroc. Refer to specialist literature. (Severe Study)
  - HIV-protease inhibitors (darunavir boosted with ritonavir) markedly increase the exposure to maraviroc. Refer to specialist literature. (Severe Study)
  - HIV-protease inhibitors (lopinavir boosted with ritonavir) moderately increase the exposure to maraviroc. Refer to specialist literature. (Severe Study)
  - HIV-protease inhibitors (ritonavir) markedly increase the exposure to maraviroc. Refer to specialist literature. (Severe Study)
  - Maraviroc potentially decreases the exposure to HIV-protease inhibitors (fosamprenavir) and HIV-protease inhibitors (fosamprenavir) potentially decrease the exposure to maraviroc. Avoid. (Severe) Study
  - Idealisib markedly increases the exposure to maraviroc. Adjust dose. (Severe Theoretical)
  - Macrolides (clarithromycin) are predicted to markedly increase the exposure to maraviroc. Adjust dose. (Severe) Study
  - Mitotane is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe Study)
  - Netupitant is predicted to increase the exposure to maraviroc. (Moderate Study)
  - Rifampicin is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe Study)
  - St John’s Wort is predicted to decrease the exposure to maraviroc. Avoid. (Severe Theoretical)

- Measles, mumps and rubella vaccine, live → see live vaccines
- Mefenamic acid → see NSAIDs
- Mefloquine → see antimalarials
- Melatonin → see TABLE 11 p. 1377 (CN5 depressant effects)
  - Antiepileptics (phenytoin) are predicted to decrease the exposure to melatonin. (Moderate Theoretical)
  - Combined hormonal contraceptives are predicted to increase the exposure to melatonin. (Moderate) Theoretical
  - HIV-protease inhibitors (ritonavir) are predicted to decrease the exposure to melatonin. (Moderate) Theoretical

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> **Leflunomide** is predicted to decrease the exposure to methotrexate. (Moderate) Theoretical

> **Mexiteline** is predicted to increase the exposure to methotrexate. (Moderate) Theoretical

> **Quinolones (ciprofloxacin)** are predicted to increase the exposure to methotrexate. (Moderate) Theoretical

> **Rifampicin** is predicted to decrease the exposure to methotrexate. (Moderate) Theoretical

> **SSRIs** (fluvoxamine) very markedly increase the exposure to methotrexate. Avoid. (Severe) Study

> **Teriflunomide** is predicted to decrease the exposure to methotrexate. (Moderate) Theoretical

> **Vandetanib** increases the urinary excretion of methotrexate. (Moderate) Theoretical

> **Acetazolamide** is predicted to decrease the efficacy of methotrexate. Avoid. (Moderate) Theoretical

> **Potassium citrate** is predicted to decrease the efficacy of methotrexate. Avoid. (Moderate) Theoretical

> **Sodium bicarbonate** is predicted to decrease the efficacy of methotrexate. Avoid. (Moderate) Theoretical

> **Sodium citrate** is predicted to decrease the efficacy of methotrexate. Avoid. (Moderate) Theoretical

> **Methocarbamol** → see TABLE 11 p. 1377 (NS depressant effects)

> **Methotrexate** → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity), TABLE 5 p. 1375 (thromboembolism)

> **Acetazolamide** increases the urinary excretion of methotrexate. (Moderate) Study

> **Methotrexate** is predicted to decrease the clearance of aminophylline. (Moderate) Theoretical

> **Antiepileptics (levetiracetam)** decrease the clearance of methotrexate. (Severe) Anecdotal

> **Antimalarials (pyrimethamine)** are predicted to increase the risk of side-effects when given with methotrexate. (Severe) Study

> **Methotrexate** is predicted to decrease the exposure to methotrexate. (Mild) Study

> **Asparaginase** affects the efficacy of methotrexate. (Severe) Anecdotal

> **Brigatinib** potentially increases the concentration of methotrexate. (Moderate) Theoretical

> **Crisantaspase affects the efficacy of methotrexate. (Severe) Anecdotal**

> **Elotrubopag** is predicted to increase the concentration of methotrexate. (Moderate) Theoretical

> **Methotrexate** potentially increases the risk of severe skin reaction when given with topical fluorouracil. (Severe) Anecdotal → Also see TABLE 15 p. 1378

> **Methotrexate** is predicted to increase the exposure to methotrexate. (Moderate) Theoretical → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378

> **Methotrexate** is predicted to increase the risk of generalised infection (possibly life-threatening) when given with methotrexate (high-dose). Use with caution or avoid. (Severe) Study

> **Methotrexate** is predicted to increase the risk of toxicity when given with methotrexate. (Severe) Anecdotal

> **Penicillins** are predicted to increase the risk of toxicity when given with methotrexate. (Severe) Anecdotal → Also see TABLE 1 p. 1375

> **Potassium aminobenzoate** increases the concentration of methotrexate. (Moderate) Theoretical

> **Proton pump inhibitors decrease the clearance of methotrexate** (high-dose). Use with caution or avoid. (Severe) Study

> **Quinolones (ciprofloxacin)** potentially increase the risk of toxicity when given with methotrexate. (Severe) Anecdotal

> **Rofecalbin** is predicted to increase the exposure to methotrexate. (Moderate) Theoretical → Also see TABLE 15 p. 1378

> **Retinoids (acitretin)** are predicted to increase the concentration of methotrexate. Avoid. (Moderate) Anecdotal

> **Rolipram** is predicted to increase the exposure to methotrexate. Avoid or monitor. (Moderate) Study

> **Methotrexate** is predicted to decrease the efficacy of sapropterin. (Moderate) Theoretical

> **Sulfonamides** are predicted to increase the exposure to methotrexate. Use with caution or avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378

> **Tetrazolol** is predicted to increase the exposure to methotrexate. Avoid. (Moderate) Theoretical

> **Methotrexate** is predicted to increase the risk of toxicity when given with tegafur. (Severe) Theoretical

**Metformin**

> **Leflunomide** is predicted to decrease the exposure to metformin. Avoid. (Moderate) Theoretical

> **Mexiteline** is predicted to increase the exposure to metformin. Avoid. (Moderate) Theoretical

> **Quinolones (ciprofloxacin)** are predicted to increase the exposure to metformin. (Moderate) Theoretical

> **Rifampicin** is predicted to decrease the exposure to metformin. (Moderate) Theoretical

> **SSRIs** (fluvoxamine) very markedly increase the exposure to metformin. Avoid. (Severe) Study

> **Teriflunomide** is predicted to decrease the exposure to metformin. (Severe) Study

> **Vandetanib** increases the exposure to metformin. Monitor and adjust dose. (Moderate) Study

> **Methadone** → see opioids
Methotrexate (continued)

- Teriflunomide is predicted to increase the exposure to methotrexate. [Moderate] Study
- Methotrexate decreases the clearance of theophylline. [Moderate] Study
- Trimethoprim is predicted to increase the risk of side-effects when given with methotrexate. Avoid. [Severe] Theoretical → Also see TABLE 2 p. 1375

Methoxyflurane → see volatile halogenated anaesthetics
Methyleneblue → see TABLE 8 p. 1376 (hyperpension)
Entacapone is predicted to increase the exposure to methyleneblue. [Moderate] Theoretical
Iron (oral) decreases the effects of methyleneblue. [Moderate] Study
Methyldopa is predicted to increase the risk of neurotoxicity when given with lithium. [Severe] Anecdotal
Monoamine-oxidase A and B inhibitors, irreversible are predicted to alter the antihypertensive effects of methyleneblue. Avoid. [Severe] Theoretical → Also see TABLE 8 p. 1376

Methylphenidate
- Methylphenidate is predicted to decrease the effects of apراقlonidine. Avoid. [Severe] Theoretical
- Methylphenidate is predicted to increase the risk of elevated blood pressure when given with finеzolоid. Avoid. [Severe] Theoretical
- Methylphenidate is predicted to increase the risk of a hypertensive crisis when given with moclobemide. [Severe] Theoretical
- Methylphenidate is predicted to increase the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. [Severe] Theoretical
- Monoamine-oxidase B inhibitors (расагилин, selegilinе) are predicted to increase the risk of a hypertensive crisis when given with methylphenidate. Avoid. [Severe] Theoretical
- Methylphenidate increases the risk of dyskinesias when given with paliperidоn. [Severe] Theoretical
- Рisperidоnе increases the risk of dyskinesias when given with methylphenidate. [Severe] Anecdotal
Methylпrednisолоnе → see corticosteroids
Methyliпhонium chloride → see TABLE 13 p. 1378 (serotonin syndrome)
- Methyliпhоnium chloride is predicted to increase the risk of severe hypertension when given with бропиопоn. Avoid. [Severe] Theoretical → Also see TABLE 13 p. 1378

Metoclopamidе
- Metoclopamidе is predicted to increase the risk of methaemoglobinemia when given with topical anаesthetic, local (прилокаине). Avoid. [Severe] Theoretical
- Metoclopamidе potentially decreases the absorption of antifungаls, azoles (posасозолеnе) (oral suspension). [Moderate] Study
- Metoclopamidе decreases the concentration of antimalarials (атоваquоне). Avoid. [Moderate] Study
- Metoclopamidе is predicted to decrease the effects of dopamine receptor agonists (апорономine, bromocriptine, cabergолине, pergolоdе, pramipеxоlе, ropinitоlе, roгitоlinе). Avoid. [Moderate] Study
- Metoclopamidе decreases the effects of levодоpа. Avoid. [Moderate] Study
- Metoclopamidе is predicted to increase the effects of neuromuscular blocking drugs, non-depolarising. [Moderate] Theoretical
- Metoclopamidе increases the effects of суxаметониум. [Moderate] Study
- Metopazоnе → see thiaide diuretics
- Metoprolоl → see β blockers, selective
- Metronidazole → see TABLE 12 p. 1378 (peripheral neuropathy)

ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

- Alcohol (beverage) potentially causes a disulfiram-like reaction when given with metronidazole. Avoid for at least 48 hours stopping treatment. [Moderate] Study
- Metronidazole increases the risk of toxicity when given with alkylating agents (busulfan). [Severe] Study
- Antiepileptics (phenobarbital, primidоnе) are predicted to decrease the exposure to метронидазоlе. [Moderate] Study
- Metronidazole is predicted to increase the risk of capetеcitabine toxicity when given with capetеcitabine. [Severe] Theoretical
- Metronidazole increases the anticoagulant effect of coumarins. Monitor INR and adjust dose. [Moderate] Study
- Disуlфiram increases the risk of acute psychoses when given with metronidazole. [Severe] Study → Also see TABLE 12 p. 1378
- Metronidazole increases the risk of toxicity when given with fluorоuracil. [Severe] Study

Метyroпаnе
- Antiepileptics (фосфоnеtоn, phenobarbital, phenytoin, primidoне) are predicted to decrease the effects of metyroпаnе. Avoid. [Moderate] Study
- Antihistamines, sedating (cypроheptаdine) decrease the effects of metyroпаnе. Avoid. [Moderate] Theoretical
- Carbimazоlе decreases the effects of metyroпаnе. Avoid. [Moderate] Theoretical
- Combined hormonal contraceptives decrease the effects of metyroпаnе. Avoid. [Moderate] Study
- Phenothiazines (chlorопроmазине) decrease the effects of metyroпаnе. Avoid. [Moderate] Theoretical
- Propylthiоurаcil is predicted to decrease the effects of metyroпаnе. Avoid. [Moderate] Theoretical
- Tricyclic antidepressants (amитрiptилине) decrease the effects of метрошеnеpаnе. Avoid. [Moderate] Theoretical

Мексилеnе

FOOD AND LIFESTYLE Dose adjustment might be necessary if smoking started or stopped during treatment.
- Mексилеnе is predicted to increase the exposure to agомелатине. [Moderate] Study
- Мексилеnе is predicted to increase the exposure to амитрiptилине. Adjust dose. [Moderate] Theoretical
- Мексилеnе is predicted to increase the exposure to anагрелиде. [Moderate] Theoretical
- Мексилеnе increases the risk of torsade de pointsеnеs when given with аntiarhythmics. Avoid. [Severe] Theoretical
- Antiepileptics (phenytoin) are predicted to increase the clearance of mexilenе. Monitor and adjust dose. [Moderate] Study
- Мексилеnе potentially increases the risk of cardiovascular side-effects when given with β blockers, non-selective. Avoid or monitor. [Severe] Theoretical
- Мексилеnе potentially increases the risk of cardiovascular side-effects when given with β blockers, selective. Avoid or monitor. [Severe] Theoretical
- Бропиопоn is predicted to increase the exposure to mексилеnе. [Moderate] Study
- Мексилеnе increases the risk of cardiovascular side-effects when given with calcium channel blockers (dilitаzеm). Avoid or monitor. [Severe] Theoretical
- Мексилеnе potentially increases the risk of cardiovascular side-effects when given with calcium channel blockers (verаnамиl). Avoid or monitor. [Severe] Theoretical
- Cinаcаlеt is predicted to increase the exposure to mексилеnе. [Moderate] Study
- Мексилеnе increases the concentration of clozаpine. Monitor side effects and adjust dose. [Moderate] Study
- Cobicistаt potentially increases the exposure to mексилеnе. [Severe] Theoretical
- Мексилеnе potentially affects the exposure to coumarins (warfarin). Avoid. [Unknown] Theoretical
- Мексилеnе is predicted to increase the exposure to dopamine receptor agonists (ropinirolе). Adjust dose. [Moderate] Study
- Мексилеnе slightly increases the exposure to etrorитinib. Monitor side effects and adjust dose. [Moderate] Study
- HIV-protease inhibitors (ритонавиr) are predicted to increase the clearance of mексилеnе. Monitor and adjust dose. [Moderate] Study
- Лефлуноде is predicted to increase the clearance of mexilenе. Monitor and adjust dose. [Moderate] Study
- Мексилеnе potentially affects the exposure to lithium. Avoid. [Unknown] Theoretical
- Мексилеnе is predicted to increase the exposure to lоxаpine. Avoid. [Unknown] Theoretical

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Mexiteline is predicted to increase the exposure to melatonin. (Moderate) Theoretical

Mexiteline is predicted to affect the exposure to metformin. (Unknown) Theoretical

Mexiteline slightly increases the exposure to monoamine-oxidase B inhibitors (rasagline). (Moderate) Study

Mexiteline is predicted to increase the exposure to olanzapine. Adjust dose. (Moderate) Anecdotal

Opioids potentially decrease the absorption of oral mexiteline. (Moderate) Study

Mexiteline is predicted to increase the exposure to pirenidone. Use with caution and adjust dose. (Moderate) Study

Rifampicin is predicted to increase the clearance of mexiteline. Monitor and adjust dose. (Moderate) Study

Mexiteline is predicted to increase the exposure to riluzole. (Moderate) Theoretical

Mexiteline is predicted to increase the exposure to romifidine. (Moderate) Theoretical

SSRIs (fluoxetine, fluvoxamine, paroxetine) are predicted to increase the exposure to mexiteline. (Moderate) Study

Terbinafine is predicted to increase the exposure to mexiteline. (Moderate) Study

Terflunomide is predicted to increase the clearance of mexiteline. Monitor and adjust dose. (Moderate) Study

Mexiteline is predicted to increase the exposure to theophylline. Monitor and adjust dose. (Moderate) Theoretical

Mexiteline increases the exposure to tizanidine. Avoid. (Moderate) Study

Mexiteline is predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. (Moderate) Theoretical

Mianserin → see TABLE 13 p. 1378 (serotonin syndrome, TABLE 11 p. 1377 (CNS depressant effects)

Antiepileptics (carbamazepine) markedly decrease the exposure to mianserin. Adjust dose. (Moderate) Study

Antiepileptics (phenobarbital, primidone) are predicted to decrease the exposure to mianserin. (Moderate) Study → Also see TABLE 11 p. 1377

Mianserin is predicted to increase the risk of toxicity when given with moclobemide. Avoid and for 1 week after stopping mianserin. (Search) Theoretical → Also see TABLE 13 p. 1378

Mianserin is predicted to increase the risk of toxicity when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. (Search) Theoretical. → Also see TABLE 13 p. 1378

Mianserin is predicted to decrease the efficacy of pitolisant. (Search) Theoretical

Mianserin decreases the effects of sympatheaminetics, vasoconstrictor (ephedrine). (Search) Anecdotal

Micafungin → see TABLE 13 p. 1375 (hepatotoxicity)

Micafungin slightly increases the exposure to amphotericin. Avoid or monitor toxicity. (Search) Study

Miconazole → see antifungals, azoles

Midazolam → see TABLE 11 p. 1377 (CNS depressant effects)

Antiepileptics (dronedarone) are predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Study → Also see TABLE 11 p. 1377

Antifungals, azoles (flucnazole, itraconazole, posaconazole, voriconazole) are predicted to increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Antifungals, azoles (miconazole) are predicted to increase the exposure to intravenous midazolam. Use with caution and adjust dose. (Search) Theoretical

Antifungals, azoles (miconazole) are predicted to increase the exposure to oral midazolam. Avoid. (Search) Theoretical

Apalutamide markedly decreases the exposure to midazolam. Avoid or monitor. (Search) Study

Aprepitant is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Boventan is predicted to decrease the concentration of midazolam. Monitor and adjust dose. (Search) Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Cobicistat is predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Crizotinib is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Dabrafenib decreases the exposure to midazolam. Monitor and adjust dose. (Search) Study

Eflavirenz is predicted to alter the effects of midazolam. Avoid. (Search) Theoretical

Enzalutamide is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Study

Fosaprepitant slightly increases the exposure to midazolam. (Search) Study

IV-protase inhibitors are predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Idelalisib is predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Imatinib is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Leteimovir slightly to moderately increases the exposure to midazolam. Monitor and adjust dose. (Search) Study

Lumacaftor is predicted to decrease the exposure to midazolam. Avoid. (Search) Theoretical

Macrolides (clarithromycin) are predicted to markedly to very markedly increase the exposure to midazolam. Avoid or adjust dose. (Search) Study

Macrolides (erythromycin) are predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Mexiletine is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Study

Midostaurin is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Study

Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Theoretical

Netupitant is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Nevirapine decreases the concentration of midazolam. Monitor and adjust dose. (Search) Study

Nilotinib is predicted to increase the exposure to midazolam. Monitor side effects and adjust dose. (Search) Study

Palbociclib increases the exposure to midazolam. (Search) Study

Ribociclib moderately increases the exposure to midazolam. Avoid. (Search) Study

Rifampicin is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Search) Study

Rucaparib slightly increases the exposure to midazolam. Monitor and adjust dose. (Search) Study

St John’s Wort moderately decreases the exposure to midazolam. Monitor and adjust dose. (Search) Study

Telotristat ethyl decreases the exposure to midazolam. (Search) Study

Midodrine → see sympathominetics, vasoconstrictor

Midostaurin

Antiarrhythmics (dronedarone) are predicted to increase the exposure to midostaurin. (Search) Theoretical

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to midostaurin. Avoid. (Search) Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to midostaurin. Avoid or monitor for toxicity. (Search) Theoretical

Aprepitant is predicted to increase the exposure to midostaurin. (Search) Theoretical
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Midostaurin (continued)
▶ Calcium channel blockers (diltiazem, verapamil) are predicted to
increase the exposure to midostaurin. o Theoretical
▶ Cobicistat is predicted to very markedly increase the exposure
to midostaurin. Avoid or monitor for toxicity. r Study
▶ Crizotinib is predicted to increase the exposure to midostaurin.

▶
▶
▶

o Theoretical
▶
▶

Enzalutamide is predicted to decrease the exposure to
midostaurin. Avoid. r Study
HIV-protease inhibitors are predicted to very markedly increase
the exposure to midostaurin. Avoid or monitor for toxicity.

▶

p. 781. o Study
▶

r Study
▶

Idelalisib is predicted to very markedly increase the exposure
to midostaurin. Avoid or monitor for toxicity. r Study
▶ Imatinib is predicted to increase the exposure to midostaurin.
o Theoretical

▶

▶
▶

Interactions | Appendix 1

A1

▶
▶

Macrolides (clarithromycin) are predicted to very markedly
increase the exposure to midostaurin. Avoid or monitor for
toxicity. r Study
Macrolides (erythromycin) are predicted to increase the
exposure to midostaurin. o Theoretical
Mitotane is predicted to decrease the exposure to midostaurin.
Avoid. r Study
Netupitant is predicted to increase the exposure to
midostaurin. o Theoretical
Nilotinib is predicted to increase the exposure to midostaurin.

▶

▶

▶

Theoretical

Minocycline → see tetracyclines
Minoxidil → see TABLE 8 p. 1376 (hypotension)
ROUTE-SPECIFIC INFORMATION Since systemic absorption can
follow topical application, the possibility of interactions
should be borne in mind.
Mirabegron
▶ Mirabegron is predicted to increase the exposure to aliskiren.
n Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to mirabegron. Adjust
mirabegron dose in hepatic and renal impairment, p. 781.
o Study

▶
▶

Mirabegron is predicted to increase the exposure to
antihistamines, non-sedating (fexofenadine). n Theoretical
Mirabegron is predicted to increase the exposure to beta
blockers, selective (metoprolol). o Study
Cobicistat is predicted to increase the exposure to mirabegron.
Adjust mirabegron dose in hepatic and renal impairment,
p. 781. o Study

▶

Mirabegron is predicted to increase the exposure to colchicine.
n Theoretical

▶
▶
▶

Mirabegron is predicted to increase the exposure to
dabigatran. r Theoretical
Mirabegron slightly increases the exposure to digoxin. Monitor
concentration and adjust dose. r Study
Mirabegron is predicted to increase the exposure to edoxaban.
n Theoretical

Mirabegron is predicted to increase the exposure to taxanes
(paclitaxel). n Theoretical
Mirabegron is predicted to increase the exposure to topotecan.
n Theoretical

Mirtazapine → see TABLE 13 p. 1378 (serotonin syndrome), TABLE 11
p. 1377 (CNS depressant effects)
▶

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure
to mirtazapine. Adjust dose. o Study → Also see TABLE 11
p. 1377

Rifampicin is predicted to decrease the exposure to
midostaurin. Avoid. r Study
▶ St John’s Wort is predicted to decrease the exposure to
midostaurin. Avoid. r Theoretical
Mifamurtide
▶ Ciclosporin is predicted to decrease the efﬁcacy of
mifamurtide. Avoid. r Theoretical
▶ Corticosteroids are predicted to decrease the efﬁcacy of
mifamurtide. Avoid. r Theoretical
▶ NSAIDs (high-dose) are predicted to decrease the efﬁcacy of
mifamurtide. Avoid. r Theoretical
▶ Pimecrolimus is predicted to decrease the efﬁcacy of
mifamurtide. Avoid. r Theoretical
▶ Sirolimus is predicted to decrease the efﬁcacy of mifamurtide.
Avoid. r Theoretical
▶ Tacrolimus is predicted to affect the efﬁcacy of mifamurtide.
Avoid. r Theoretical
Mifepristone
▶ Mifepristone is predicted to decrease the efﬁcacy of
corticosteroids. Use with caution and adjust dose. o

▶

Mirabegron is predicted to increase the exposure to
loperamide. n Theoretical
Macrolides (clarithromycin) are predicted to increase the
exposure to mirabegron. Adjust mirabegron dose in hepatic
and renal impairment, p. 781. o Study
Mirabegron is predicted to increase the exposure to sirolimus.
n Theoretical

▶

o Theoretical
▶

▶

Mirabegron is predicted to increase the exposure to eliglustat.
Avoid or adjust dose—consult product literature. r Study
Mirabegron is predicted to increase the exposure to
everolimus. n Theoretical
HIV-protease inhibitors are predicted to increase the exposure
to mirabegron. Adjust mirabegron dose in hepatic and renal
impairment, p. 781. o Study
Idelalisib is predicted to increase the exposure to mirabegron.
Adjust mirabegron dose in hepatic and renal impairment,

▶

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to mirtazapine. o
Study

▶

Cobicistat is predicted to increase the exposure to mirtazapine.
o Study

▶
▶

Enzalutamide is predicted to decrease the exposure to
mirtazapine. Adjust dose. o Study
H2 receptor antagonists (cimetidine) slightly increase the
exposure to mirtazapine. Use with caution and adjust dose.
o Theoretical

▶
▶

HIV-protease inhibitors are predicted to increase the exposure
to mirtazapine. o Study
Idelalisib is predicted to increase the exposure to mirtazapine.
o Study

Macrolides (clarithromycin) are predicted to increase the
exposure to mirtazapine. o Study
▶ Mitotane is predicted to decrease the exposure to mirtazapine.
Adjust dose. o Study
▶ Mirtazapine is predicted to decrease the efﬁcacy of pitolisant.
▶

o Theoretical
▶

Rifampicin is predicted to decrease the exposure to
mirtazapine. Adjust dose. o Study
Mitomycin → see TABLE 15 p. 1378 (myelosuppression), TABLE 5 p. 1375
(thromboembolism)
▶

Live vaccines are predicted to increase the risk of generalised
infection (possibly life-threatening) when given with
mitomycin. Public Health England advises avoid (refer to
Green Book). r Theoretical
Mitotane → see TABLE 15 p. 1378 (myelosuppression)
▶ Mitotane is predicted to markedly decrease the exposure to
abemaciclib. Avoid. r Study
▶ Mitotane is predicted to decrease the exposure to abiraterone.
Avoid. r Study
▶ Aldosterone antagonists (spironolactone) are predicted to
decrease the effects of mitotane. Avoid. r Anecdotal
▶ Mitotane is predicted to decrease the exposure to aldosterone
antagonists (eplerenone). Avoid. o Theoretical
▶ Mitotane is predicted to decrease the exposure to alprazolam.
Adjust dose. o Theoretical
▶ Mitotane is predicted to decrease the exposure to
antiarrhythmics (disopyramide, dronedarone). Avoid. r
Study
▶
▶
▶

Mitotane is predicted to decrease the efﬁcacy of antiarrhythmics
(propafenone). o Study
Mitotane is predicted to decrease the exposure to
anticholinesterases, centrally acting (donepezil). n Study
Mitotane is predicted to decrease the exposure to antiepileptics
(perampanel). Monitor and adjust dose. o Study

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Mitotane is predicted to decrease the exposure to antifungals, azoles (inaconazole). Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to antimalarials (artemether) (with lumefantrine). Avoid. [Severe] Study
 Mitotane is predicted to decrease the concentration of antimalarials (piperazine). Avoid. [Moderate] Theoretical
 Mitotane is predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. [Severe] Study
 Mitotane moderately decreases the exposure to aripiprazole. Avoid. [Severe] Study
 Mitotane is predicted to markedly decrease the exposure to aripiprazole. Avoid. [Moderate] Study
 Mitotane is predicted to moderately decrease the exposure to aripiprazole. Adjust aripiprazole dose, p. 39. [Moderate] Study
 Mitotane is predicted to decrease the exposure to axitinib. Avoid or adjust dose. [Moderate] Study → Also see TABLE 15 p. 1378
 Mitotane decreases the exposure to bedaquiline. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to bicalutamide. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane affects the exposure to bosentan. Avoid. [Severe] Study
 Mitotane is predicted to very markedly decrease the exposure to bosutinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to brigatinib. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to buspirone. Use with caution and adjust dose. [Severe] Study
 Mitotane moderately decreases the exposure to cabozantinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nimodipine). Monitor and adjust dose. [Moderate]
 Mitotane is predicted to decrease the exposure to cannabis extract. Avoid. [Severe] Theoretical
 Mitotane is predicted to decrease the exposure to cariprazine. Avoid. [Severe] Theoretical
 Mitotane is predicted to decrease the exposure to ceritinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane decreases the concentration of ciclosporin. [Severe] Study
 Mitotane is predicted to alter the effects of cilostazol. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to cinacalcet. Monitor and adjust dose. [Moderate] Study
 Mitotane decreases the exposure to clomethiazole. Monitor and adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to clomipramine. Monitor and adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to colchicine. Monitor and adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fluocortolone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to corticosteroids (fluticasone). [Unknown] Theoretical
 Mitotane is predicted to markedly decrease the exposure to crizotinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to dabrafenib. Avoid. [Moderate] Theoretical → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to darifenacin. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
 Mitotane is predicted to markedly decrease the exposure to dasatinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to slightly decrease the exposure to delamanid. Avoid. [Moderate] Study
 Mitotane decreases the exposure to dolutegravir. Adjust dose. [Severe] Study
 Mitotane is predicted to decrease the exposure to doravirine. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to elbasvir. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to eligulstat. Avoid. [Severe] Study
 Mitotane is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical
 Mitotane is predicted to decrease the exposure to encorafenib. [Moderate] Theoretical
 Mitotane is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to erlotinib. Avoid or adjust erlotinib dose, p. 979. [Severe] Study
 Mitotane is predicted to decrease the exposure to esketamine. Adjust dose. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to everolimus. Avoid or adjust dose. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane moderately decreases the exposure to exemestane. [Moderate] Study
 Mitotane is predicted to decrease the exposure to fesoterodine. Avoid. [Moderate] Study
 Mitotane is predicted to decrease the exposure to fingolimod. [Moderate] Study
 Mitotane is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to gefitinib. Avoid. [Moderate] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to greatly decrease the concentration of glecaprevir. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to grazoprevir. Avoid. [Severe] Study
 Mitotane is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. [Moderate] Study
 Mitotane decreases the concentration of haloperidol. Adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to ibrutinib. Avoid or adjust ibrutinib dose, p. 983. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to idelalisib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to imatinib. Avoid. [Moderate] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to irinotecan. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
 Mitotane is predicted to decrease the exposure to ivabradine. Adjust dose. [Moderate] Theoretical
 Mitotane is predicted to moderately to markedly decrease the exposure to ivacaftor. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to ixazomib. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to lapatinib. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to linagliptin. [Moderate] Study
 Mitotane is predicted to decrease the exposure to lomitapide. Monitor and adjust dose. [Moderate] Theoretical
 Mitotane is predicted to decrease the exposure to lurasiadone. Avoid. [Moderate] Study
 Mitotane is predicted to decrease the exposure to macitentan. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to maraviroc. Adjust dose. [Severe] Study
 Mitotane is predicted to decrease the exposure to midazolam. Monitor and adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to midostaurin. Avoid. [Severe] Study
 Mitotane is predicted to decrease the exposure to mirtazapine. Adjust dose. [Moderate] Study
 Mitotane is predicted to decrease the exposure to montelukast. [Mild] Study
Mitotane (continued)

- Mitotane is predicted to markedly decrease the exposure to naloxegol. Avoid. (Moderate) Study
- Mitotane is predicted to slightly decrease the exposure to digoxine. (Blind) Study
- Mitotane is predicted to decrease the exposure to netupitant. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to nevirapine. (Severe) Theoretical
- Mitotane is predicted to moderately decrease the exposure to nitinib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to ritinidine. Adjust dose. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to omibatrasib. Avoid. (Severe) Theoretical
- Mitotane is predicted to decrease the exposure to ondasertnon. (Moderate) Study
- Mitotane is predicted to decrease the exposure to opioids (alfentanil, fentanyl). Monitor and adjust dose. (Moderate) Theoretical
- Mitotane decreases the exposure to opioids (methadone). Monitor and adjust dose. (Severe) Study
- Mitotane is predicted to decrease the exposure to oxiseline. Avoid. (Moderate) Study
- Mitotane is predicted to moderately decrease the exposure to osimertinib. Avoid. (Moderate) Study
- Mitotane is predicted to moderately decrease the exposure to pazopanib. Avoid. (Severe) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to palbociclib. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to paliperidone. Monitor and adjust dose. (Severe) Study
- Mitotane is predicted to decrease the exposure to panobinostat. Avoid. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to paritaprevir (with ritonavir and omibatrasib). Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to pazopanib. Avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, tadalaflil). Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenafil). Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to pizolins. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to ponatinib. Avoid. (Moderate) Theoretical
- Mitotane is predicted to moderately decrease the exposure to praziquantel. Avoid. (Moderate) Study
- Mitotane is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Mitotane is predicted to decrease the exposure to ranolazine. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to reboxetine. (Moderate) Aneodotnal
- Mitotane is predicted to decrease the exposure to regorafenib. Avoid. (Moderate) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to repaglinide. Monitor blood glucose and adjust dose. (Moderate) Study
- Mitotane is predicted to markedly decrease the exposure to ribociclib. Avoid. (Severe) Study
- Mitotane markedly decreases the exposure to ritipiravine. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to risperidone. Adjust dose. (Moderate) Study
- Mitotane is predicted to moderately decrease the exposure to rivaroxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- Mitotane is predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- Mitotane is predicted to markedly decrease the exposure to rolapitant. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to ruxolitinib. Monitor and adjust dose. (Moderate) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to moderately decrease the exposure to saxaglupin. (Moderate) Study
- Mitotane is predicted to decrease the concentration of sirolimus. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to solifenacin. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to sorafenib. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to statins (simvastatin). Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to sunitinib. Avoid or adjust sunitinib dose. p. 999. (Moderate) Study → Also see TABLE 15 p. 1378
- Mitotane decreases the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study
- Mitotane is predicted to decrease the exposure to taxanes (cabazitaxel, paclitaxel). Avoid. (Severe) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to taxanes (docetaxel). (Severe) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the concentration of temsirolimus. Avoid. (Severe) Study → Also see TABLE 15 p. 1378
- Mitotane decreases the exposure to tetracyclines (doxycycline). Monitor and adjust dose. (Moderate) Study
- Mitotane is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical
- Mitotane is predicted to markedly decrease the exposure to ticagrelor. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to tivozanib. (Severe) Study
- Mitotane is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to tolvapatan. Use with caution or avoid depending on indication. (Severe) Study
- Mitotane is predicted to decrease the exposure to toremifene. Adjust dose. (Moderate) Study
- Mitotane is predicted to decrease the exposure to trabectedin. Avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to vandetanib. Avoid. (Moderate) Study
- Mitotane is predicted to moderately decrease the exposure to velpatasavir. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to vemurafenib. Avoid. (Severe) Theoretical
- Mitotane is predicted to decrease the exposure to venetoclax. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vindeine). Avoid. (Moderate) Study → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to vinca alkaloids (vinflunine). Avoid. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to vinca alkaloids (vinorelbine). Use with caution or avoid. (Severe) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the exposure to vismodegib. Avoid. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Mitotane is predicted to decrease the concentration of vorinostatin. Monitor and adjust dose. (Moderate) Study
- Mitotane is predicted to decrease the concentration of v oralaprevir. Avoid. (Severe) Study
- Mitotane is predicted to decrease the exposure to zopiclone. Adjust dose. (Moderate) Study
- Mitoxantrone → see anthracyclines
- Mivacurium → see neuromuscular blocking drugs, non-depolarising
- Mizolastine → see antihistamines, non-sedating
Moclobemide: Moclobemide is claimed to cause less potentiation of the pressor effect of tyramine than the traditional (irreversible) MAOIs, but patients should avoid consuming large amounts of tyramine-rich foods such as mature cheese, salami, pickled herring, Bovril®, Oxo®️, Marmite®️️ or any similar meat or yeast extract or fermented soya bean extract, and some beers, lagers or wines.

- Moclobemide is predicted to increase the risk of a hypertensive crisis when given with amfetamines. Avoid. (Severe) Theoretical
- Amapalutamide is predicted to increase the exposure to moclobemide. Avoid or monitor. (MOD) Study
- Moclobemide is predicted to increase the risk of severe hypertension when given with bupropion. Avoid. (Severe) Theoretical
- Moclobemide is predicted to increase the exposure to clonazepam. Adjust dose. (Moderate) Theoretical
- Moclobemide is predicted to decrease the efficacy of clodipogrel. Avoid. (Moderate) Study
- Moclobemide is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Theoretical
- H₂ receptor antagonists (cimetidine) increase the exposure to moclobemide. Adjust moclobemide dose, p. 362. (MOD) Study
- Levodopa increases the risk of side-effects when given with moclobemide. (Moderate) Study
- Moclobemide is predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping moclobemide. (Severe) Theoretical
- Methylphenidate is predicted to increase the risk of a hypertensive crisis when given with moclobemide. (Severe) Theoretical
- Mianserin is predicted to increase the risk of toxicity when given with moclobemide. Avoid and for 1 week after stopping mianserin. (Severe) Theoretical
- Moclobemide is predicted to increase the effects of monoamine-oxidase B inhibitors (rasagiline, selegiline). Avoid. (Severe) Theoretical
- Moclobemide is predicted to increase the risk of side-effects when given with monoamine-oxidase B inhibitors (safinamide). Avoid and for 1 week after stopping safinamide. (Severe) Theoretical
- Opicapone is predicted to increase the risk of elevated blood pressure when given with moclobemide. Avoid. (Severe) Theoretical
- Moclobemide increases the risk of side-effects when given with phenothiazines (leomepromazine). (Moderate) Study
- Reboxetine is predicted to increase the risk of a hypertensive crisis when given with moclobemide. Avoid. (Severe) Theoretical
- Moclobemide moderately increases the exposure to ritazmethan. Avoid. (Moderate) Study
- Moclobemide moderately increases the exposure to sumatriptan. Avoid. (Moderate) Study
- Moclobemide is predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, vasconstrictor (ephedrine, isomethephene, phenylephrine, pseudoephedrine). Avoid. (Severe) Study
- Tricyclic antidepressants are predicted to increase the risk of severe toxic reaction when given with moclobemide. Avoid. (Severe) Theoretical
- Moclobemide slightly increases the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. (Moderate) Study
- Modafinil
  - Antiepileptics (carbamazepine, phenobarbital, primidone) are predicted to decrease the exposure to modafinil. (Mild) Theoretical
  - Antiepileptics (fosphenytoin, phenytoin) are predicted to decrease the exposure to modafinil and modafinil is predicted to increase the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to modafinil. (Mild) Theoretical
- Modafinil is predicted to decrease the exposure to bosutinib. Avoid. (Severe) Theoretical
- Cobicistat is predicted to increase the exposure to modafinil. Avoid. (Severe) Theoretical
- Modafinil is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Study
- Modafinil is predicted to increase the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Modafinil is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. (Severe) Theoretical
- Modafinil is predicted to decrease the exposure to elbasvir. Avoid. (Unknown) Theoretical
- Modafinil is predicted to decrease the efficacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Modafinil is predicted to increase the exposure to grazoprevir. Avoid. (Severe) Theoretical
- HIV- protease inhibitors are predicted to increase the exposure to modafinil. (Mild) Theoretical
- Modafinil is predicted to decrease the effects of hormone replacement therapy, (Moderate) Anecdotal
- Idelalisib is predicted to increase the exposure to modafinil. (Mild) Theoretical
- Modafinil is predicted to decrease the concentration of ketorolac. (Moderate) Theoretical
- Modafinil is predicted to decrease the efficacy of levonorogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Macrolides (clarithromycin) are predicted to increase the exposure to modafinil. (Mild) Theoretical
- Modafinil is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal
- Rifampicin is predicted to decrease the exposure to modafinil. (Moderate) Theoretical
- Modafinil is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Modafinil decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal
- Modafinil is predicted to decrease the exposure to velpatasvir. Avoid. (Severe) Theoretical
- Modafinil is predicted to decrease the concentration of voxilaprevir. Avoid. (Severe) Theoretical
- Mometasone: see corticosteroids

Moclobemide — Monoamine-oxidase A and B inhibitors, irreversible

Table 8 p. 1376 (hypotension), Table 13 p. 1378 (serotonin syndrome)

Isocarboxazid - phenelzine - tranylcypromine

Food and Lifestyle

Potentially life-threatening hypertensive crisis can develop in those taking MAOIs who eat tyramine-rich food (such as mature cheese, salami, pickled herring, Bovril®, Oxo®, Marmite®️️ or any similar meat or yeast extract or fermented soya bean extract, and some beers, lagers or wines). Avoid tyramine-rich or dopa-rich food or drinks with, or for 2 to 3 weeks after stopping, the MAOI.

- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the effects of alpha blockers (indomarin). Avoid. (Severe) Theoretical
- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of a hypertensive crisis when given with amfetamines. Avoid and for 14 days after stopping the MAOI. (Severe) Anecdotal
- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of severe toxic reaction when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. (Severe) Theoretical
Monoamine-oxidase A and B inhibitors, irreversible (continued)

- **Antiepileptics** *(phenobarbital, primidone)* are predicted to increase the effects of monoamine-oxidase A and B inhibitors, irreversible. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of antimuscarinic side-effects when given with *antihistamines, non-sedating*. Avoid. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of antimuscarinic side-effects when given with *antihistamines, sedating*. Avoid. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of side-effects when given with *Nefopam*. Avoid and for 2 weeks after stopping the MAOI. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of cardiovascular side-effects when given with *beta, agonists*. **(Moderate)** Anecdotal
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of severe hypotension when given with *Buspirone*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 8 p. 1376
- **Entacapone** is predicted to increase the risk of elevated blood pressure when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. **(Severe)** Anecdotal → Also see TABLE 13 p. 1378
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the effects of *Doxapram*. **(Moderate)**
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to decrease the antihypertensive effects of *guanethidine*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 8 p. 1376
- **Levodopa** increases the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Study → Also see TABLE 13 p. 1378
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of side-effects when given with *linezolid*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 8 p. 1376
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to alter the antihypertensive effects of *methyl dopa*. Avoid. **(Severe)** Theoretical → Also see TABLE 8 p. 1376
- **Methylphenidate** is predicted to increase the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Mianserin** is predicted to increase the risk of toxicity when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors (rasagline, selegiline)** are predicted to increase the risk of side-effects when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 8 p. 1376 → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors (safinamide)** are predicted to increase the risk of side-effects when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 1 week after stopping safinamide. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Nefopam** is predicted to increase the risk of serious elevations in blood pressure when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. **(Severe)** Theoretical
- **Opioids** are predicted to increase the risk of CNS excitation or depression when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of the syndrome when given with *beta, agonists*. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Phenoxybenzamine** is predicted to increase the risk of CNS excitation or depression when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. And for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Reboxetine** is predicted to increase the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the exposure to *rizatriptan*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical → Also see TABLE 8 p. 1376
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the exposure to *sumatriptan*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of hypertensive crisis when given with *sympathomimetics, inotropic*. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of a hypertensive crisis when given with *sympathomimetics, vasoconstrictor*. Avoid. And for 14 days after stopping the MAOI. **(Severe)** Study
- **Tetrabenazine** is predicted to increase the risk of CNS toxicity when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Tolcapone** is predicted to increase the effects of monoamine-oxidase A and B inhibitors, irreversible. Avoid. **(Severe)** Theoretical
- **Tricyclic antidepressants** are predicted to increase the risk of severe toxic reaction when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAOI. **(Severe)** Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the exposure to *zolmitriptan*. Avoid. **(Severe)** Theoretical
- **Monoamine-oxidase B inhibitors** are predicted to increase the effect of *rasagline, selegiline* (bradycardia), **(Severe)** TABLE 6 p. 1376 (hypotension), **(Severe)** TABLE 13 p. 1378 (serotonin syndrome)

rasagline - selegiline

**FOOD AND LIFESTYLE** Hypertension is predicted to occur when high-dose selegiline is taken with tyramine-rich foods (such as mature cheese, salami, pickled herring, *Bovril®, Oxo®, Marmite®* or any similar meat or yeast extract or fermented soya bean extract, and some beers, lagers or wines).

- **Monoamine-oxidase B inhibitors (rasagline, selegiline)** are predicted to increase the risk of severe hypertension when given with *amfetamines*. Avoid. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Safinamide** is predicted to increase the risk of severe hypertension when given with *amfetamines*. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors (rasagline, selegiline)** are predicted to increase the risk of severe hypertension when given with *beta, agonists*. Avoid. **(Severe)** Theoretical
- **Safinamide** is predicted to increase the risk of severe hypertension when given with *beta, agonists*. **(Severe)** Theoretical → Also see TABLE 13 p. 1378
- **Combined hormonal contraceptives slightly increase the exposure to rasagline. **(Moderate)** Study
- **Combined hormonal contraceptives increase the exposure to selegiline. Avoid. **(Severe)** Study
Hormone replacement therapy is predicted to increase the exposure to selegiline. Avoid. [Moderate: Study]

Monoamine-oxidase B inhibitors are predicted to increase the effects of levodopa. Adjust dose. [Mild: Study] → Also see TABLE 8 p. 1376.

Monoamine-oxidase B inhibitors (rasagiline, selegiline) are predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping the MAOI. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Safinamide is predicted to increase the risk of side-effects when given with linezolid. Avoid and for 1 week after stopping safinamide. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Monoamine-oxidase B inhibitors (rasagiline, selegiline) are predicted to increase the risk of a hypertensive crisis when given with methylphenidate. Avoid. [Severe: Theoretical]

Mexiteline slightly increases the exposure to rasagiline. [Moderate: Study]

Moclobemide is predicted to increase the effects of monoamine-oxidase B inhibitors (rasagiline, selegiline). Avoid. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Moclobemide is predicted to increase the risk of side-effects when given with safinamide. Avoid and for 1 week after stopping safinamide. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Monoamine-oxidase B inhibitors (rasagiline, selegiline) are predicted to increase the risk of side-effects when given with linezolid. Avoid and for 14 days after stopping the MAOI. [Severe: Theoretical] → Also see TABLE 8 p. 1376 → Also see TABLE 13 p. 1378.

Safinamide is predicted to increase the risk of side-effects when given with linezolid. Avoid and for 1 week after stopping safinamide. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Rasagiline is predicted to increase the risk of side-effects when given with opioids (pethidine). Avoid and for 14 days after stopping rasagiline. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Safinamide is predicted to increase the risk of side-effects when given with opioids (pethidine). Avoid and for 1 week after stopping safinamide. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Selelgiline increases the risk of side-effects when given with opioids (pethidine). Avoid. [Severe: Anecdotal] → Also see TABLE 13 p. 1378.

Quinolones (ciprofloxacin) slightly increase the exposure to rasagiline. [Moderate: Study]

Reboxetine is predicted to increase the risk of a hypertensive crisis when given with monoamine-oxidase A and B inhibitors, reversible. Avoid and for 14 days after stopping reboxetine. [Severe: Theoretical] → Also see TABLE 13 p. 1378.

Monoamine-oxidase B inhibitors are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, inotropic. Avoid. [Severe: Anecdotal]

Monoamine-oxidase B inhibitors are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, vasoconstrictor. Avoid. [Severe: Anecdotal]

Monovalent antibodies → see TABLE 15 p. 1378 (myelosuppression), TABLE 12 p. 1378 (peripheral neuropathy), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 4 p. 1375 (antiplaquelet effects)

adalimumab, alemtuzumab, atezolizumab, avadelumab, basiliximab, belimumab, bevacizumab, binatumab, brentuximab vedotin, brodalumab, canakinumab, certolizumab pegol, cetuximab, daratumumab, dinutuzumab, dupilumab, durvalumab, eculizumab, elotuzumab, golimumab, guselukimab, infliximab, inotuzumab ozogamicin, ipilimumab, ixekizumab, natalizumab, necitumumab, nivolumab, obinutuzumab, ocrolizumab, olaratumab, panitumumab, pembrolizumab, pertuzumab, ramucirumab, rituximab, sarilumab, secukinumab, siuximizum, tildrakizumab, tocilizumab, trastuzumab, trastuzumab emtansine, ustekinumab, vedolizumab

Abatacept is predicted to increase the risk of generalised infection (possibly life-threatening) when given with golimumab. Avoid. [Severe: Theoretical]

Tocilizumab is predicted to increase the exposure to abatacept. Monitor and adjust dose. [Moderate: Theoretical]

Blinatumumab is predicted to transiently increase the exposure to aminophylline. Monitor and adjust dose. [Moderate: Theoretical]

Sarilumab potentially affects the exposure to aminophylline. Monitor and adjust dose. [Moderate: Theoretical]

Tocilizumab is predicted to decrease the exposure to aminophylline. Monitor and adjust dose. [Moderate: Theoretical]

Anakinra is predicted to increase the risk of generalised infection (possibly life-threatening) when given with golimumab. Avoid. [Severe: Theoretical]

Anthracyclines are predicted to increase the risk of cardiotoxicity when given with monoclonal antibodies (trastuzumab, trastuzumab emtansine). Avoid. [Severe: Theoretical] → Also see TABLE 15 p. 1378.

Antihypertensives (dronedarone) increase the risk of neutropenia when given with brentuximab vedotin. Monitor and adjust dose. [Severe: Theoretical]

Antiepileptics (carbamazepine) are predicted to decrease the effects of brentuximab vedotin. [Severe: Theoretical]

Tocilizumab is predicted to decrease the exposure to antiepileptics (fosphenytoin, phenytoin). Monitor and adjust dose. [Moderate: Theoretical]

Antifungals, azoles (itraconazole, ketoconazole) increase the risk of neutropenia when given with brentuximab vedotin. Monitor and adjust dose. [Severe: Study]

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to trastuzumab emtansine. Avoid. [Severe: Theoretical]

Brentuximab vedotin increases the risk of pulmonary toxicity when given with bleomycin. Avoid. [Severe: Study] → Also see TABLE 15 p. 1378.

Tocilizumab is predicted to decrease the exposure to calcium channel blockers. Monitor and adjust dose. [Moderate: Theoretical]

Blinatumumab is predicted to transiently increase the exposure to ciclosporin. Monitor and adjust dose. [Moderate: Theoretical]

Sarilumab potentially affects the exposure to ciclosporin. Monitor and adjust dose. [Severe: Theoretical]

Tocilizumab is predicted to decrease the exposure to ciclosporin. Monitor and adjust dose. [Moderate: Theoretical]

Cobicistat is predicted to increase the exposure to trastuzumab emtansine. Avoid. [Severe: Theoretical]

Sarilumab potentially decreases the exposure to combined hormonal contraceptives. [Severe: Theoretical]

Corticosteroids are predicted to increase the risk of immunosuppression when given with dinutuzumab. Avoid except in life-threatening situations. [Severe: Theoretical]

Corticosteroids (betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisolone) are predicted to decrease the efficacy of monoclonal antibodies (atezolizumab, ipilimumab, nivolumab, pembrolizumab). Use with caution or avoid. [Severe: Theoretical]

Tocilizumab is predicted to decrease the exposure to corticosteroids (dexamethasone, methylprednisolone). Monitor and adjust dose. [Moderate: Theoretical]

Blinatumumab is predicted to transiently increase the exposure to coumarins (warfarin). Monitor and adjust dose. [Severe: Theoretical]

Sarilumab potentially affects the exposure to coumarins (warfarin). Monitor and adjust dose. [Moderate: Theoretical]

Tocilizumab is predicted to decrease the exposure to coumarins (warfarin). Monitor and adjust dose. [Moderate: Theoretical]

Tocilizumab is predicted to decrease the exposure to diazepam. Monitor and adjust dose. [Moderate: Theoretical]

HIV- protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the risk of neutropenia when given with brentuximab vedotin. Monitor and adjust dose. [Severe: Study]

HIV- protease inhibitors are predicted to increase the exposure to trastuzumab emtansine. Avoid. [Severe: Theoretical]

Idelalisib is predicted to increase the exposure to trastuzumab emtansine. Avoid. [Severe: Theoretical] → Also see TABLE 15 p. 1378.

Immunoglobulins are predicted to alter the effects of dinutuzumab. Avoid. [Severe: Theoretical]

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with monoclonal antibodies. Public Health England advises avoid (refer to Green Book). [Severe: Theoretical]
Monoclonal antibodies (continued)

- **Macrolides (clarithromycin)** increase the risk of neutropenia when given with brentuximab vedotin. Monitor and adjust dose. (Severe) Theoretical

- **Macrolides (erythromycin)** may increase the exposure to trastuzumab emtansine. Avoid. (Severe) Theoretical

- **Tocilizumab** is predicted to decrease the exposure to midazolam. Monitor and adjust dose. (Moderate) Theoretical

- **Rifampicin** decreases the effects of brentuximab vedotin. (Severe) Study

- **Sarilumab** potentially affects the exposure to sirolimus. Monitor and adjust dose. (Moderate) Theoretical

- **Sarilumab** is predicted to decrease the exposure to statins (atorvastatin, simvastatin). Monitor and adjust dose. (Moderate) Study

- **Tocilizumab** is predicted to decrease the exposure to statins (atorvastatin, simvastatin). Monitor and adjust dose. (Moderate) Study

- **Sarilumab** potentially affects the exposure to tacrolimus. Monitor and adjust dose. (Moderate) Theoretical

- **Blinatumomab** is predicted to transiently increase the exposure to theophylline. Monitor and adjust dose. (Moderate) Theoretical

- **Sarilumab** potentially affects the exposure to theophylline. Monitor and adjust dose. (Moderate) Theoretical

- **Tocilizumab** is predicted to decrease the exposure to theophylline. Monitor and adjust dose. (Moderate) Theoretical

**Montelukast**

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to markedly increase the exposure to montelukast. (Severe) Study

- **Clopidogrel** is predicted to moderately increase the exposure to montelukast. (Moderate) Study

- **Enzalutamide** is predicted to decrease the exposure to montelukast. (Mild) Study

- **Fibrate (gemfibrozil)** are predicted to moderately increase the exposure to montelukast. (Moderate) Study

- **Leflunomide** is predicted to increase the exposure to montelukast. (Moderate) Theoretical

- **Teriflunomide** is predicted to decrease the effects of montelukast. (Moderate) Theoretical

- **Methotrexate** is predicted to increase the risk of haematological toxicity when given with amfetamines. (Severe) Theoretical

- **Naltrexone**

  - **GENERAL INFORMATION** Discontinue treatment 1 week before anticipated use of opioids; if emergency analgesia is required during treatment, an increased dose of opioid analgesic might be necessary (monitor for opioid intoxication).

- **Nalmefene** is predicted to decrease the efficacy of opioids. Avoid. (Severe) Theoretical

**Naloxegol**

- **Antiarhythms (dronedarone)** are predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to markedly decrease the exposure to naloxegol. Avoid. (Moderate) Study

- **Antifungals, azoles (itraconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Cobicistat** is predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

- **Crizotinib** is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Enzalutamide** is predicted to markedly decrease the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Grapefruit juice** is predicted to increase the exposure to naloxegol. Avoid. (Severe) Study

- **HIV-protease inhibitors** are predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

- **Idealisib** is predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

- **Imatinib** is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Macrolides (clarithromycin)** are predicted to markedly increase the exposure to naloxegol. Avoid. (Severe) Study

- **Macrolides (erythromycin)** are predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Mefloquine** is predicted to markedly decrease the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Nexavar** is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Nilotinib** is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

- **Valacyclovir** is predicted to increase the exposure to naloxegol. Adjust naloxegol dose and monitor side effects, p. 65. (Moderate) Study

**Naloxone**

- **GENERAL INFORMATION** Avoid concurrent use of opioids.

**Nandrolone**

- **Nandrolone** is predicted to increase the anticoagulant effect of coumarins. Monitor and adjust dose. (Severe) Theoretical

- **Mycophenolate** is predicted to increase the risk of haematological toxicity when given with valganciclovir. (Moderate) Theoretical → Also see TABLE 15 p. 1378

- **Nabumetone** → see NSAIDs

- **Nadolol** → see beta blockers, non-selective

- **Naltrexone**

  - **GENERAL INFORMATION** Avoid concurrent use of opioids.
Nandrolone is predicted to increase the anticoagulant effect of phenindione. Monitor and adjust dose. [Severe] Theoretical

Naproxen  → see NSAIDs

Naratiprant  → see TABLE 13 p. 1378 (serotonin syndrome)

Naratiprant is predicted to increase the risk of vasodilation when given with ergotamine. Separate administration by 24 hours. [Severe] Theoretical

Natalizumab  → see monoclonal antibodies

Nateglinide  → see TABLE 14 p. 1378 (antidiabetic drugs)

Anti-epileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to slightly decrease the exposure to nateglinide. [Mild] Study

Enalaprilat is predicted to slightly decrease the exposure to nateglinide. [Mild] Study

Leflunomide is predicted to increase the exposure to nateglinide. [Moderate] Theoretical

Miotane is predicted to slightly decrease the exposure to nateglinide. [Mild] Study

Rifampicin is predicted to slightly decrease the exposure to nateglinide. [Mild] Study

Teriflunomide is predicted to increase the exposure to nateglinide. [Moderate] Theoretical

Nebivolol  → see beta blockers, selective

Nectumumab  → see monoclonal antibodies

Nefopam  → see TABLE 10 p. 1377 (anxiolytics/narcotics)

Nefopam is predicted to increase the risk of serious elevations in blood pressure when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. [Severe] Theoretical

Neolarabine  → see TABLE 15 p. 1378 (myelosuppression)

Neomycin  → see TABLE 2 p. 1375 (nephrotoxicity), TABLE 19 p. 1379 (toxicity), TABLE 20 p. 1379 (neuromuscular blocking effects)

ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

Neomycin decreases the absorption of digoxin. [Moderate] Study

Neomycin moderately decreases the exposure to sorafenib. [Moderate] Study

Neostigmine  → see TABLE 6 p. 1376 (brady/cardia)

Aminoglycosides are predicted to decrease the effects of neostigmine. [Moderate] Theoretical

Nepafenac  → see NSAIDs

Netupitant  → see TABLE 13 p. 1378 (serotonin syndrome)

Netupitant is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical

Netupitant is predicted to increase the exposure to beta2 agonists (salmeterol). [Moderate] Study

Bosentan is predicted to decrease the exposure to netupitant. [Moderate] Theoretical

Netupitant is predicted to increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Theoretical

Netupitant is predicted to increase the exposure to buspirone. Avoid or adjust dose. [Moderate] Study

Netupitant is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical

Netupitant is predicted to increase the exposure to calcium channel blockers (lamotrigine, felodipine, nifedipine, nimodipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

Netupitant is predicted to increase the exposure to cariprazine. Avoid. [Severe] Study

Netupitant is predicted to increase the exposure to ceritinib. [Moderate] Theoretical

Netupitant is predicted to increase the concentration of ciclosporin. [Severe] Study

Cobicistat is predicted to increase the exposure to netupitant. [Moderate] Study

Netupitant is predicted to increase the exposure to cobimetinib. [Severe] Theoretical

Netupitant is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 1120. [Severe] Study

Netupitant is predicted to increase the exposure to oral corticosteroids (budesonide). [Moderate] Study

Netupitant is predicted to increase the exposure to corticosteroids (dexamethasone). Adjust dose. [Moderate] Study

Netupitant is predicted to increase the exposure to corticosteroids (fluticasone). [Moderate] Study

Netupitant is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. [Moderate] Study

Netupitant is predicted to slightly increase the exposure to darifenacin. [Moderate] Study

Netupitant is predicted to increase the exposure to dasatinib. [Severe] Study

Netupitant increases the risk of QT-prolongation when given with domperidone. Avoid. [Severe] Study

Netupitant is predicted to increase the exposure to dopamine receptor agonists (bromocriptine). [Severe] Theoretical

Netupitant is predicted to increase the concentration of dopamine receptor agonists (cabergoline). [Moderate] Anecdotal

Netupitant is predicted to moderately increase the exposure to dutasteride. [Mild] Study

Efavirenz is predicted to decrease the exposure to netupitant. [Moderate] Theoretical

Netupitant is predicted to increase the exposure to elotristat. [Moderate] Study

Netupitant is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. [Severe] Study

Netupitant is predicted to moderately increase the exposure to encorafenib. [Moderate] Study

Enalaprilat is predicted to decrease the exposure to netupitant. Avoid. [Severe] Study

Netupitant is predicted to increase the risk of ergotism when given with ergometrine. [Severe] Theoretical

Netupitant is predicted to increase the risk of ergotism when given with ergotamine. [Severe] Theoretical

Netupitant is predicted to increase the exposure to erlotinib. [Moderate] Theoretical

Netupitant slightly increases the exposure to etoposide. [Mild] Study

Netupitant is predicted to increase the concentration of everolimus. Avoid or adjust dose. [Moderate] Study

Netupitant is predicted to increase the exposure to fesoterodine. Adjust fesoterodine dose with moderate inhibitors of CYP3A4 in hepatic and renal impairment, p. 777. [Mild] Study
Netupitant is predicted to increase the exposure to gefitinib. (Moderate) Theoretical

Netupitant is predicted to increase the concentration of guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Theoretical

Netupitant is predicted to increase the concentration of prilosec. Avoid prilosec dose, p. 159. (Severe) Theoretical

Netupitant is predicted to increase the exposure to irinotecan. (Moderate) Study

Netupitant is predicted to increase the exposure to lapatinib. (Moderate) Study

Netupitant is predicted to increase the exposure to lomitapide. Avoid. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to nilotinib. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study

Netupitant is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical

Netupitant is predicted to increase the exposure to oxybutynin. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to pazopanib. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil). Adjust avanafil dose, p. 812. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. (Moderate) Study

Netupitant is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (tadalafil). (Severe) Theoretical

Netupitant is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (vardenafil). Adjust dose. (Severe) Theoretical

Netupitant is predicted to increase the exposure to pimozide. Avoid. (Severe) Theoretical

Netupitant is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study

Netupitant is predicted to increase the exposure to ranolazine. (Severe) Study

Netupitant is predicted to increase the exposure to ribociclib. (Moderate) Study

Rifampicin is predicted to decrease the exposure to netupitant. Avoid. (Severe) Study

Netupitant is predicted to increase the exposure to ruxolitinib. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to saxagliptin. (Mild) Study

Netupitant increases the concentration of sirolimus. Monitor and adjust dose. (Severe) Study

Netupitant is predicted to increase the exposure to SSRIs. (dapoxetine). Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. (Moderate) Theoretical

St John’s Wort is predicted to decrease the exposure to netupitant. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to statins (atorvastatin). Monitor and adjust dose. (Severe) Study

Netupitant is predicted to increase the exposure to statins (simvastatin). Use with caution and adjust simvastatin dose, p. 205. (Severe) Study

Netupitant is predicted to increase the exposure to sunifatinib. (Moderate) Theoretical

Netupitant is predicted to increase the concentration of tacrolimus. (Severe) Study

Netupitant is predicted to increase the exposure to taxanes (cabazitaxel). (Moderate) Theoretical

Netupitant is predicted to increase the concentration of temsirolimus. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to tezacafator. Adjust tezacafator with ivacafar p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study

Netupitant is predicted to increase the concentration of tensirolimus. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Netupitant is predicted to increase the exposure to tolterodine. (Mild) Theoretical

Netupitant is predicted to increase the exposure to tolvaptan. Manufacturer advises caution or adjust tolvaptan dose with moderate inhibitors of CYP3A4, p. 666. (Moderate) Study

Netupitant is predicted to increase the exposure to trazodone. (Moderate) Theoretical

Netupitant is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

Netupitant is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. (Severe) Study

Netupitant is predicted to increase the exposure to vinca alkaloids. (Severe) Theoretical

Netupitant is predicted to increase the exposure to zopiclone. Adjust dose. (Moderate) Study

Neuromuscular blocking drugs, non-depolarising → see TABLE 6 p. 1376 (bradycardia), TABLE 20 p. 1379 (neuromuscular blocking effects)

atrocurium - cisatracurium - mivacurium - pancuronium - rocuronium

Anticholinesterases, centrally acting are predicted to decrease the effects of neuromuscular blocking drugs, non-depolarising. (Moderate) Theoretical → Also see TABLE 6 p. 1376

Antiepileptics (carbamazepine) are predicted to decrease the effects of (but acute use increases the effects of) neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium). Monitor and adjust dose. (Moderate) Study

Antiepileptics (fosphenytoin, phenytoin) decrease the effects of (but acute use increases the effects of) neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium). (Moderate) Study

Clindamycin increases the effects of neuromuscular blocking drugs, non-depolarising. (Severe) Anecdotal

Corticosteroids are predicted to decrease the effects of neuromuscular blocking drugs, non-depolarising. (Severe) Anecdotal
Neuromuscular blocking drugs, non-depolarising — Nevirapine

- Nevirapine is predicted to decrease the exposure to antifungals, azoles (fluconazole) slightly to moderately increase the exposure to nevirapine. Monitor and adjust dose. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to antifungals, azoles (itraconazole), azoles (ketoconazole). Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to azoles (itraconazole), azoles (ketoconazole). Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to bedaquiline. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to bosutinib. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to cariprazine. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the effect of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Nevirapine is predicted to decrease the efficacy of magnesium. Theoretical
- Nevirapine is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- Nevirapine is predicted to decrease the exposure to dasabuvir. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to dasatinib. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Nevirapine decreases the exposure to doravirine. Adjust dose. (Severe) Study
- Nevirapine is predicted to decrease the exposure to elbasvir. Avoid. (Severe) Study
- Nevirapine is predicted to decrease the exposure to eliglustat. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the concentration of elvitegravir. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to fosaprepitant. (Moderate) Theoretical
- Nevirapine is predicted to decrease the exposure to gefitinib. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to glecaprevir. Avoid. (Severe) Study
- Nevirapine is predicted to markedly decrease the exposure to grazoprevir. Avoid. (Severe) Study
- Nevirapine is predicted to decrease the concentration of guanfacine. Adjust dose. (Moderate) Theoretical
- Nevirapine decreases the exposure to HIV-protease inhibitors. Refer to specialist literature. (Moderate) Study
- Nevirapine is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal
- Nevirapine is predicted to decrease the exposure to idelalisib. Avoid. (Moderate) Theoretical
- Nevirapine is predicted to decrease the exposure to imatinib. Avoid. (Moderate) Study
- Nevirapine is predicted to decrease the exposure to ivacaftor. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to lapatinib. Avoid. (Severe) Study
- Nevirapine is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to lurasidone. Monitor and adjust dose. (Moderate) Theoretical
- Nevirapine decreases the exposure to macrolides (clarithromycin). (Moderate) Study
- Nevirapine decreases the concentration of midazolam. Monitor and adjust dose. (Moderate) Study
- Mitotane is predicted to decrease the exposure to nevirapine. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the exposure to netupitant. (Moderate) Theoretical
- Nevirapine is predicted to decrease the exposure to nilotinib. Avoid. (Severe) Theoretical
- Nevirapine is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal
- Nevirapine is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
Nevirapine (continued)

Nevirapine is predicted to decrease the exposure to omibitasvir. Avoid. [Moderate] Theoretical

Nevirapine decreases the exposure to opioids (methadone). Monitor and adjust dose. [Severe] Study

Nevirapine is predicted to decrease the exposure to osimertinib. [Severe] Theoretical

Nevirapine is predicted to decrease the exposure to ospemifene. [Moderate] Study

Nevirapine is predicted to decrease the exposure to paritaprevir (with ritonavir and omibitasvir). Avoid. [Severe] Study

Nevirapine is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to ribociclib. [Severe] Study

Nevirapine is predicted to decrease the exposure to rolapitant. Avoid. [Severe] Study

Nevirapine is predicted to decrease the exposure to ruxolitinib. Monitor and adjust dose. [Moderate] Theoretical

Nevirapine is predicted to decrease the concentration of sirolimus. Monitor and adjust dose. [Moderate] Theoretical

St John’s Wort is predicted to decrease the concentration of nevirapine. Avoid. [Severe] Theoretical

Nevirapine slightly decreases the exposure to statins (atorvastatin). [Mild] Study

Nevirapine moderately decreases the exposure to statins (simvastatin). [Moderate] Study

Nevirapine is predicted to decrease the concentration of tacrolimus. Monitor and adjust dose. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to taxanes (cabazitaxel). Avoid. [Severe] Study

Nevirapine is predicted to decrease the concentration of temsirolimus. Avoid. [Severe] Theoretical

Nevirapine is predicted to decrease the exposure to ticagrelor. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to tofacitinib. [Moderate] Study

Nevirapine decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

Nevirapine is predicted to decrease the exposure to velpatasvir. Avoid. [Moderate] Theoretical

Nevirapine is predicted to decrease the exposure to venoclax. Avoid. [Severe] Study

Nevirapine is predicted to decrease the concentration of vorapaxir. Avoid. [Severe] Theoretical

Nevirapine is predicted to decrease the concentration of zidovudine. Refer to specialist literature. [Severe] Theoretical

Nicardipine → see calcium channel blockers

Nicorandil → see TABLE 8 p. 1376 (hypotension)

Aspirin is predicted to increase the risk of gastrointestinal perforation when given with nicorandil. [Severe] Theoretical

Corticosteroids increase the risk of gastrointestinal perforation when given with nicorandil. [Severe] Anecdotal

Nicorandil is predicted to increase the risk of gastrointestinal perforation when given with NSAIDs. [Severe] Theoretical

Nicorandil is predicted to increase the risk of hypotension when given with phosphodiesterase type-5 inhibitors. Avoid. [Severe] Theoretical → Also see TABLE 8 p. 1376

Nicotinic acid → see TABLE 3 p. 1375 (anticoagulant effects)

Nicotinic acid is predicted to increase the risk of rhabdomyolysis when given with statins. [Severe] Theoretical

Nifedipine → see calcium channel blockers

Nilotinib → see TABLE 15 p. 1378 (myelosuppression), TABLE 9 p. 1377 (QT-interval prolongation)

Nilotinib is predicted to increase the exposure to abemaciclib. [Moderate] Study

Nilotinib is predicted to increase the exposure to aldosterone antagonists (epileron). Adjust epileron dose, p. 193. [Severe] Study

Nilotinib is predicted to increase the exposure to alpha blockers (tamsulosin). [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to alprazolam. [Severe] Study

Antacids is predicted to decrease the absorption of nilotinib. Separate administration by at least 2 hours. [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to antiarrhythmics (propafenone). Monitor and adjust dose. [Moderate] Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to nilotinib. Avoid. [Severe] Study

Antifungals, azoles (fluconazole, posaconazole) are predicted to increase the exposure to nilotinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to nilotinib. Avoid. [Severe] Study → Also see TABLE 9 p. 1377

Nilotinib is predicted to increase the exposure to antituberculars, non-sedating (rifampicin). [Severe] Study

Nilotinib is predicted to increase the exposure to antituberculars, non-sedating (rupatadine). Avoid. [Moderate] Study

Nilotinib is predicted to increase the concentration of antimarials (piperazine). [Severe] Theoretical

Aprepitant is predicted to increase the exposure to nilotinib. [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to axitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378

Nilotinib is predicted to increase the exposure to bedaquiline. Avoid prolonged use. [Mild] Theoretical → Also see TABLE 9 p. 1377

Bosentan is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical

Nilotinib is predicted to increase the exposure to bosutinib. Avoid or adjust dose. [Severe] Theoretical → Also see TABLE 15 p. 1378

Nilotinib is predicted to increase the exposure to buprionate.

Use with caution and adjust dose. [Moderate] Study

Nilotinib is predicted to increase the exposure to cabozantinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to nilotinib. [Moderate] Theoretical

Nilotinib is predicted to increase the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Study

Nilotinib is predicted to increase the exposure to cariprazine. Avoid. [Severe] Study

Nilotinib is predicted to increase the exposure to ceritinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377

Nilotinib is predicted to increase the concentration of ciclosporin. [Severe] Study

Cobicistat is predicted to moderately increase the exposure to nilotinib. Avoid. [Severe] Study

Nilotinib is predicted to increase the exposure to cobimetinib. [Severe] Theoretical

Nilotinib is predicted to increase the exposure to colchicine. Adjust colchicine dose with moderate inhibitors of CYP3A4, p. 120. [Severe] Study

Nilotinib is predicted to increase the exposure to corticosteroids (methylprednisolone). Monitor and adjust dose. [Moderate] Study

Nilotinib is predicted to increase the risk of bleeding events when given with coumarins. [Severe] Theoretical

Nilotinib is predicted to slightly increase the exposure to darifenacin. [Moderate] Study

Nilotinib is predicted to increase the exposure to dasatinib. [Severe] Study → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377
Nilotinib increases the risk of QT prolongation when given with **dopamine receptor agonists (bromocriptine).** Avoid. [Severe] Study

- **Nilotinib** is predicted to increase the exposure to dopamine receptor agonists (cabergoline). [Moderate] Acetadote
- **Nilotinib** is predicted to moderately decrease the exposure to **duasteride.** [Mild] Study
- **Efavirenz** is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **eplerenone.** Avoid or adjust dose—consult product literature. [Severe] Study
- **Nilotinib** is predicted to moderately decrease the exposure to **encorafenib.** [Moderate] Study → Also see TABLE 9 p. 1377
- **Enalapril** is predicted to moderately decrease the exposure to nilotinib. Avoid. [Severe] Study

**Nilotinib** is predicted to increase the risk of ergotism when given with **ergotamine.** [Severe] Theoretical

- **Nilotinib** is predicted to increase the exposure to **erlotinib.** [Moderate] Theoretical
- **Nilotinib** is predicted to increase the concentration of **everolimus.** Avoid or adjust dose. [Moderate] Study → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the exposure to **fesoterodine.** Adjust **fesoterodine** dose with moderate inhibitors of CYP3A4, p. 983. [Severe] Study → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the exposure to **ibrutinib.** Adjust **ibrutinib** dose with moderate inhibitors of CYP3A4, p. 983. [Severe] Study → Also see TABLE 15 p. 1378
- **Idealisib** is predicted to moderately increase the exposure to **nilotinib.** Avoid. [Severe] Study → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **ibrutinib.** Adjust **ibrutinib** dose with moderate inhibitors of CYP3A4, p. 983. [Severe] Study → Also see TABLE 15 p. 1378
- **Idealisib** is predicted to moderately increase the exposure to nilotinib. Avoid. [Severe] Study → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **ibandronate.** Adjust **ibandronate** dose, p. 211. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **icavacaptor.** Adjust **icavacaptor** p. 293 or **tezacaftor with ivacaftor** p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to **lappatinib.** [Moderate] Study → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **lomitapide.** Avoid. [Moderate] Theoretical
- **Nilotinib** is predicted to increase the exposure to **lorazepam.** Avoid. [Moderate] Study
- **Macrolides (clarithromycin)** are predicted to moderately increase the exposure to nilotinib. Avoid. [Severe] Study → Also see TABLE 9 p. 1377
- **Macrolides (erythromycin)** are predicted to increase the exposure to nilotinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to decrease the exposure to **midazolam.** Monitor side effects and adjust dose. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to **midostaurin.** [Moderate] Theoretical
- **Mitottane** is predicted to moderately decrease the exposure to nilotinib. Avoid. [Severe] Study → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the exposure to **naloxegol.** Adjust **naloxegol** dose and monitor side effects, p. 65. [Moderate] Study
- **Netupitant** is predicted to increase the exposure to nilotinib. [Moderate] Theoretical
- **Nevirapine** is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical

- **Nilotinib** is predicted to increase the exposure to **olaparib.** Avoid moderate inhibitors of CYP3A4 or adjust **olaparib** dose, p. 1005. [Moderate] Theoretical → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the exposure to **opioids (alfentanil, buprenorphine, fentanyl, oxycodone).** Monitor and adjust dose. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to **opioids (methadone, sufentanil).** [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **oxybutynin.** [Mild] Theoretical
- **Nilotinib** is predicted to increase the exposure to **pazopanib.** [Moderate] Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the risk of bleeding events when given with **phenindione.** [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors (avanaflif).** Adjust **avanaflif** dose, p. 812. [Moderate] Theoretical
- **Nilotinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors (sildenafil).** Monitor or adjust **sildenafil** dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **phosphodiesterase type-5 inhibitors (vardenif).** Adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **pimozide.** Avoid. [Severe] Theoretical → Also see TABLE 9 p. 1377
- **Prilocain** is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **quetiapine.** Avoid. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to **ranolazine.** Avoid. [Severe] Study → Also see TABLE 9 p. 1377
- **Rifampicin** is predicted to moderately decrease the exposure to nilotinib. Avoid. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to **rubicon.** [Moderate] Study → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the exposure to **saxagliptin.** [Mild] Study
- **Nilotinib** increases the concentration of **sirolimus.** Monitor and adjust dose. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to **SSRIs (dopoxetin).** Adjust **dopoxetin** dose with moderate inhibitors of CYP3A4, p. 821. [Moderate] Theoretical
- **St John’s Wort** is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **statins (atorvastatin).** Monitor and adjust dose. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to **statins (simvastatin).** Use with caution and adjust **simvastatin** dose, p. 206. [Severe] Study
- **Nilotinib** is predicted to increase the exposure to **sunitinib.** [Moderate] Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377
- **Nilotinib** is predicted to increase the concentration of **tacrolimus.** [Severe] Theoretical
- **Nilotinib** is predicted to increase the exposure to **taxanes (cabazitaxel).** [Moderate] Theoretical → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the concentration of **tepsirostrum.** [Moderate] Theoretical → Also see TABLE 15 p. 1378
- **Nilotinib** is predicted to increase the exposure to **tezacaftor.** Adjust **tezacaftor with ivacaftor** p. 295 dose with moderate inhibitors of CYP3A4. [Severe] Study
- **Nilotinib** given with a potent CYP3A4 inhibitor is predicted to increase the exposure to **tofacitinib.** Adjust **tofacitinib** dose, p. 1105. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to **tolerodine.** [Mild] Theoretical → Also see TABLE 9 p. 1377
Nilotinib (continued)

- Nitrates are predicted to increase the risk of methaemoglobinaemia when given with dipson. Severe
- Theoretical

- Nitrates potentially increase the risk of hypotension when given with phosphodiesterase type-5 inhibitors. Avoid. Severe
- Study → Also see TABLE 8 p. 1376

Nitrazepam → see TABLE 11 p. 1377 (CNS depressant effects)

- Rifampicin increases the clearance of nitrazepam. Moderate Study

- Nitrofurantoin → see TABLE 12 p. 1378 (peripheral neuropathy)

- Nitrofurantoin is predicted to increase the risk of methaemoglobinaemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. Severe Theoretical

- Antacids (magnesium trisilicate) decrease the absorption of nitrofurantoin. Moderate Study

- Nitrofurantoin is predicted to increase the risk of methaemoglobinaemia when given with dipson. Severe
- Theoretical

- Nitrous oxide → see TABLE B p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)

- Nitrous oxide potentially increases the risk of methotrexate toxicity when given with methotrexate. Avoid. Severe Study

- Nivolumab → see monoclonal antibodies

- Nizatidine → see H₂ receptor antagonists

- Noradrenaline/norepinephrine → see sympathomimetics, vasoconstrictor

Norethisterone

- Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) are predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Aprepitant is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Bosantan is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Efavirenz is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Fosaprepitant is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Gabeefulvin potentially decreases the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- HIV-protease inhibitors (ritonavir) are predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Mifepristone potentially increases the risk of methotrexate toxicity when given with methotrexate. Avoid. Severe Study

- Modafinil is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Nevirapine is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Rifabutin is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Rifampicin is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- St John’s Wort is predicted to decrease the efficacy of norethisterone. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p. 794. Severe Anecdotal

- Sugammadex is predicted to decrease the exposure to norethisterone. Use additional contraceptive precautions. Severe Theoretical

- Ulipristal is predicted to decrease the efficacy of norethisterone. Avoid. Severe Theoretical

NSAIDs → see TABLE 18 p. 1379 (hypotension), TABLE 2 p. 1375 (nephrotoxicity), TABLE 16 p. 1379 (increased serum potassium), TABLE 4 p. 1375 (antiplatelet effects)
aceclofenac • benzydamine • bromfenac • celecoxib • dexibuprofen • dexketoprofen • diclofenac • etodolac • etoricoxib • flurbiprofen • ibuprofen • indometacin • ketoprofen • ketorolac • mefenamic acid • meloxicam • nabumetone • naproxen • nepafenac • parecoxib • piroxicam • sulindac • tenoxicam • tiaprofenic acid • tolprofen acid

- Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
- Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

- Celecoxib is predicted to increase the exposure to antiarhythmics (flecainide, propafenone). Monitor and adjust dose. (Moderate) Theoretical
- Antifungals, azoles (flucanazole) moderately increase the exposure to celecoxib. Adjust celecoxib dose, p. 1132. (Moderate) Study
- Antifungals, azoles (voriconazole) moderately increase the exposure to ibuprofen. Adjust dose. (Moderate) Study
- NSAIDs are predicted to increase the risk of gastrointestinal irritation when given with bisphosphonates (alendronic acid, ibandronic acid). (Moderate) Study
- NSAIDs are predicted to increase the risk of renal impairment when given with bisphosphonates (sodium clodronate). Severe Theoretical
- Ceritinib is predicted to increase the exposure to NSAIAs (celecoxib, diclofenac). Adjust dose. (Moderate) Theoretical
- Ciclesonin increases the concentration of diclofenac. Severe Study → Also see TABLE 2 p. 1375 → Also see TABLE 16 p. 1379
- Etoricoxib slightly increases the exposure to combined hormonal contraceptives. (Moderate) Study
- NSAIDs increase the risk of gastrointestinal bleeding when given with corticosteroids. (Severe) Study
- NSAIDs increase the risk of renal impairment when given with daptomycin. (Moderate) Theoretical
- Indometacin increases the concentration of digoxin. Severe
- Erlotinib is predicted to increase the risk of gastrointestinal perforation when given with NSAIAs. Severe Theoretical
- Etoricoxib slightly increases the exposure to hormone replacement therapy. (Moderate) Study
- NSAIDs are predicted to increase the risk of gastrointestinal bleeding when given with iron chelators (deferasirox). Severe Theoretical
- Leflunomide is predicted to increase the exposure to NSAIAs (indomethacin, ketoprofen). (Moderate) Theoretical
- NSAIDs increase the concentration of lithium. Monitor and adjust dose. (Severe) Study
- NSAIDs are predicted to increase the risk of toxicity when given with methotrexate. Severe Study → Also see TABLE 2 p. 1375
- NSAIDs (high-dose) are predicted to decrease the efficacy of mifamurtide. Avoid. (Severe) Theoretical
- Nicardipin is predicted to increase the risk of gastrointestinal perforation when given with NSAIAs. Severe Theoretical
- NSAIDs are predicted to increase the exposure to pemetrexed. Use with caution or avoid. (Severe) Theoretical → Also see TABLE 2 p. 1375
- NSAIDs potentially increase the risk of seizures when given with quinolones. Severe Theoretical
- Regorafenib is predicted to increase the exposure to mefenamic acid. Avoid. (Moderate) Theoretical → Also see TABLE 4 p. 1377
- Rifampicin moderately decreases the exposure to NSAIAs (celecoxib, diclofenac, etoricoxib). Moderate Study
- Teriflunomide is predicted to increase the exposure to NSAIAs (indomethacin, ketoprofen). (Moderate) Theoretical
- NSAIDs increase the risk of acute renal failure when given with thiazide diuretics. (Severe) Theoretical → Also see TABLE 18 p. 1379
- Zidovudine increases the possibility of interactions should be borne in mind.

Obeticholic acid
- Obeticholic acid decreases the anticoagulant effect of coumarins (warfarin). (Severe) Study
- Obeticholic acid is predicted to increase the exposure to theophylline. (Severe) Theoretical
- Obeticholic acid is predicted to increase the exposure to tizanidine. (Severe) Theoretical

Oblinutuzumab → see monoclonal antibodies
Ocrelizumab → see monoclonal antibodies
Octreotide
- Octreotide decreases the absorption of oral ciclosporin. Adjust ciclosporin dose, p. 838. (Severe) Anecdotal
- Octreotide (short-acting) decreases the exposure to telotristat ethyl. Telotristat ethyl should be taken at least 30 minutes before octreotide. (Moderate) Study
- Ofoxacin → see quinolones
Olanzapine → see TABLE 8 p. 1376 (hypotension), TABLE 15 p. 1378

FOOD AND LIFESTYLE. Dose adjustment might be necessary if smoking started or stopped during treatment.
- Antiarrhythmics (carbamazepine) potentially decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study
- Antiarrhythmics (phenytoin) are predicted to decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study
- Olanzapine is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see TABLE 8 p. 1376
- HIV-protective inhibitors (ritonavir) are predicted to decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study
- Leflunomide is predicted to decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study → Also see TABLE 15 p. 1378
- Olanzapine decreases the effects of levodopa. Avoid or monitor worsening parkinsonism symptoms. (Severe) Anecdotal → Also see TABLE 8 p. 1376
- Mesiletine is predicted to increase the exposure to olanzapine. Adjust dose. (Moderate) Anecdotal
- Quinolones (ciprofloxacin) are predicted to increase the exposure to olanzapine. Adjust dose. (Moderate) Anecdotal
- Rifampicin is predicted to decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study
- SSSi (fluvoxamine) moderately increase the exposure to olanzapine. Adjust dose. (Severe) Anecdotal
- Teriflunomide is predicted to decrease the exposure to olanzapine. Monitor and adjust dose. (Moderate) Study
- Olaparib → see TABLE 15 p. 1378 (myelosuppression)

FOOD AND LIFESTYLE. Bitter (Seville) orange is predicted to increase the exposure to olaparib.
- Antiarrhythmics (dronedaron) are predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical
- Antiarrhythmics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- Antifungals, azoles (flucanazole, isavuconazole, posaconazole) are predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study
- Aprepitant is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical
- Bosentan is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical

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Olaparib (continued)

- **Cobicistat** is predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study
- **Cyclosporine** is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- **Efavirenz** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- **Enalapril** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- **Grapefruit juice** is predicted to increase the exposure to olaparib. Avoid. (Moderate) Theoretical
- **HIV-protease inhibitors** are predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study
- **Idelalisib** is predicted to increase the exposure to olaparib. Avoid potent inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Study
- **Midazolam** is predicted to increase the exposure to olaparib. Avoid. (Moderate) Theoretical
- **Nevirapine** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- **Nilotinib** is predicted to increase the exposure to olaparib. Avoid moderate inhibitors of CYP3A4 or adjust olaparib dose, p. 1005. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- **Rifampicin** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical
- **St John's Wort** is predicted to decrease the exposure to olaparib. Avoid. (Moderate) Theoretical

**Olaratubam** → see monoclonal antibodies

**Olicesmatan** → see angiotensin-II receptor antagonists

**Olefaltorol** → see beta, agonists

**Olsalazine** → see TABLE 15 p. 1378 (myelosuppression)

**Ombitasvir**

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin)** are predicted to decrease the exposure to ombitasvir. Avoid. (Severe) Theoretical
- **Efavirenz** is predicted to decrease the exposure to ombitasvir. Avoid. (Severe) Theoretical
- **Enalapril** is predicted to decrease the exposure to ombitasvir. Avoid. (Moderate) Theoretical
- **St John's Wort** is predicted to decrease the exposure to ombitasvir. Avoid. (Severe) Theoretical

**Ombitasvir (in fixed-dose combination with dasabuvir)** decreases the concentration of HIV-protease inhibitors (daunavir). Avoid or adjust dose. (Moderate) Study

**Ondansetron** is predicted to decrease the exposure to ombitasvir. Avoid. (Severe) Theoretical

**Omega-3-acid ethyl esters** → see TABLE 3 p. 1375 (anticoagulant effects)

**Omeprazole** → see proton pump inhibitors

**Ondansetron** → see TABLE 13 p. 1378 (serotonin syndrome), TABLE 9 p. 1377 (QT-interval prolongation)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to ondansetron. (Moderate) Study

- **Dopamine receptor agonists (apomorphine)** increase the risk of severe hypotension when given with ondansetron. Avoid. (Severe) Study → Also see TABLE 9 p. 1377

- **Enzalutamide** is predicted to decrease the exposure to ondansetron. (Moderate) Study

- **Mitotane** is predicted to decrease the exposure to ondansetron. (Moderate) Study

- **Rifampicin** is predicted to decrease the exposure to ondansetron. (Moderate) Study

**Opicapone**

- **Opicapone** increases the exposure to levodopa. Adjust dose. (Moderate) Study

- **Opicapone** is predicted to increase the exposure to loperamide. Avoid. (Moderate) Study

- **Opicapone** is predicted to increase the risk of elevated blood pressure when given with moclobemide. Avoid. (Severe) Theoretical

- **Opicapone** is predicted to increase the risk of elevated blood pressure when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. (Severe) Theoretical

- **Opicapone** is predicted to increase the exposure to montelukast. Avoid. (Moderate) Study

- **Opicapone** is predicted to increase the exposure to pioglitazone. Avoid. (Moderate) Study

- **Opicapone** is predicted to increase the exposure to repaglinide. Avoid. (Moderate) Study

- **Opicapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropic. (Severe) Theoretical

- **Opicapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Severe) Theoretical

**Opioids** → see TABLE 6 p. 1376 (bradycardia), TABLE 13 p. 1378 (serotonin syndrome), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 11 p. 1377 (CNS depressant effects)

- **alfentanil**
- **buprenorphine**
- **codeine**
- **diamorphine**
- **dihydrocodeine**
- **diphenoxylate**
- **dipipanone**
- **fentanyl**
- **hydromorphone**
- **meptazinol**
- **methadone**
- **morphine**
- **oxycodone**
- **papaveretum**
- **pentazocine**
- **pethidine**
- **remifentanil**
- **sufentanil**
- **tapentadol**
- **tramadol**

- **Alcohol (beverage)** causes rapid release of opioids (hydromorphone, morphine) (from extended-release preparations). Avoid. (Severe) Study → Also see TABLE 11 p. 1377

- **Antiarrhythmics (amiodarone)** are predicted to increase the concentration of fentanyl. (Moderate) Theoretical → Also see TABLE 6 p. 1376

- **Antiarrhythmics (dronedarone)** are predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study

- **Antiarrhythmics (dronedarone)** are predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 9 p. 1377

- **Antiepileptics (carbamazepine)** decrease the concentration of tramadol. Adjust dose. (Severe) Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to buprenorphine. Monitor and adjust dose. (Moderate) Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** decrease the exposure to methadone. Monitor and adjust dose. (Severe) Study → Also see TABLE 11 p. 1377

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to opioids (alfentanil, fentanyl). (Moderate) Study → Also see TABLE 11 p. 1377

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to oxycodone. Monitor and adjust dose. (Moderate) Study → Also see TABLE 11 p. 1377

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to methadone. Adjust dose. (Severe) Theoretical → Also see TABLE 9 p. 1377
Opioids

- **Antifungals, azoles** (miconazole) are predicted to increase the exposure to alfentanil. Use with caution and adjust dose. (Moderate) Theoretical
- **Antifungals, azoles** (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to alfentanil. Monitor and adjust dose. (Moderate) Study
- **Antifungals, azoles** (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to alfentanil. Monitor and adjust dose. (Severe) Study
- **Antifungals, azoles** (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 9 p. 1377
- **Apatamidine** is predicted to decrease the exposure to alfentanil. Avoid or monitor. (Moderate) Study
- **Aprepitant** is predicted to increase the exposure to alfentanil, buprenorphine, fentanyl, oxycodone. Monitor and adjust dose. (Moderate) Study
- **Bictegravir** is predicted to increase the exposure to methadone. (Moderate) Theoretical
- **Bosentan** decreases the exposure to methadone. Monitor and adjust dose. (Severe) Study
- **Brigatinib** potentially decreases the concentration of opioids (alfentanil, fentanyl). Avoid. (Moderate) Theoretical
- **Bupropion** is predicted to decrease the efficacy of codeine. (Moderate) Theoretical
- **Calcium channel blockers** (diltiazem, verapamil) are predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Calcium channel blockers** (diltiazem, verapamil) are predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 6 p. 1376
- **Cationic amphiphiles** (ritonavir) are predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 6 p. 1376
- **Cen痫ib** is predicted to increase the exposure to opioids (alfentanil, fentanyl). Avoid. (Severe) Theoretical
- **Cinacalcet** is predicted to decrease the efficacy of tramadol. (Severe) Study
- **Cobicistat** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. (Severe) Study
- **Crizotinib** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Crizotinib** is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 6 p. 1376
- **Efavirenz** decreases the exposure to methadone. Monitor and adjust dose. (Severe) Study → Also see TABLE 9 p. 1377
- **Enalapril** is predicted to decrease the exposure to buprenorphine. Monitor and adjust dose. (Moderate) Theoretical
- **Enalapril** decreases the exposure to methadone. Monitor and adjust dose. (Severe) Study
- **Enalapril** is predicted to decrease the exposure to opioids (alfentanil, fentanyl). (Moderate) Study
- **Enalapril** is predicted to decrease the exposure to oxycodone. Monitor and adjust dose. (Moderate) Study
- **H₂ receptor antagonists** (cimetidine) increase the concentration of alfentanil. Use with caution and adjust dose. (Severe) Study
- **H₂ receptor antagonists** (cimetidine) increase the exposure to fentanyl. (Moderate) Study
- **HIV-protease inhibitors** (boosted with ritonavir) are predicted to decrease the exposure to methadone. (Moderate) Study → Also see TABLE 9 p. 1377
- **HIV-protease inhibitors** (ritonavir) are predicted to decrease the concentration of morphine. (Moderate) Theoretical
- **HIV-protease inhibitors** (ritonavir) increase the risk of CNS toxicity when given with pethidine. Avoid. (Severe) Study
- **HIV-protease inhibitors** are predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. (Severe) Study
- **Idelalisib** is predicted to increase the exposure to methadone. (Severe) Theoretical
- **Idelalisib** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone, sufentanil). Monitor and adjust dose. (Severe) Study
- **Imatinib** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Imatinib** is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical
- **Letemodir** is predicted to increase the exposure to opioids (alfentanil, fentanyl). Monitor and adjust dose. (Moderate) Study
- **Macrolides (clarithromycin)** are predicted to increase the concentration of methadone. (Severe) Theoretical → Also see TABLE 9 p. 1377
- **Macrolides (erythromycin)** are predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Macrolides (erythromycin)** are predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical → Also see TABLE 9 p. 1377
- **Opioids potentially decrease the absorption of oral methylxanthine.** (Moderate) Study
- **Mitotane** is predicted to decrease the exposure to buprenorphine. Monitor and adjust dose. (Moderate) Theoretical
- **Mitotane** decreases the exposure to methadone. Monitor and adjust dose. (Severe) Study
- **Mitotane** is predicted to decrease the exposure to opioids (alfentanil, fentanyl). (Moderate) Study
- **Mitotane** is predicted to decrease the exposure to oxycodone. Monitor and adjust dose. (Moderate) Study
- **Mitotane** is predicted to increase the risk of CNS excitation or depression when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid. (Severe) Study → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors** (rasagiline) are predicted to increase the risk of side-effects when given with pethidine. Avoid and for 14 days after stopping rasagiline. (Severe) Theoretical → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors** (safinamide) are predicted to increase the risk of side-effects when given with pethidine. Avoid and for 1 week after stopping safinamide. (Severe) Theoretical → Also see TABLE 13 p. 1378
- **Monoamine-oxidase B inhibitors** (rasagiline) increase the risk of side-effects when given with pethidine. Avoid. (Severe) Theoretical → Also see TABLE 13 p. 1378
- **Mao inhibitors** (methylphenidate) are predicted to increase the concentration of alfentanil. (Moderate) Theoretical → Also see TABLE 9 p. 1377
- **Naloxone** is predicted to decrease the efficacy of opioids. Avoid. (Severe) Theoretical
- **Netupitant** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Netupitant** is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical
- **Netupitant** decreases the exposure to methadone. Monitor and adjust dose. (Severe) Study
- **Nilotinib** is predicted to increase the exposure to opioids (alfentanil, buprenorphine, fentanyl, oxycodone). Monitor and adjust dose. (Moderate) Study
- **Nilotinib** is predicted to increase the exposure to opioids (methadone, sufentanil). (Moderate) Theoretical
- **Opioids (buprenorphine)** are predicted to increase the risk of opiate withdrawal when given with opioids (alfentanil). (Severe) Theoretical → Also see TABLE 11 p. 1377
- **Opioids (pentazocine)** are predicted to increase the risk of opiate withdrawal when given with opioids (alfentanil, codeine, diamorphine, dihydrocodeine, dipropionate, fentanyl, hydromorphone, meptazinol, methadone, morphine, oxycodone, pethidine). Avoid. (Severe) Theoretical
Opioids (continued) papaveretum.  [Severe] Theoretical  →  Also see TABLE 13 p. 1378  →  Also see TABLE 11 p. 1377

Opioids (buprenorphine) are predicted to increase the risk of opiate withdrawal when given with opioids (codeine, diamorphine, dihydrocodeine, dipipanone, fentanyl, hydromorphone, meptazinol, methadone, morphine, oxycodeone, papaveretum, pentazocine, pethidine, remifentanil, sufentanil, tapentadol, tramadol).  [Severe] Theoretical  →  Also see TABLE 11 p. 1377

Opioids (pentazocine) are predicted to increase the risk of opiate withdrawal when given with opioids (pethidine, remifentanil, tapentadol, tramadol).  [Severe] Theoretical  →  Also see TABLE 11 p. 1377

Opioids (pentazocine) are predicted to increase the risk of opiate withdrawal when given with opioids (sufentanil).  [Severe] Theoretical  →  Also see TABLE 11 p. 1377

Palbociclib is predicted to increase the exposure to opioids (alfentanil, fentanyl).  [Moderate] Theoretical  →  Adjust dose.  [Moderate] Theoretical

Rifampicin is predicted to decrease the exposure to buprenorphine.  Monitor and adjust dose.  [Moderate] Theoretical

Rifampicin decreases the exposure to methadone.  Monitor and adjust dose.  [Severe] Study

Rifampicin is predicted to decrease the exposure to opioids (alfentanil, fentanyl).  [Moderate] Study

Rifampicin is predicted to decrease the exposure to opioids (codeine, morphine).  [Moderate] Study

Rifampicin is predicted to decrease the exposure to oxycodeone.  Monitor and adjust dose.  [Moderate] Study

Ruxpar becomes predicted to increase the exposure to opioids (alfentanil, fentanyl).  Monitor and adjust dose.  [Moderate] Study

SSRIs (fluoxetine, paroxetine) are predicted to decrease the efficacy of codeine.  [Moderate] Theoretical

SSRIs (fluoxetine, paroxetine) are predicted to decrease the efficacy of tramadol.  [Severe] Study  →  Also see TABLE 13 p. 1378

St John’s Wort moderately decreases the exposure to oxycodeone.  Adjust dose.  [Moderate] Study

Terbinafine is predicted to decrease the efficacy of codeine.  [Moderate] Theoretical

Terbinafine is predicted to decrease the efficacy of tramadol.  [Severe] Study

Oxaliplatin → see platinum compounds

Oxcarbazepine → see TABLE 11 p. 1377 (CNS depressant effects)

Oxybuprocaine → see anaesthetics, local

Oxybutynin → see TABLE 10 p. 1377 (antimuscarinics)

Orlistat

SEPARATION OF ADMINISTRATION Orlistat might affect the absorption of concurrently administered drugs—consider separating administration. Particular care should be taken with antiepileptics, antiretrovirals, and drugs that have a narrow therapeutic index.

Orphenadrine → see TABLE 10 p. 1377 (antimuscarinics)

Oxelamivir

Leflunomide is predicted to increase the exposure to oxelamivir.  [Moderate] Theoretical

Teriflunomide is predicted to increase the exposure to oxelamivir.  [Moderate] Study

Osimertinib → see TABLE 9 p. 1377 (CYP prodrug metabolism and P-gp efflux)

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to osimertinib.  [Moderate] Study

Bosantan is predicted to decrease the exposure to osimertinib.  [Moderate] Theoretical

Efavirenz is predicted to decrease the exposure to osimertinib.  [Moderate] Theoretical

Enzalutamide is predicted to moderately decrease the exposure to osimertinib.  [Moderate] Study

Mitotane is predicted to moderately decrease the exposure to osimertinib.  [Severe] Theoretical

Rifaximin is predicted to decrease the exposure to osimertinib.  [Moderate] Study

St John’s Wort is predicted to decrease the exposure to osimertinib.  [Moderate] Theoretical

Osimertinib slightly increases the exposure to statins (lovastatin).  [Moderate] Study

Osimertinib is predicted to increase the exposure to osemifene.  [Moderate] Study

Antifungals, azoles (fluconazole) increase the exposure to osemifene.  Use with caution or avoid.  [Moderate] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to osemifene.  Avoid in poor CYp2C9 metabolisers.  [Moderate] Study

Bosantan is predicted to decrease the exposure to osemifene.  [Moderate] Study

Cobicistat is predicted to increase the exposure to osemifene.  Avoid in poor CYp2C9 metabolisers.  [Moderate] Study

Combined hormonal contraceptives potentially oppose the effects of osemifene.  Avoid.  [Severe] Theoretical

Efavirenz is predicted to decrease the exposure to osemifene.  [Moderate] Study

Enzalutamide is predicted to moderately decrease the exposure to osemifene.  [Moderate] Study

HIV-protease inhibitors are predicted to increase the exposure to osemifene.  Avoid in poor CYp2C9 metabolisers.  [Moderate] Study

Macrolides (clarithromycin) are predicted to increase the exposure to osemifene.  Avoid in poor CYp2C9 metabolisers.  [Moderate] Study

Mitotane is predicted to moderately decrease the exposure to osemifene.  [Moderate] Study

 Nevirapine is predicted to decrease the exposure to osemifene.  [Moderate] Study

Rifaximin is predicted to decrease the exposure to osemifene.  [Moderate] Study

St John’s Wort is predicted to decrease the exposure to osemifene.  [Moderate] Study

Oxalacetate see platinum compounds

Oxcarbazepine → see antiepileptics

Oxybutynin see antimuscarinics

Oxybuprocaine → see anaesthetics, local

Oxybutynin see TABLE 10 p. 1377 (antimuscarinics)

Antiarhythmics (dronedarone) are predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

Oxybutynin potentially increases the risk of overheating and dehydration when given with antiepileptics (zonisamide).  Avoid in children.  [Severe] Theoretical

Antifungals, azoles (fluconazole, itraconazole, ketoconazole, posaconazole) are predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to oxybutynin.  [Moderate] Study

Aprelant is predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to oxybutynin.  [Moderate] Study

Crizotinib is predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to oxybutynin.  [Moderate] Study

Imatinib is predicted to increase the exposure to oxybutynin.  [Moderate] Theoretical

Macrolides (clarithromycin) are predicted to increase the exposure to oxybutynin.  [Moderate] Study
Paliperidone is predicted to decrease the exposure to paliperidone. Monitor and adjust dose. [Severe] Study

Rifampicin is predicted to decrease the exposure to paliperidone. Monitor and adjust dose. [Severe] Study

St John's Wort is predicted to decrease the exposure to paliperidone. [Severe] Theoretical

Palonosetron is predicted to decrease the exposure to paliperidone. [Severe] Theoretical

Dopamine receptor agonists (apomorphine) are predicted to increase the risk of severe hypotension when given with palonosetron. [Severe] Theoretical

Pamidronate is predicted to increase the exposure to bisphosphonates

Pancreatin is predicted to decrease the effects of acarbose. Avoid. [Moderate] Theoretical

Pancuronium is predicted to increase neuromuscular blocking drugs, non-depolarising

Panitumumab is predicted to monoclonal antibodies

Panobinostat is predicted to increase the exposure to enzalutamide. Adjust dose. [Moderate] Theoretical

Enzalutamide is predicted to decrease the exposure to panobinostat. Adjust dose; in hepatic impairment avoid, [Severe] Study

Panobinostat is predicted to increase the exposure to beta blockers, selective (metoprolol). Monitor and adjust dose. [Moderate] Theoretical

Panobinostat is predicted to increase the exposure to beta blockers, selective (nебивол). Monitor and adjust dose. [Mild] Theoretical

Calcium channel blockers (verapamil) are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Ciclosporin is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Panobinostat is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. [Severe] Theoretical

Panobinostat is predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. [Moderate] Study

Enzalutamide is predicted to decrease the exposure to panobinostat. Avoid. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. [Moderate] Study

Idelalisib is predicted to increase the exposure to enzalutamide. Adjust dose. [Severe] Study

Idelalisib is predicted to increase the exposure to panobinostat. Adjust dose. [Severe] Study

Idelalisib is predicted to decrease the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to beta blockers, selective (metoprolol). Monitor and adjust dose. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to beta blockers, selective (nебивол). Monitor and adjust dose. [Mild] Theoretical

Calcium channel blockers (verapamil) are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Ciclosporin is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical

Panobinostat is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. [Severe] Theoretical

Panobinostat is predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. [Moderate] Study

Enzalutamide is predicted to decrease the exposure to panobinostat. Avoid. [Moderate] Theoretical

HIV-protease inhibitors are predicted to increase the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. [Moderate] Study

Idelalisib is predicted to decrease the exposure to panobinostat. Adjust panobinostat dose; in hepatic impairment avoid, p. 936. [Moderate] Study
Panobinostat is predicted to increase the exposure to paritaprevir. Adjust dose. [Moderate] Theoretical

Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to ritonavir. Avoid. [Severe] Theoretical

Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to edoxaban. [Severe] Study

Efavirenz is predicted to decrease the exposure to paritaprevir (with ritonavir and ombitasvir). Avoid. [Severe] Study

Enalapril is predicted to decrease the exposure to paritaprevir (with ritonavir and ombitasvir). Avoid. [Severe] Study

Panobinostat (in fixed-dose combination) decreases the anticoagulant effect of coumarins (warfarin). Monitor INR and adjust dose. [Severe] Anecdotal

Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to dabigatran. [Study]

Paritaprevir (with ritonavir and ombitasvir) increases the exposure to digoxin. Monitor and adjust digoxin dose, p. 109. [Moderate] Study

Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to edoxaban. [Severe] Study

Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to thyroid hormones (levothyroxine). Monitor and adjust dose. [Moderate] Theoretical

Table 9
Paritaprevir is predicted to decrease the exposure to pazopanib. Avoid. (Severe) Theoretical

Pazopanib is predicted to affect the exposure to statins (atorvastatin). (Moderate) Anecdotal

Pazopanib is predicted to affect the exposure to statins (pravastatin, rosuvastatin, simvastatin). (Moderate) Theoretical

Pegasparagse is predicted to increase the risk of hepatotoxicity when given with imatinib. (Severe) Theoretical → Also see TABLE 15 p. 1378

Pegasparagse affects the efficacy of methotrexate. (Severe) Anecdotal → Also see TABLE 15 p. 1375 → Also see TABLE 15 p. 1378

Pegasparagse potentially increases the risk of neurotoxicity when given with vinca alkaloids (vincristine). Vincristine should be taken 3 to 24 hours before pegaspargase. (Severe) Anecdotal → Also see TABLE 15 p. 1375 → Also see TABLE 15 p. 1378

Peginferon alfa → see interferons

Peginferon beta-1a → see TABLE 15 p. 1378 (myelosuppression)

Pembrolizumab → see monoclonal antibodies

Pemetrexed → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity)

Antimalarials (pyrimethamine) are predicted to increase the risk of side-effects when given with pemetrexed. (Severe) Theoretical → Also see TABLE 15 p. 1376

Asparin (high-dose) potentially increases the exposure to pemetrexed. Use with caution or avoid. (Severe) Theoretical

Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with pemetrexed. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

NSAIDs are predicted to increase the exposure to pemetrexed. Use with caution or avoid. (Severe) Theoretical → Also see TABLE 2 p. 1375

Penicillamine → see TABLE 2 p. 1375 (nephrotoxicity)

Antacids decrease the absorption of penicillamine. Separate administration by 2 hours. (Mild) Study

Antimalarials (chloroquine) are predicted to increase the risk of haematological toxicity when given with penicillamine. Avoid. (Severe) Theoretical

Penicillamine potentially decreases the concentration of digoxin. Separate administration by 2 hours. (Severe) Anecdotal

Hydroxychloroquine is predicted to increase the risk of haematological toxicity when given with penicillamine. Avoid. (Severe) Theoretical

Iron (oral) is predicted to decrease the absorption of penicillamine. Separate administration by at least 2 hours. (Mild) Study

Sodium aurothiomalate potentially increases the risk of side-effects when given with penicillamine (in those who have had previous adverse reactions to gold). Avoid. (Severe) Study

Zinc is predicted to decrease the absorption of penicillamine. (Mild) Theoretical

Penicillins → see TABLE 1 p. 1375 (hepatotoxicity)

• Ampicillin, ampicillin, benzylpenicillin, flucloxacillin, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin

• Alloxdin increases the risk of skin rash when given with penicillins (ampicillin, ampicillin). (Moderate) Study

• Antiepileptics (valproate) increase the risk of side-effects when given with penicillamin. Avoid. (Severe) Anecdotal

• Penicillins potentially alter the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Severe) Anecdotal

• Leflunomide is predicted to increase the exposure to benzylpenicillin. (Moderate) Theoretical

• Penicillins are predicted to increase the risk of toxicity when given with methotrexate. (Severe) Anecdotal → Also see TABLE 1 p. 1378

• Piperacillin increases the effects of neuromuscular blocking drugs, non-depolarising. (Moderate) Study

• Paracetamol potentially increases the risk of high anion gap metabolic acidosis when given with flucloxacillin. (Severe) Theoretical → Also see TABLE 1 p. 1375

• Penicillins are predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical

• Rifampicin is predicted to decrease the exposure to pazopanib. Avoid. (Severe) Theoretical

• Pazopanib is predicted to affect the exposure to statins (atorvastatin). (Moderate) Anecdotal

• Pazopanib is predicted to affect the exposure to statins (pravastatin, rosuvastatin, simvastatin). (Moderate) Theoretical

• Pegasparagse → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 15 p. 1378 (myelosuppression)

Paracetamol potentially increases the risk of high anion gap metabolic acidosis when given with flucloxacillin. (Severe) Theoretical → Also see TABLE 1 p. 1375

Penicillins are predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical

Penicillamine → see TABLE 2 p. 1375 (nephrotoxicity)

Antacids decrease the absorption of penicillamine. Separate administration by 2 hours. (Mild) Study

Antimalarials (chloroquine) are predicted to increase the risk of haematological toxicity when given with penicillamine. Avoid. (Severe) Theoretical

Penicillamine potentially decreases the concentration of digoxin. Separate administration by 2 hours. (Severe) Anecdotal

Hydroxychloroquine is predicted to increase the risk of haematological toxicity when given with penicillamine. Avoid. (Severe) Theoretical

Iron (oral) is predicted to decrease the absorption of penicillamine. Separate administration by at least 2 hours. (Mild) Study

Sodium aurothiomalate potentially increases the risk of side-effects when given with penicillamine (in those who have had previous adverse reactions to gold). Avoid. (Severe) Study

Zinc is predicted to decrease the absorption of penicillamine. (Mild) Theoretical

Penicillins → see TABLE 1 p. 1375 (hepatotoxicity)

amoxicillin, ampicillin, benzylpenicillin, flucloxacillin, penicillin, penicillin, penicillin, penicillin, penicillin

Alloxdin increases the risk of skin rash when given with penicillins (amoxicillin, ampicillin). (Moderate) Study

Antiepileptics (valproate) increase the risk of side-effects when given with penicillamin. Avoid. (Severe) Anecdotal

Penicillins potentially alter the anticoagulant effect of coumarins. Monitor INR and adjust dose. (Severe) Anecdotal

Leflunomide is predicted to increase the exposure to benzylpenicillin. (Moderate) Theoretical

Penicillins are predicted to increase the risk of toxicity when given with methotrexate. (Severe) Anecdotal → Also see TABLE 1 p. 1378

Piperacillin increases the effects of neuromuscular blocking drugs, non-depolarising. (Moderate) Study

Paracetamol potentially increases the risk of high anion gap metabolic acidosis when given with flucloxacillin. (Severe) Theoretical → Also see TABLE 1 p. 1375

Penicillins are predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical

Rifampicin is predicted to decrease the exposure to pazopanib. Avoid. (Severe) Theoretical

Pazopanib is predicted to affect the exposure to statins (atorvastatin). (Moderate) Anecdotal

Pazopanib is predicted to affect the exposure to statins (pravastatin, rosuvastatin, simvastatin). (Moderate) Theoretical

Pegasparagse → see TABLE 1 p. 1375 (hepatotoxicity), TABLE 15 p. 1378 (myelosuppression)

Paracetamol potentially increases the risk of hepatotoxicity when given with imatinib. (Severe) Theoretical → Also see TABLE 15 p. 1378

Pegasparagse affects the efficacy of methotrexate. (Severe) Anecdotal → Also see TABLE 15 p. 1375 → Also see TABLE 15 p. 1378

Pegasparagse potentially increases the risk of neurotoxicity when given with vinca alkaloids (vincristine). Vincristine should be taken 3 to 24 hours before pegaspargase. (Severe) Anecdotal → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378
Penicillins – Phenothiazines

**Penicillins (continued)**
- Piperacillin increases the effects of saxmethonium. [Moderate]
  - Study
- Teriflunomide is predicted to increase the exposure to benzylpenicillin. [Moderate]
  - Study

**Penicillins**
- See [TABLE 9](https://www.getintopharma.com/pdfs/BNF78/Table9.pdf) (QT-interval prolongation), [TABLE 15 p. 1378](https://www.getintopharma.com/pdfs/BNF78/Table15.pdf) (myelosuppression), [TABLE 2 p. 1375](https://www.getintopharma.com/pdfs/BNF78/Table2.pdf) (nephrotoxicity)
- Didanosine is predicted to increase the risk of pancreatitis when given with pentamidine. Avoid. [Severe]
  - Study
- Fludarabine increases the risk of hypocalcaemia when given with pentamidine. [Severe]
  - Anecdotal
  - Also see [TABLE 2 p. 1375](https://www.getintopharma.com/pdfs/BNF78/Table2.pdf)

**Pentazocine**
-» see opioids

**Pentostatin**
- See [TABLE 15 p. 1378](https://www.getintopharma.com/pdfs/BNF78/Table15.pdf) (myelosuppression), [TABLE 5 p. 1375](https://www.getintopharma.com/pdfs/BNF78/Table5.pdf) (thromboembolism)
- Aldizing agents (cyclophosphamide) (high-dose) increase the risk of toxicity when given with pentostatin. Avoid. [Severe]
  - Anecdotal
  - Also see [TABLE 15 p. 1378](https://www.getintopharma.com/pdfs/BNF78/Table15.pdf) → Also see [TABLE 5 p. 1375](https://www.getintopharma.com/pdfs/BNF78/Table5.pdf)

**Pentoxifylline**
- Pentoxifylline is predicted to increase the concentration of aminohippurate. Use with caution or avoid. [Severe]
  - Theoretical
- Quinolones (ciprofloxacin) very slightly increase the exposure to pentoxifylline. [Moderate]
  - Study
- Pentoxifylline increases the concentration of theophylline. Monitor and adjust dose. [Severe]
  - Study
  - Also see [TABLE 15 p. 1378](https://www.getintopharma.com/pdfs/BNF78/Table15.pdf)

**Peppermint oil**
- Peppermint oil is predicted to increase the exposure to lomitaipide. Separate administration by 12 hours. [Moderate]
  - Theoretical

**Perampanel**
- See antiepileptics

**Perazine**
- See dopamine receptor agonists

**Pericyazine**
- See phenothiazines

**Perindopril**
- See ACE inhibitors

**Pertuzumab**
- See monoclonal antibodies

**Pethidine**
- See opioids

**Phenelzine**
- See monoamine-oxidase A and B inhibitors, irreversible

**Phenindione**
- See [TABLE 3 p. 1375](https://www.getintopharma.com/pdfs/BNF78/Table3.pdf) (anticoagulant effects)

**FOOD AND LIFESTYLE**

The effects of phenindione can be reduced or abolished by vitamin K, including that found in foods, foot supplements, enteral feeds, or large amounts of some green vegetables or green tea. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption can affect anticoagulant control.

- Antiarrhythmics (propafenone) are predicted to increase the anticoagulant effect of phenindione. Monitor and adjust dose. [Moderate]
  - Theoretical
- Antifungals, azoles (miconazole) greatly increase the anticoagulant effect of phenindione. [Severe]
  - Theoretical
- Axitinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Bosutinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Cabozantinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Cephalexins (ceftiraxone) potentially increase the risk of bleeding events when given with phenindione. [Severe]
  - Anecdotal
- Corticosteroids are predicted to increase the effects of phenindione. [Moderate]
  - Anecdotal
- Crizotinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Dasatinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Disulfiram is predicted to increase the anticoagulant effect of phenindione. [Severe]
  - Theoretical
- Enteral feeds (vitamin-K containing) potentially decrease the effects of phenindione. [Severe]
  - Theoretical
- Erlotinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Fibrates are predicted to increase the anticoagulant effect of phenindione. Monitor INR and adjust dose. [Severe]
  - Study
- Gefitinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- H1 receptor antagonists (cimetidine) increase the exposure to phenindione. [Severe]
  - Theoretical
- Imatinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Lapatinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Nandrolone is predicted to increase the anticoagulant effect of phenindione. Monitor and adjust dose. [Severe]
  - Theoretical
- Nilotinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Oxymetholone increases the anticoagulant effect of phenindione. [Severe]
  - Anecdotal
- Paracetalol is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Penicillins are predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Pentoxifylline is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Ranibizumab is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Regorafenib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Ruxolitinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Sorafenib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Statins (rosuvastatin) are predicted to increase the anticoagulant effect of phenindione. Monitor INR and adjust dose. [Severe]
  - Theoretical
- Sunitinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical
- Vandetanib is predicted to increase the risk of bleeding events when given with phenindione. [Severe]
  - Theoretical

**Phenobarbital**
- See antiepileptics

**Phenothiazines**
- See [TABLE 8 p. 1376](https://www.getintopharma.com/pdfs/BNF78/Table8.pdf) (hypotension), [TABLE 9 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table9.pdf) (QT-interval prolongation), [TABLE 11 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table11.pdf) (CNS depressant effects), [TABLE 10 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table10.pdf) (antimuscarinic)

- Chlorpromazine, fluphenazine, levomepromazine, pericyazine, prochlorperazine, promazine, trifluoperazine

**FOOD AND LIFESTYLE**

Chlorpromazine and fluphenazine dose adjustment might be necessary if smoking started or stopped during treatment.

- Phenothiazines are predicted to decrease the effects of amfetamines and amphetamine. They are predicted to decrease the effects of phenothiazines. [Moderate]
  - Study
- Antacids decrease the absorption of phenothiazines. [Moderate]
  - Anecdotal
- Chlorpromazine decreases the concentration of antiepileptics (phenobarbital, primidone) and antiepileptics (phenobarbital, primidone) decrease the concentration of chlorpromazine. [Moderate]
  - Study
  - Also see [TABLE 11 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table11.pdf)
- Chlorpromazine is predicted to increase the risk of hypotension when given with desmopressin. [Severe]
  - Theoretical
- Phenothiazines are predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate]
  - Theoretical
  - Also see [TABLE 8 p. 1376](https://www.getintopharma.com/pdfs/BNF78/Table8.pdf) → Also see [TABLE 9 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table9.pdf) → Also see [TABLE 10 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table10.pdf)
- Phenothiazines are predicted to decrease the antihypertensive effects of guanethidine. [Moderate]
  - Theoretical
  - Also see [TABLE 8 p. 1376](https://www.getintopharma.com/pdfs/BNF78/Table8.pdf)
- Phenothiazines decrease the effects of levodopa. Avoid or monitor worsening parkinsonian symptoms. [Severe]
  - Study
  - Also see [TABLE 8 p. 1376](https://www.getintopharma.com/pdfs/BNF78/Table8.pdf)
- Phenothiazines potentially increase the risk of neurotoxicity when given with lithium. [Severe]
  - Anecdotal
  - Also see [TABLE 9 p. 1377](https://www.getintopharma.com/pdfs/BNF78/Table9.pdf)
- Chlorpromazine decreases the effects of metyrapone. Avoid. [Moderate]
  - Theoretical
Phenothiazines – Phosphodiesterase type-5 inhibitors 1513

Aprepitant is predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study

Aprepitant is predicted to increase the exposure to tadafalif. [Severe] Theoretical

Aprepitant is predicted to increase the exposure to vardenafil. Adjust dose. [Severe] Theoretical

Bosentan decreases the exposure to phosphodiesterase type-5 inhibitors. [Moderate] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to vardenafil. Adjust vardenafil dose, p. 812. [Moderate] Theoretical → Also see TABLE 8 p. 1376

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to tadafalif. [Severe] Theoretical → Also see TABLE 8 p. 1376

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to vardenafil. Adjust vardenafil dose, p. 812. [Moderate] Theoretical → Also see TABLE 8 p. 1376

Calcium channel blockers are predicted to increase the exposure to tadafalif. [Severe] Theoretical → Also see TABLE 8 p. 1376

Cobicistat is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study

Cobicistat is predicted to increase the exposure to tadafalif. [Severe] Theoretical → Also see TABLE 9 p. 1377

Cobicistat is predicted to increase the exposure to vardenafil. Avoid. [Severe] Study

Crizotinib is predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. [Moderate] Theoretical

Crizotinib is predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377

Crizotinib is predicted to increase the exposure to tadafalif. [Severe] Theoretical

Crizotinib is predicted to increase the exposure to tadafalif. Adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377

Eflavirenz is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors. [Moderate] Theoretical → Also see TABLE 9 p. 1377

Enzalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study

Enzalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenafil). [Moderate] Theoretical

Efavirenz moderately decreases the exposure to phosphodiesterase type-5 inhibitors. Adjust dose. [Moderate] Study

Grapefruit juice is predicted to increase the exposure to phosphodiesterase type-5 inhibitors. Use with caution or avoid. [Moderate] Study

HIV-protease inhibitors are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study → Also see TABLE 9 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to tadafalif. Use with caution or avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study

Idelalisib is predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study

Idelalisib is predicted to increase the exposure to tadafalif. Use with caution or avoid. [Severe] Study

Imatinib is predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. [Moderate] Theoretical

Imatinib is predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study

α-Blockers cause significant hypotensive effects when given with phosphodiesterase type-5 inhibitors. Patients should be stabilised on first drug then second drug should be added at the lowest recommended dose. [Severe] Study → Also see TABLE 8 p. 1376

Antiarrhythmics (dronedarone) are predicted to increase the exposure to sildenafil. Adjust avanafil dose, p. 812. [Moderate] Theoretical

Antiarrhythmics (dronedarone) are predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377

Antiarrhythmics (dronedarone) are predicted to increase the exposure to tadafalif. [Severe] Theoretical

Antiarrhythmics (dronedarone) are predicted to increase the exposure to vardenafil. Adjust dose. [Severe] Theoretical → Also see TABLE 9 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, tadafalif). Avoid. [Severe] Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenafil). [Moderate] Theoretical

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. [Moderate] Theoretical

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to tadafalif. [Severe] Theoretical

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to vardenafil. Use caution or avoid. [Severe] Study

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tadafalif. [Severe] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to vardenafil. Use caution or avoid. [Severe] Study

Antifungals, azoles (micronazole) are predicted to increase the exposure to sildenafil. Use with caution and adjust dose. [Severe] Theoretical

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to phosphodiesterase type-5 inhibitors (avanafil, vardenafil). Avoid. [Severe] Study → Also see TABLE 9 p. 1377

Apalutamide is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, sildenafil, vardenafil). Avoid or monitor. [Moderate] Study → Also see TABLE 9 p. 1377

Aprepitant is predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. [Moderate] Theoretical

Moclobemide increases the risk of side-effects when given with levomepromazine. [Moderate] Study

Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the risk of neuroleptic malignant syndrome when given with phenothiazines. [Severe] Theoretical → Also see TABLE 8 p. 1376

Phenothiazines are predicted to increase the exposure to sildenafil. [Extensive] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. [Moderate] Study → Also see TABLE 8 p. 1376

Phenothiazines are predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Use with caution or avoid. [Severe] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Theoretical

Phenothiazines are predicted to increase the exposure to sildenafil. Adjust dose, p. 812. [Moderate] Theoretical

Phenothiazines are predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. [Severe] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Theoretical

Phenothiazines are predicted to increase the exposure to sildenafil. Avoid. [Severe] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Theoretical

Phenothiazines are predicted to increase the exposure to sildenafil. Theoretical

Phenothiazines are predicted to increase the exposure to sildenafil. Avoid. [Severe] Study

Phenothiazines are predicted to increase the exposure to sildenafil. Theoretical
Phosphodiesterase type-5 inhibitors (continued)

- **Imatinib** is predicted to increase the exposure to tadalafil. Avoid. 

  - **Severe** Theoretical

- Imatinib is predicted to increase the exposure to vardenafil.

  - Adjust dose. 

  - **Severe** Theoretical

- Macrolides (clarithromycin) are predicted to increase the exposure to sildenafil. Avoid potent inhibitors of CYP3A4 or adjust sildenafil dose, p. 813. 

  - **Severe** Study 

  - Also see TABLE 9 p. 1377

- Macrolides (erythromycin) are predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. 

  - **Moderate** Theoretical

- Macrolides (erythromycin) are predicted to increase the exposure to vardenafil. Adjust dose. 

  - **Severe** Theoretical 

  - Also see TABLE 8 p. 1376

- Mitotane is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, tadalafil). Avoid. 

  - **Severe** Study

- Mitotane is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenafil). 

  - **Moderate** Theoretical

- Netupitant is predicted to increase the exposure to avanafil. Adjust avanafil dose, p. 812. 

  - **Moderate** Theoretical

- Netupitant is predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. 

  - **Moderate** Study 

  - Also see TABLE 9 p. 1377

- Nitrofurantoin is predicted to increase the exposure to tadalafil. Adjust dose. 

  - **Severe** Theoretical

- Nitrofurantoin is predicted to increase the exposure to vardenafil. 

  - **Severe** Theoretical

- Nevirapine is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors. 

  - **Moderate** Theoretical

- Nicorandil is predicted to increase the risk of hypotension when given with phosphodiesterase type-5 inhibitors. 

  - Avoid. 

  - **Severe** Study 

  - Also see TABLE 9 p. 1377

- Nitrofurantoin is predicted to increase the exposure to avanafil. 

  - Adjust avanafil dose, p. 812. 

  - **Moderate** Theoretical

- Nitrofurantoin is predicted to increase the exposure to sildenafil. Monitor or adjust sildenafil dose with moderate inhibitors of CYP3A4, p. 813. 

  - **Moderate** Study 

  - Also see TABLE 9 p. 1377

- Nitrofurantoin is predicted to increase the exposure to tadalafil. 

  - **Severe** Theoretical

- Nitrofurantoin is predicted to increase the exposure to vardenafil. 

  - Adjust dose. 

  - **Severe** Theoretical 

  - Also see TABLE 8 p. 1376

- Ribociclib is predicted to increase the exposure to sildenafil. 

  - **Moderate** Theoretical 

  - Also see TABLE 9 p. 1377

- Rifampicin is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, tadalafil). 

  - Avoid. 

  - **Severe** Study

- Rifampicin is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (sildenafil, vardenafil). 

  - **Moderate** Theoretical

- Riociguat is predicted to increase the risk of hypotension when given with phosphodiesterase type-5 inhibitors. 

  - Avoid. 

  - **Severe** Theoretical 

  - Also see TABLE 8 p. 1376

- Phosphodiesterase type-5 inhibitors are predicted to increase the risk of hypotension when given with sapropterin. 

  - **Moderate** Theoretical 

  - Also see TABLE 8 p. 1376

- St John's Wort is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors. 

  - **Moderate** Theoretical

Pibrentasvir

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to aliskiren. 

  - **Moderate** Study

- Antiarrhythmics (amiodarone) are predicted to increase the exposure to pibrentasvir. 

  - **Moderate** Theoretical

- Antiarrhythmics (dronedarone) potentially increase the exposure to pibrentasvir. 

  - **Moderate** Theoretical

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately to markedly decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Antiepileptics (eslicarbazepine, oxcarbazepine) potentially decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Theoretical

- Antifungals, azoles (itraconazole, ketoconazole) are predicted to increase the exposure to pibrentasvir. 

  - **Moderate** Theoretical

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to antihistamines, non-sedating (fexofenadine). 

  - Avoid. 

  - **Moderate** Study

- Bosentan is predicted to decrease the exposure to pibrentasvir.

  - Avoid. 

  - **Severe** Study

- Calcium channel blockers (verapamil) are predicted to increase the exposure to pibrentasvir. 

  - **Moderate** Theoretical

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to colchicine. 

  - **Moderate** Study

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to digoxin. 

  - **Moderate** Study

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to edoxaban. 

  - **Moderate** Study

- Efavirenz is predicted to decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Enalaprilat is predicted to moderately to markedly decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to everolimus. 

  - **Moderate** Study

- HIV-protease inhibitors (atazanavir, lopinavir) (boosted with ritonavir) increase the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- HIV-protease inhibitors (ritonavir) potentially increase the exposure to pibrentasvir. 

  - **Severe** Theoretical

- HIV-protease inhibitors (saquinavir) are predicted to increase the exposure to pibrentasvir. 

  - **Moderate** Theoretical

- Lapatinib is predicted to increase the exposure to pibrentasvir. 

  - **Theoretical**

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to lopinavir. 

  - **Moderate** Study

- Lumacaftor potentially decreases the exposure to pibrentasvir. 

  - Avoid. 

  - **Theoretical**

- Macrolides are predicted to increase the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Mitotane is predicted to moderately to markedly decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Nevirapine is predicted to decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Ranolazine is predicted to increase the exposure to pibrentasvir. 

  - **Moderate** Study

- Rifampicin is predicted to decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- St John's Wort is predicted to decrease the exposure to pibrentasvir. 

  - Avoid. 

  - **Severe** Study

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to stanno (atorvastatin). 

  - Avoid. 

  - **Severe** Study

- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to statins (fluvastatin). 

  - **Moderate** Theoretical

- Pibrentasvir (with glecaprevir) increases the exposure to statins (pravastatin). 

  - Use with caution and adjust pravastatin dose. 

  - **Moderate** Study
Pibrentasvir – Pitolisant

**Pibrentasvir** (with glecaprevir) increases the exposure to statins (rosuvastatin). Use with caution and adjust rosuvastatin dose, p. 204. (Moderate) Study

**Pibrentasvir** (with glecaprevir) increases the exposure to statins (simvastatin). Avoid. (Moderate) Study

**Pibrentasvir** (with glecaprevir) slightly increases the exposure to tacrolimus. Monitor and adjust dose. (Mild) Study

**Pibrentasvir** (with glecaprevir) is predicted to increase the exposure to taxanes (paclitaxel). (Moderate) Study

**Pibrentasvir** (with glecaprevir) is predicted to increase the exposure to topotecan. (Moderate) Study

**Vemurafenib** is predicted to increase the exposure to pibrentasvir. (Moderate) Theoretical

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

**Pimecrolimus**
- **Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical pimecrolimus. (Moderate) Study

**Pimecrolimus** is predicted to decrease the efficacy of mifamurtide. Avoid. (Severe) Theoretical

**Pimozone** → see **TABLE 8** p. 1376 (hypotension), **TABLE 9** p. 1377 (QT-interval prolongation), **TABLE 11** p. 1377 (CNS depressant effects), **TABLE 10** p. 1377 (antimuscarnics)

**Antiepileptics**
- **Antihistamines, sedating** are predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Antifungals, azoles** (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Antifungals, azoles (fluconazole, itasucronazole, posaconazole)** are predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Ciclosporin**
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 8** p. 1376

**Clobazam** is predicted to increase the exposure to pimozone. Avoid. (Severe) Study

**Crisantropin** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical

**Pimozone** is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see **TABLE 8** p. 1376 → Also see **TABLE 9** p. 1377 → Also see **TABLE 10** p. 1377

**Fosaprepitant** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical

**Grapefruit juice** increases the exposure to pimozone. Avoid. (Severe) Theoretical

**HIV protease inhibitors** are predicted to increase the exposure to pimozone. Avoid. (Severe) Study → Also see **TABLE 9** p. 1377

**Idelalisib** is predicted to increase the exposure to pimozone. Avoid. (Severe) Study

**Imatinib** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical

**Leteomorfin** is predicted to increase the concentration of pimozone. Avoid. (Severe) Theoretical

**Pimozone** decreases the effects of levodopa. (Severe) Theoretical → Also see **TABLE 8** p. 1376

**Macrolides** (clarithromycin) are predicted to increase the exposure to pimozone. Avoid. (Severe) Study → Also see **TABLE 9** p. 1377

**Macrolides** (erythromycin) are predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Netupitant** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical

**Nilotinib** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Palbociclib** is predicted to increase the exposure to pimozone. Adjust dose. (Moderate) Theoretical

**Panobinostat** is predicted to increase the exposure to pimozone. Avoid. (Severe) Theoretical → Also see **TABLE 9** p. 1377

**Pitolisant** is predicted to decrease the exposure to pimozone. Avoid. (Severe) Theoretical

**Ribociclib** (high-dose) is predicted to increase the exposure to pimozone. Avoid. (Moderate) Theoretical → Also see **TABLE 9** p. 1377

**Rolapitant** is predicted to increase the exposure to pimozone. (Severe) Study

**Rucaparib** is predicted to increase the exposure to pimozone. Monitor and adjust dose. (Moderate) Study

**Pindolol** → see beta blockers, non-selective

**Pioglitazone** potentially decreases the exposure to antifungals, azoles (itraconazole). Use with caution or avoid. (Moderate) Theoretical

**Clopigogrel** increases the exposure to pioglitazone. Monitor blood glucose and adjust dose. (Severe) Study

**Fibrate (gemfibrozil)** increase the exposure to pioglitazone. Monitor blood glucose and adjust dose. (Severe) Study

**Leflunomide** is predicted to increase the exposure to pioglitazone. (Moderate) Study

**Oticapone** is predicted to increase the exposure to pioglitazone. (Moderate) Study

**Pioglitazone** decreases the exposure to pioglitazone. (Severe) Study

**Teriflunomide** is predicted to decrease the exposure to pioglitazone. (Moderate) Study

**Piperacillin** → see penicillins

**Piperazine** → see antimalarials

**Pirfenidone**

**FOOD AND LIFESTYLE** Smoking increases pirfenidone clearance; patients should be encouraged to stop smoking before and during treatment with pirfenidone.

- **Antiepileptics (fosphenytoin, phenytoin)** are predicted to decrease the exposure to pirfenidone. (Moderate) Theoretical

- **Combined hormonal contraceptives** are predicted to increase the exposure to pirfenidone. Use with caution and adjust dose. (Moderate) Study

**HIV protease inhibitors** (ritonavir) are predicted to decrease the exposure to pirfenidone. (Moderate) Theoretical

**Leflunomide** is predicted to decrease the exposure to pirfenidone. (Moderate) Theoretical

- **SSRIs (fluvoxamine)** are predicted to moderately increase the exposure to pirfenidone. Avoid. (Moderate) Study

**Teriflunomide** is predicted to decrease the exposure to pirfenidone. (Moderate) Theoretical

**Piroxicam** → see NSAIDs

**Pitolisant**
- **Pitolisant** is predicted to decrease the exposure to aliskiren. (Mild) Theoretical

**Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to pitolisant. (Moderate) Study

**Pitolisant** is predicted to decrease the exposure to antihistamines, non-sedating (fexofenadine). (Mild) Theoretical

**Antihistamines, sedating** are predicted to decrease the efficacy of pitolisant. (Moderate) Theoretical

**Pitolisant** is predicted to decrease the exposure to bosutinib. Avoid. (Severe) Theoretical

**Bupropion** is predicted to moderately increase the exposure to pitolisant. Use with caution and adjust dose. (Moderate) Study

**Pitolisant** is predicted to decrease the exposure to ciclosporin. Avoid. (Severe) Theoretical
Pitolisant (continued)

- Cinnarizine is predicted to moderately increase the exposure to pitolisant. Use with caution and adjust dose. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to colchicine. [Hard] Theoretical
- Pitolisant is predicted to decrease the efficacy of combined hormonal contraceptives. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to coumarins (warfarin). [Hard] Theoretical
- Pitolisant is predicted to decrease the exposure to crizotinib. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to dabigatran. [Hard] Theoretical
- Pitolisant is predicted to decrease the exposure to dasatinib. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to digoxin. [Hard] Theoretical
- Duloxetine is predicted to increase the exposure to pitolisant. Use with caution and adjust dose. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to efavirenz. [Hard] Theoretical
- Enzalutamide is predicted to moderately decrease the exposure to pitolisant. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to everolimus. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to irinotecan. [Hard] Theoretical
- Pitolisant is predicted to decrease the exposure to lapatinib. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to loperamide. [Hard] Theoretical
- Pitolisant is predicted to increase the exposure to metformin. [Hard] Theoretical
- Mianserin is predicted to decrease the efficacy of pitolisant. [Moderate] Theoretical
- Mirtazapine is predicted to decrease the efficacy of pitolisant. [Moderate] Theoretical
- Mitotane is predicted to moderately decrease the exposure to pitolisant. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to paracetamol. [Hard] Theoretical
- Pitolisant is predicted to decrease the exposure to pimozide. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to repaglinide. [Hard] Theoretical
- Rifampicin is predicted to moderately decrease the exposure to pitolisant. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to sirolimus. Avoid. [Severe] Theoretical
- SSRIs (fluoxetine, paroxetine) are predicted to moderately increase the exposure to pitolisant. Use with caution and adjust dose. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to topotecan. Avoid. [Severe] Theoretical
- Pitolisant is predicted to decrease the exposure to temsirolimus. Avoid. [Severe] Theoretical
- Terbinafine is predicted to moderately increase the exposure to pitolisant. Use with caution and adjust dose. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to topotecan. [Hard] Theoretical
- Tricyclic antidepressants are predicted to decrease the efficacy of pitolisant. [Hard] Theoretical

- Venlafaxine is predicted to increase the exposure to pitolisant. Use with caution and adjust dose. [Hard] Theoretical
- Pivmecillinam → see penicillins
- Pixintrone → see antracyclines
- Pizotifen → see antihistamines, sedating
- Platinum compounds → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1378 (neutropenia), TABLE 19 p. 1379 (ototoxicity), TABLE 12 p. 1378 (peripheral neuropathy)
- Carboplatin - cisplatin - oxaliplatin
- Cisplatin increases the risk of pulmonary toxicity when given with bleomycin. [Severe] Study → Also see TABLE 15 p. 1378
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with platinum compounds. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Polyoxymyxins → see TABLE 2 p. 1375 (neurotoxicity), TABLE 20 p. 1379 (neuromuscular blocking effects)

ROUTE-SPECIFIC INFORMATION Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

Polyostyrene sulfonate

SEPARATION OF ADMINISTRATION Manufacturers advise take other drugs at least 3 hours before or after calcium- or sodium-polyostyrene sulfonate; a 6-hour separation should be considered in gastroparesis.

- Antacids increase the risk of metabolic alkalosis when given with polyostyrene sulfonate. [Severe] Anecdotal

Pomalidomide → see TABLE 15 p. 1378 (myelosuppression), TABLE 5 p. 1375 (thromboembolism)

- Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with pomalidomide. Avoid. [Severe] Theoretical
- Hormone replacement therapy is predicted to increase the risk of venous thromboembolism when given with pomalidomide. [Severe] Theoretical
- Quinolones (ciprofloxacin) are predicted to increase the exposure to pomalidomide. Adjust pomalidomide dose, p. 961. [Moderate] Theoretical
- Pomalidomide, (itraconazole, ketoconazole, voriconazole) are predicted to decrease the exposure to pomalidomide. Adjust pomalidomide dose, p. 961. [Moderate] Study

- Antipiepletics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to pomalidomide. Avoid. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to slightly increase the exposure to pomalidomide. Monitor and adjust pomalidomide dose, p. 994. [Moderate] Study
- Cobrincistat is predicted to slightly increase the exposure to pomalidomide. Monitor and adjust pomalidomide dose, p. 994. [Moderate] Study
- Ponatinib is predicted to increase the risk of bleeding events when given with coumarins. [Severe] Theoretical
- Enzalutamide is predicted to decrease the exposure to ponatinib. Avoid. [Moderate] Theoretical
- Grapefruit juice is predicted to increase the exposure to ponatinib. [Moderate] Theoretical
- HIV-protease inhibitors are predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study
- Idelalisib is predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study
- Macrolides (clarithromycin) are predicted to slightly increase the exposure to ponatinib. Monitor and adjust ponatinib dose, p. 994. [Moderate] Study
- Mitotane is predicted to decrease the exposure to ponatinib. Avoid. [Moderate] Theoretical
- Ponatinib is predicted to increase the risk of bleeding events when given with phenindione. [Severe] Theoretical
- Rifampicin is predicted to decrease the exposure to ponatinib. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to ponatinib. Avoid. [Severe] Theoretical
Posaconazole → see antifungals, azoles
Potassium aminobenzoate → see TABLE 16 p. 1379 (increased serum potassium)
  » Potassium aminobenzoate increases the concentration of methotrexate. (Moderate) Theoretical
  » Potassium aminobenzoate is predicted to affect the efficacy of sulfonamides. Avoid. (Severe) Theoretical
Potassium canrenoate → see TABLE 16 p. 1379 (increased serum potassium)
Potassium chloride → see TABLE 16 p. 1379 (increased serum potassium)
Potassium citrate
  » Potassium citrate is predicted to decrease the efficacy of methenamine. Avoid. (Moderate) Theoretical
  » Potassium citrate increases the risk of side-effects when given with primidone. Avoid. (Moderate) Theoretical
Potassium-sparing diuretics → see TABLE 18 p. 1379 (hypotension), TABLE 16 p. 1379 (increased serum potassium)
milrinone - triamterene
  » Triamterene potentially increases the clearance of lithium. (Moderate) Study
Pramipexole → see dopamine receptor agonists
Prasugrel
  → see statins
Praziquantel
  » Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to praziquantel. Avoid. (Moderate) Study
  » Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to moderately increase the exposure to praziquantel. (Mild) Study
  » Antimalarials (chloroquine) moderately decrease the exposure to praziquantel. Use with caution and adjust dose. (Moderate) Study
  » Cocystis is predicted to moderately increase the exposure to praziquantel. (Mild) Study
  » Corticosteroids (dexamethasone) increase the exposure to praziquantel. (Moderate) Study
  » Enalaprilat is predicted to markedly decrease the exposure to praziquantel. Avoid. (Moderate) Study
  » Grapefruit juice is predicted to increase the exposure to praziquantel. (Moderate) Study
  » H₂ receptor antagonists (cimetidine) moderately increase the exposure to praziquantel. (Mild) Study
  » HIV-protease inhibitors are predicted to moderately increase the exposure to praziquantel. (Mild) Study
  » Idealisil is predicted to moderately increase the exposure to praziquantel. (Mild) Study
  » Macrolides (clarithromycin) are predicted to moderately increase the exposure to praziquantel. (Mild) Study
  » Mitotane is predicted to markedly decrease the exposure to praziquantel. (Mild) Study
  » Rifampicin is predicted to markedly decrease the exposure to praziquantel. Avoid. (Moderate) Study
Prazosin → see alpha blockers
Prednisolone → see corticosteroids
Pregabalin → see antiepileptics
Prilocaine → see anaesthetics, local
Primaquine → see antimalarials
Primidone → see antiepileptics
Procarbazine → see TABLE 15 p. 1378 (myelosuppression), TABLE 13 p. 1378 (serotonin syndrome)
  » Alcohol (beverage) potentially causes a disulfiram-like reaction when given with procarbazine. (Moderate) Anecdotal
  » Antiepileptics (carbamazepine, phenobarbital, phenytoin, primidone) are predicted to increase the risk of hypersensitivity reactions when given with procarbazine. (Severe) Anecdotal
  » Antiepileptics (fosphenytoin) are predicted to increase the risk of hypersensitivity when given with procarbazine. (Severe) Anecdotal
  » Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with procarbazine. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
Procyclidine → see phenothiazines
Procyclophosphamide → see TABLE 10 p. 1377 (antimuscarnics)
  » SSRIs (paroxetine) slightly increase the exposure to procyclidine. Monitor and adjust dose. (Moderate) Study
Propafenone → see antiarrhythmics
Propargylamine → see TABLE 13 p. 1377 (antimuscarnics)
Propiverine → see TABLE 10 p. 1377 (antimuscarnics)
  » Propiverine is predicted to increase the exposure to lomiptapide. Separate administration by 12 hours. (Moderate) Theoretical
Propofol → see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)
  » Antiepileptics (valproate) potentially increase the concentration of propofol. Adjust dose. (Severe) Theoretical
Propionol → see beta blockers, non-selective
Propylthiouracil → see TABLE 15 p. 1378 (myelosuppression)
  » Propylthiouracil is predicted to decrease the effects of metryrapone. Avoid. (Moderate) Theoretical
Proton pump inhibitors
esomeprazole - lansoprazole - omeprazole - pantoprazole - rabeprazole
  » Antifungals, azoles (voriconazole) increase the exposure to proton pump inhibitors (esomeprazole, omeprazole). Adjust dose. (Moderate) Study
  » Proton pump inhibitors decrease the absorption of antifungals, azoles (itraconazole). Administer itraconazole capsules with an acidic beverage. (Moderate) Study
  » Proton pump inhibitors decrease the absorption of antifungals, azoles (ketoconazole). Administer ketoconazole with an acidic beverage. (Moderate) Study
  » Proton pump inhibitors decrease the absorption of antifungals, azoles (posaconazole) (oral suspension). Avoid. (Moderate) Study
  » Apalutamide markedly decreases the exposure to omeprazole. Avoid or monitor. (Moderate) Study
  » Apalutamide is predicted to decrease the exposure to proton pump inhibitors (lansoprazole, rabeprazole). Avoid or monitor. (Mild) Study
  » Proton pump inhibitors are predicted to decrease the absorption of bosutinib. (Moderate) Study
  » Proton pump inhibitors are predicted to decrease the absorption of ceritinib. (Moderate) Theoretical
  » Esomeprazole is predicted to increase the exposure to ceritinib. (Moderate) Theoretical
  » Omeprazole is predicted to increase the exposure to cilostazol. Adjust cilostazol dose, p. 232. (Moderate) Study
  » Proton pump inhibitors (esomeprazole, omeprazole) potentially increase the exposure to cilobazam. Adjust dose. (Moderate) Theoretical
  » Proton pump inhibitors (esomeprazole, omeprazole) are predicted to decrease the efficacy of clonipidine. Avoid. (Moderate) Study
  » Proton pump inhibitors are predicted to slightly to moderately decrease the exposure to dasatinib. Avoid. (Severe) Study
  » Proton pump inhibitors are predicted to decrease the absorption of dipyridamole (immediate release tablets). (Moderate) Theoretical
  » Proton pump inhibitors are predicted to slightly decrease the exposure to erlotinib. Avoid. (Moderate) Study
  » Proton pump inhibitors are predicted to decrease the exposure to gefitinib. (Severe) Theoretical
  » HIV-protease inhibitors (tipranavir) decrease the exposure to proton pump inhibitors. Avoid. (Severe) Study
  » Proton pump inhibitors decrease the exposure to HIV-protease inhibitors (atazanavir). Avoid or adjust dose. (Severe) Study
Proton pump inhibitors (continued)

- Proton pump inhibitors increase the exposure to HIV-protease inhibitors (saquinavir). Avoid. (Severe) Study
- Proton pump inhibitors are predicted to decrease the exposure to ledipasvir. Adjust dose, see ledipasvir with sofosbuvir p. 628. (Moderate) Theoretical
- Proton pump inhibitors decrease the clearance of methotrexate (high-dose). Use with caution or avoid. (Severe) Study
- Proton pump inhibitors are predicted to decrease the exposure to pazopanib. Avoid or administer concurrently without food. (Moderate) Study
- Proton pump inhibitors are predicted to decrease the exposure to ripilivirine. Avoid. (Severe) Study
- Proton pump inhibitors potentially decrease the exposure to sofosbuvir. Adjust dose, see sofosbuvir with velpatasvir p. 629, and sofosbuvir with velpatasvir and voxilaprevir p. 630. (Moderate) Study
- Esomeprazole is predicted to slightly to moderately increase the exposure to SSRIs (citalopram, escitalopram). Monitor and adjust dose. (Severe) Study
- Omeprazole slightly to moderately increases the exposure to SSRIs (citalopram, escitalopram). Monitor and adjust dose. (Severe) Study
- Proton pump inhibitors are predicted to decrease the concentration of velpatasvir. Adjust dose, see sofosbuvir with velpatasvir p. 629. (Moderate) Study
- Proton pump inhibitors are predicted to decrease the exposure to voxilaprevir. Adjust dose, see sofosbuvir with velpatasvir and voxilaprevir p. 630. (Moderate) Study
- Pseudoephedrine → see anaesthetics, local
- Quinazinamide
  - Allopurinol is predicted to increase the risk of hyperuricaemia when given with pyrazinamide. (Moderate) Theoretical
- Pyridostigmine → see TABLE 6 p. 1376 (bradycardia)
- Aminoglycosides are predicted to decrease the effects of pyridostigmine. (Moderate) Theoretical
- Pyrimethamine → see antimalarials
- Quetiapine → see TABLE 8 p. 9 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)
- Antiarthrythmics (dronedarone) are predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to quetiapine. (Moderate) Study → Also see TABLE 11 p. 1377
- Antiepileptics (valproate) potentially increase the risk of neuropenia when given with quetiapine. (Moderate) Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to quetiapine. Avoid. (Severe) Study
- Apalutamide is predicted to decrease the exposure to quetiapine. Avoid or monitor. (Moderate) Study
- Apraciptan is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Bosentan is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study → Also see TABLE 8 p. 9 1376
- Cobicistat is predicted to increase the exposure to quetiapine. Avoid. (Severe) Study
- Crizotinib is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Quetiapine is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical → Also see TABLE 8 p. 9 1376
- Efavirenz is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Enalapril is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Grapefruit juice is predicted to increase the exposure to quetiapine. Avoid. (Severe) Theoretical
- HIV-protease inhibitors are predicted to increase the exposure to quetiapine. Avoid. (Severe) Study
- Idelelisib is predicted to increase the exposure to quetiapine. Avoid. (Severe) Study
- Imatinib is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Quetiapine decreases the effects of levodopa. (Severe) Anecdotal → Also see TABLE 8 p. 1376
- Quetiapine potentially increases the risk of neurotoxicity when given with lithium. (Severe) Anecdotal
- Macrolides (clarithromycin) are predicted to increase the exposure to quetiapine. Avoid. (Severe) Study
- Macrolides (erythromycin) are predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Mitotane is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Netupitant is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Nilotinib is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Study
- Ribociclib (high-dose) is predicted to increase the exposure to quetiapine. Avoid. (Moderate) Theoretical
- Rifampicin is predicted to decrease the exposure to quetiapine. (Moderate) Study
- St John’s Wort is predicted to decrease the exposure to quetiapine. (Moderate) Study
- Quinagolide → see dopamine receptor agonists
- Quinapril → see ACE inhibitors
- Quinine → see antimalarials
- Quinolones → see TABLE 9 p. 9 1377 (QT-interval prolongation)

  - Ciprofloxacin - levofloxacin - moxifloxacin - ofloxacin
  - Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
  - Interactions do not generally apply to topical use of moxifloxacin unless specified.
  - Ciprofloxacin is predicted to increase the exposure to agomelatine. (Moderate) Study
  - Ciprofloxacin is predicted to increase the exposure to aminophylline. Adjust dose. (Moderate) Theoretical
  - Ciprofloxacin is predicted to increase the exposure to anagrelide. (Moderate) Theoretical
  - Antacids decrease the absorption of quinolones. Quinolones should be taken 2 hours before or 4 hours after antacids. (Moderate) Study
  - Ciprofloxacin slightly increases the exposure to antiarrhythmics (lidocaine). (High) Study
  - Ciprofloxacin affects the concentration of antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Severe) Study
  - Calcium salts (calcium carbonate) decrease the absorption of ciprofloxacin. Separate administration by 2 hours. (Moderate) Study
  - Ciprofloxacin increases the concentration of clozapine. Monitor side effects and adjust dose. (Severe) Study
  - Quinolones increase the anticoagulant effect of coumarins. (Severe) Anecdotal
  - Didanosine (buffered) is predicted to greatly decrease the exposure to oral quinolones. Didanosine should be taken 2 hours after quinolones. (Moderate) Study
  - Ciprofloxacin is predicted to increase the exposure to dopamine receptor agonists (ropinirole). Adjust dose. (Moderate) Study
  - Ciprofloxacin is predicted to increase the exposure to duloxetine. Avoid. (Moderate) Theoretical
  - Ciprofloxacin is predicted to increase the exposure to eliglustat. Avoid or adjust dose—consult product literature. (Severe) Theoretical
  - Enteral feeds decrease the exposure to ciprofloxacin. (Moderate) Study
  - Ciprofloxacin slightly increases the exposure to erlotinib. Monitor side effects and adjust dose. (Moderate) Study
  - Ciprofloxacin is predicted to increase the exposure to ibrutinib. Adjust ibrutinib dose, p. 983. (Severe) Theoretical

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Quinolones – Ranolazine

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- Iron (oral) decreases the exposure to quinolones. Separate administration by at least 2 hours. Moderate Study
- Lanthanum moderately decreases the exposure to quinolones. Quinolones should be taken 2 hours before or 4 hours after lanthanum. Moderate Study
- Leflunomide is predicted to increase the exposure to ciprofloxacin. Moderate Theoretical
- Ciprofloxacin is predicted to increase the exposure to cloxacillin. Avoid. Unknown Theoretical
- Ciprofloxacin is predicted to increase the exposure to methotrexate. Severe Anecdotal
- Ciprofloxacin slightly increases the exposure to monoamine-oxidase B inhibitors (rasagiline). Moderate Study
- NSAIDs potentially increase the risk of seizures when given with quinolones. Severe Theoretical
- Ciprofloxacin is predicted to increase the exposure to olanzapine. Adjust dose. Moderate Anecdotal
- Ciprofloxacin very slightly increases the exposure to pentoxyfylline. Moderate Study
- Ciprofloxacin is predicted to increase the exposure to pirfenidone. Use with caution and adjust dose. Moderate Study
- Ciprofloxacin is predicted to increase the exposure to pomalidomide. Adjust pomalidomide dose, p. 961. Moderate Theoretical
- Ciprofloxacin is predicted to increase the exposure to rifuzole. Moderate Theoretical
- Ciprofloxacin is predicted to increase the exposure to tolvaptan. Use with caution and adjust tolvaptan dose, p. 669. Moderate Theoretical
- Zinc is predicted to decrease the exposure to quinolones. Separate administration by 2 hours. Moderate Study
- Ciprofloxacin is predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. Moderate Theoretical
- Rabeprazole → see proton pump inhibitors
- Rabies immunoglobulin → see immunoglobulins
- Rabies vaccine
  - Antimalarial (chloroquine) decrease the efficacy of rabies vaccine. Avoid. Moderate Study
  - Hydroxychloroquine is predicted to decrease efficacy of rabies vaccine. Moderate Theoretical
- Raloxifene → see Table 5 p. 1375 (thromboembolism)
  - Combined hormonal contraceptives potentially oppose the effects of raloxifene. Avoid. Severe Theoretical
  - Hormone replacement therapy potentially opposes the effects of raloxifene. Avoid. Severe Theoretical
- Raltegravir
  - Antacids slightly decrease the exposure to raltegravir. Avoid. Moderate Study
  - Antiepileptics (carbamazepine) are predicted to affect the exposure to raltegravir. Moderate Theoretical
  - Antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to affect the exposure to raltegravir. Use with caution or avoid. Moderate Theoretical
  - Calcium salts (calcium carbonate) greatly decrease the exposure to raltegravir (high-dose). Avoid. Severe Study
  - Encorafenib is predicted to increase the exposure to raltegravir. Moderate Theoretical
  - HIV-protease inhibitors (atazanavir) increase the exposure to raltegravir (high-dose). Avoid. Moderate Study
  - HIV-protease inhibitors (darunavir) increase the risk of rash when given with raltegravir. Moderate Study
  - HIV-protease inhibitors (fosamprenavir) (boosted with ritonavir) decrease the exposure to raltegravir and raltegravir decreases the exposure to HIV-protease inhibitors (fosamprenavir) (boosted with ritonavir). Avoid. Severe Study
  - HIV-protease inhibitors (tritapevir boosted with ritonavir) are predicted to decrease the exposure to raltegravir (high-dose). Avoid. Moderate Study
  - Rifampicin slightly decreases the exposure to raltegravir. Avoid or adjust dose—consult product literature. Moderate Study
- Raltitrexed → see Table 15 p. 1378 (myelosuppression)
- Folates are predicted to alter the effects of raltitrexed. Avoid. Moderate Study
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with raltitrexed. Public Health England advises avoid (refer to Green Book). Severe Theoretical
- Ramipril → see ACE inhibitors
- Ramucirumab → see monoclonal antibodies
- Ranibizumab
  - Ranibizumab is predicted to increase the risk of bleeding events when given with argatroban. Severe Theoretical
  - Ranibizumab is predicted to increase the risk of bleeding events when given with bivalirudin. Moderate Theoretical
  - Ranibizumab increases the risk of bleeding events when given with coumarins. Severe Theoretical
  - Ranibizumab is predicted to increase the risk of bleeding events when given with danaparoid. Severe Theoretical
  - Ranibizumab increases the risk of bleeding events when given with heparin (unfractionated). Severe Theoretical
  - Ranibizumab increases the risk of bleeding events when given with low molecular-weight heparins. Severe Theoretical
  - Ranibizumab is predicted to increase the risk of bleeding events when given with phenindione. Severe Theoretical
- Ranitidine → see H₂ receptor antagonists
- Ranolazine → see Table 9 p. 1377 (QT-interval prolongation)
- Ranolazine is predicted to increase the exposure to aefatinib. Separate administration by 12 hours. Moderate Study
- Ranolazine is predicted to increase the exposure to aliskiren. Moderate Theoretical
- Antiarhythmics (dronedarone) are predicted to increase the exposure to ranolazine. Severe Study → Also see Table 9 p. 1377
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to ranolazine. Avoid. Severe Study
- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ranolazine. Severe Study → Also see Table 9 p. 1377
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ranolazine. Severe Study → Also see Table 9 p. 1377
- Aprepitant is predicted to increase the exposure to ranolazine. Severe Study
- Ranolazine is predicted to increase the exposure to beta blockers, non-selective (nadolol). Moderate Study
- Ranolazine is predicted to increase the exposure to bictegravir. Use with caution or avoid. Moderate Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ranolazine. Severe Study
- Ranolazine is predicted to increase the exposure to ceritinib. Moderate Theoretical → Also see Table 9 p. 1377
- Ciclosporin is predicted to increase the concentration of ranolazine and ranolazine is predicted to increase the concentration of ciclosporin. Moderate Theoretical
- Cobimetinib is predicted to increase the exposure to ranolazine. Severe Study → Also see Table 9 p. 1377
- Ranolazine is predicted to increase the exposure to dabigatran. Severe Theoretical
- Ranolazine increases the concentration of digoxin. Moderate Study
1520 Ranolazine — Repaglinide
Ranolazine (continued)
▶ Ranolazine is predicted to increase the exposure to dopamine
receptor agonists (pramipexole). Adjust dose. o Study
▶ Ranolazine is predicted to slightly increase the exposure to
edoxaban. r Theoretical
▶ Enzalutamide is predicted to decrease the exposure to
ranolazine. Avoid. r Study
▶ Ranolazine is predicted to increase the exposure to erlotinib.
o Theoretical
▶
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Ranolazine is predicted to increase the exposure to
fidaxomicin. Avoid. o Study
Grapefruit juice is predicted to increase the concentration of
ranolazine. Avoid. r Theoretical
HIV-protease inhibitors are predicted to increase the exposure
to ranolazine. Avoid. r Study → Also see TABLE 9 p. 1377
Idelalisib is predicted to increase the exposure to ranolazine.
Avoid. r Study
Imatinib is predicted to increase the exposure to ranolazine.

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▶

Idelalisib is predicted to increase the exposure to reboxetine.
Avoid. o Study
Reboxetine is predicted to increase the risk of a hypertensive
crisis when given with linezolid. Avoid. r Theoretical
▶ Reboxetine is predicted to increase the risk of hypokalaemia
when given with loop diuretics. o Theoretical
▶ Macrolides (clarithromycin) are predicted to increase the
exposure to reboxetine. Avoid. o Study
▶ Mitotane is predicted to decrease the exposure to reboxetine.
▶

o Anecdotal
▶
▶

▶

▶

r Study

o Anecdotal

▶

Ranolazine is predicted to increase the exposure to lomitapide.
Separate administration by 12 hours. o Theoretical
▶ Macrolides (clarithromycin) are predicted to increase the
exposure to ranolazine. Avoid. r Study → Also see TABLE 9

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Reboxetine is predicted to increase the risk of hypokalaemia
when given with thiazide diuretics. o Anecdotal
Regorafenib → see TABLE 15 p. 1378 (myelosuppression), TABLE 4

p. 1377

p. 1375 (antiplatelet effects)

Macrolides (erythromycin) are predicted to increase the
exposure to ranolazine. r Study → Also see TABLE 9 p. 1377
▶ Mitotane is predicted to decrease the exposure to ranolazine.
Avoid. r Study
▶ Netupitant is predicted to increase the exposure to ranolazine.
▶

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure
to regorafenib. Avoid. o Study
▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to regorafenib. Avoid.
▶

r Study
▶
▶

o Study

Nilotinib is predicted to increase the exposure to ranolazine.
r Study → Also see TABLE 9 p. 1377
Ranolazine is predicted to increase the exposure to nintedanib.

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o Study
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Ranolazine is predicted to increase the exposure to
panobinostat. Adjust dose. o Theoretical → Also see

▶

TABLE 9 p. 1377

▶

Ranolazine is predicted to increase the exposure to
pibrentasvir. o Theoretical
Rifampicin is predicted to decrease the exposure to ranolazine.
Avoid. r Study
St John’s Wort is predicted to decrease the exposure to
ranolazine. Avoid. r Study
Ranolazine is predicted to increase the exposure to statins
(atorvastatin). o Theoretical
Ranolazine slightly increases the exposure to statins
(simvastatin). Adjust simvastatin dose, p. 205. o Study
Ranolazine increases the concentration of tacrolimus. Adjust
dose. r Anecdotal
Ranolazine is predicted to increase the exposure to ticagrelor.
Use with caution or avoid. r Study
Ranolazine is predicted to increase the exposure to topotecan.
r Study

▶

Ranolazine is predicted to increase the concentration of
trametinib. o Theoretical
Ranolazine is predicted to increase the exposure to venetoclax.
Avoid or monitor for toxicity. r Theoretical
Rasagiline → see monoamine-oxidase B inhibitors
Reboxetine
▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure
to reboxetine. o Anecdotal
▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to reboxetine. Avoid.
▶

o Study

▶

Antifungals, azoles (miconazole) are predicted to increase the
concentration of reboxetine. Use with caution and adjust dose.
o Theoretical

▶
▶
▶

Reboxetine is predicted to increase the risk of a hypertensive
crisis when given with moclobemide. Avoid. r Theoretical
Reboxetine is predicted to increase the risk of a hypertensive
crisis when given with monoamine-oxidase A and B inhibitors,
irreversible. Avoid. r Theoretical
Reboxetine is predicted to increase the risk of a hypertensive
crisis when given with monoamine-oxidase B inhibitors
(rasagiline, selegiline). Avoid. r Theoretical
Rifampicin is predicted to decrease the exposure to reboxetine.

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p. 1375
▶

Regorafenib is predicted to increase the risk of bleeding events
when given with phenindione. r Theoretical
▶ Rifampicin is predicted to decrease the exposure to
regorafenib. Avoid. o Study
▶ Regorafenib is predicted to increase the exposure to statins
(atorvastatin, fluvastatin, rosuvastatin). o Study
▶ Regorafenib is predicted to increase the exposure to
sulfasalazine. o Study → Also see TABLE 15 p. 1378
▶ Regorafenib is predicted to increase the exposure to topotecan.
o Study → Also see TABLE 15 p. 1378
Remifentanil → see opioids
Repaglinide → see TABLE 14 p. 1378 (antidiabetic drugs)
▶ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure
to repaglinide. Monitor blood glucose and adjust dose.
o Study
▶

Cobicistat is predicted to increase the exposure to reboxetine.
Avoid. o Study
Enzalutamide is predicted to decrease the exposure to
reboxetine. o Anecdotal
HIV-protease inhibitors are predicted to increase the exposure
to reboxetine. Avoid. o Study

Cobicistat is predicted to increase the exposure to regorafenib.
Avoid. o Study
Regorafenib is predicted to increase the risk of bleeding events
when given with coumarins. r Study
Enzalutamide is predicted to decrease the exposure to
regorafenib. Avoid. o Study
Grapefruit juice is predicted to increase the exposure to
regorafenib. Avoid. o Theoretical
HIV-protease inhibitors are predicted to increase the exposure
to regorafenib. Avoid. o Study
Idelalisib is predicted to increase the exposure to regorafenib.
Avoid. o Study → Also see TABLE 15 p. 1378
Macrolides (clarithromycin) are predicted to increase the
exposure to regorafenib. Avoid. o Study
Regorafenib is predicted to increase the exposure to
methotrexate. o Theoretical → Also see TABLE 15 p. 1378
Mitotane is predicted to decrease the exposure to regorafenib.
Avoid. o Study → Also see TABLE 15 p. 1378
Regorafenib is predicted to increase the exposure to NSAIDs
(mefenamic acid). Avoid. o Theoretical → Also see TABLE 4

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to repaglinide. o
Study

▶

Ciclosporin moderately increases the exposure to repaglinide.
o Study

▶

Clopidogrel increases the exposure to repaglinide. Avoid.
r Study

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Cobicistat is predicted to increase the exposure to repaglinide. [Moderate] Study

Enalaprilat is predicted to decrease the exposure to repaglinide. Monitor blood glucose and adjust dose. [Moderate] Study

Fibrates (gemfibrozil) increase the exposure to repaglinide. Avoid. [Severe] Study

HIV-protease inhibitors are predicted to increase the exposure to repaglinide. [Moderate] Study

Idelalisib is predicted to increase the exposure to repaglinide. [Moderate] Study

Iron chelators (deferasirox) moderately increase the exposure to repaglinide. Avoid. [Moderate] Study

Leflunomide is predicted to increase the exposure to repaglinide. Avoid. [Moderate] Theoretical

Macrolides (clarithromycin) are predicted to increase the exposure to repaglinide. Avoid. [Moderate] Study

Mitotane is predicted to decrease the exposure to repaglinide. Monitor blood glucose and adjust dose. [Moderate] Study

Opicapone is predicted to decrease the exposure to repaglinide. [Moderate] Study

Pitolisant is predicted to decrease the exposure to repaglinide. [Moderate] Theoretical

Rifampicin is predicted to decrease the exposure to repaglinide. [Moderate] Study

Teriflunomide is predicted to increase the exposure to repaglinide. Monitor blood glucose and adjust dose. [Moderate] Study

Trimetrexate moderately increases the exposure to repaglinide. Avoid or monitor blood glucose. [Moderate] Study

Venetoclax is predicted to increase the exposure to repaglinide. [Moderate] Theoretical

Retigabine — see antiepileptics

Retinoids — see TABLE 5 p. 1375 (thromboembolism)

Acitretin, adapalene, altretinoin, bexarotene, isotretinoin, tazarotene, tretinoin

Avoid concomitant use of keratolytics in patients taking acitretin and isotretinoin. Since systemic absorption can follow topical application of isotretinoin and tretinoin, the possibility of interactions should be borne in mind.

Alcohol (beverage) potentially increases the concentration of acitretin. Avoid and for 2 months after stopping acitretin. [Moderate] Study

Antiarhythmics (amiodarone) are predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Antifungals, azoles (fluconazole, itraconazole, ketoconazole, miconazole, posaconazole) are predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Antifungals, azoles (fluconazole, ketoconazole, voriconazole) are predicted to predict the risk of tretinoin toxicity when given with tretinoin. [Moderate] Study

Ciclosporin is predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Fibrates (gemfibrozil) are predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Fibrates (gemfibrozil) increase the concentration of bexarotene. Avoid. [Severe] Study

HIV-protease inhibitors are predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Idelalisib is predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Macrolides (clarithromycin) are predicted to increase the exposure to altretinoin. Adjust altretinoin dose, p. 1262. [Moderate] Theoretical

Acitretin is predicted to increase the concentration of methotrexate. Avoid. [Moderate] Anecdotal

Retinoids (acitretin, altretinoin, isotretinoin, tretinoin) increase the risk of benign intracranial hypertension when given with tetracyclines. Avoid. [Severe] Anecdotal

Bexarotene is predicted to increase the risk of toxicity when given with vitamin A. Adjust dose. [Moderate] Theoretical

Retinoids (acitretin, altretinoin, isotretinoin) are predicted to increase the risk of vitamin A toxicity when given with vitamin A. Avoid. [Severe] Theoretical

Tretinoin is predicted to increase the risk of vitamin A toxicity when given with vitamin A. Avoid. [Severe] Study

Ribavirin is predicted to increase the exposure to didanosine. Avoid. [Severe] Study

Ribavirin increases the risk of toxicity when given with stavudine. Avoid. [Severe] Study

Ribavirin increases the risk of anaemia and/or leucopenia when given with zidovudine. Avoid. [Severe] Study

Ribociclib — see TABLE 9 p. 1377 (QT-interval prolongation)

Food and lifestyle

Avoid concomitant use of pomegranate or pomegranate juice as it is predicted to increase ribociclib exposure.

Ribociclib (high-dose) is predicted to increase the exposure to alpha blockers (alfuzosin). Avoid. [Moderate] Theoretical

Antiarhythmics (dronedarone) are predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

Ribociclib (high-dose) is predicted to increase the exposure to antiarhythmics (amiodarone). Avoid. [Moderate] Theoretical → Also see TABLE 9 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to ribociclib. Avoid. [Severe] Study

Antifungals, azoles (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study → Also see TABLE 9 p. 1377

Aprepitant is predicted to increase the exposure to ribociclib. [Moderate] Study

Bosentan is predicted to decrease the exposure to ribociclib. [Moderate] Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ribociclib. [Moderate] Study

Ribociclib is predicted to increase the exposure to ciclosporin. Use with caution and adjust dose. [Moderate] Theoretical

Cobicistat is predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study

Crizotinib is predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

Ribociclib is predicted to increase the exposure to digoxin. [Moderate] Theoretical

Efavirenz is predicted to decrease the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study

Ribociclib is predicted to increase the exposure to everolimus. Use with caution and adjust dose. [Moderate] Theoretical

Grapefruit juice is predicted to increase the exposure to ribociclib. Avoid. [Moderate] Theoretical

Food and lifestyle

Ribociclib (high-dose) is predicted to increase the exposure to ergotamine. Avoid. [Moderate] Theoretical

Ribociclib is predicted to increase the exposure to everolimus. Use with caution and adjust dose. [Moderate] Theoretical

Ribociclib is predicted to increase the exposure to ribociclib. Avoid or adjust ribociclib dose, p. 997. [Moderate] Study

Macrolides (clarithromycin) are predicted to increase the exposure to ribociclib. Avoid. [Moderate] Study

Macrolides (erythromycin) are predicted to increase the exposure to ribociclib. [Moderate] Study → Also see TABLE 9 p. 1377

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Ribociclib (continued)

- **Ribociclib** is predicted to increase the exposure to metformin. (Moderate) Theoretical

- **Ribociclib** is predicted to markedly decrease the exposure to rifabutin. Avoid. (Moderate) Study

- **Mitotane** is predicted to markedly decrease the exposure to rifabutin. Avoid. (Severe) Study

- **Netupitant** is predicted to increase the exposure to ribociclib. (Moderate) Study

- **Nevirapine** is predicted to decrease the exposure to ribociclib. (Moderate) Study

- **Nilotinib** is predicted to increase the exposure to ribociclib. (Moderate) Study → Also see TABLE 9 p. 1377

- **Ribociclib** is predicted to increase the exposure to opioids (alfentanil, fentanyl). Use with caution and adjust dose. (Moderate) Theoretical

- **Ribociclib** is predicted to increase the exposure to phosphodiesterase type-5 inhibitors (sildenafil). Avoid. (Moderate) Theoretical → Also see TABLE 9 p. 1377

- **Ribociclib** (high-dose) is predicted to increase the exposure to pimodendrene. Avoid. (Moderate) Theoretical → Also see TABLE 9 p. 1377

- **Ribociclib** (high-dose) is predicted to increase the exposure to sirolimus. Use with caution and adjust dose. (Moderate) Theoretical

- **St John’s Wort** is predicted to decrease the exposure to ribociclib. Avoid. (Severe) Study

- **Ribociclib** is predicted to increase the exposure to statins (lovastatin, rosuvastatin). (Moderate) Theoretical

- **Ribociclib** is predicted to increase the exposure to statins (simvastatin). Avoid. (Moderate) Theoretical

- **Ribociclib** is predicted to increase the exposure to tacrolimus. Use with caution and adjust dose. (Moderate) Theoretical

### Rifabutin

**GENERAL INFORMATION**  Although some manufacturers class rifabutin as a potent inducer of CYP3A4, clinical data suggests it is potentially a weak inducer, and therefore the BNF does not extrapolate the interactions of potent CYP3A4 inducers to rifabutin. For those who wish to err on the side of caution, see the interactions of rifampicin but bear in mind other mechanisms might be involved.

- **Antifungals, azoles** (*fluconazole*) increase the risk of uveitis when given with rifabutin. Adjust dose. (Severe) Study

- **Antifungals, azoles** (*itraconazole, posaconazole*) increase the concentration of rifabutin and rifabutin decreases the concentration of antifungals, azoles (*itraconazole, posaconazole*). Avoid. (Severe) Study

- **Antifungals, azoles** (*ketoconazole*) are predicted to increase the concentration of rifabutin and rifabutin is predicted to decrease the concentration of antifungals, azoles (*ketoconazole*). Avoid. (Severe) Theoretical

- **Antifungals, azoles** (*miconazole*) are predicted to increase the concentration of rifabutin. Use with caution and adjust dose. (Moderate) Theoretical

- **Rifabutin** is predicted to decrease the exposure to antifungals, azoles (*itraconazole*). Avoid, (Severe) Theoretical

- **Rifabutin** decreases the concentration of antifungals, azoles (*voriconazole*) and antifungals, azoles (*voriconazole*) increase the concentration of rifabutin. Avoid or adjust voriconazole dose. p. 599. (Severe) Study

- **Rifabutin** slightly decreases the exposure to atorvastatin (*atorvastatin*). Avoid. (Moderate) Study

- **Rifabutin** slightly decreases the exposure to bictegravir. Avoid. (Moderate) Study

- **Rifabutin** is predicted to decrease the exposure to brigitinib. Avoid. (Moderate) Theoretical

- **Rifabutin** decreases the concentration of cobicistat and cobicistat increases the exposure to rifabutin. Avoid or adjust dose. (Severe) Study

- **Rifabutin** is predicted to decrease the efficacy of combined hormonal contraceptives. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Study

- **Rifabutin** decreases the exposure to dapson. (Moderate) Study

- **Rifabutin** is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

- **Rifabutin** moderately decreases the exposure to doravirine. Adjust doravirine dose. p. 644. (Severe) Study

- **Efavirenz** slightly decreases the exposure to rifabutin. Adjust dose. (Severe) Study

- **Rifabutin** is predicted to decrease the efficacy of etonogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

- **Rifabutin** decreases the exposure to estradiol. (Moderate) Study

- **HIV-protease inhibitors** (*atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir*) (boosted with ritonavir) increase the exposure to rifabutin. Monitor and adjust dose. (Severe) Study

- **HIV-protease inhibitors** (*ritonavir*) markedly increase the exposure to rifabutin. Avoid or adjust dose. (Severe) Study

- **Rifabutin** is predicted to decrease the effects of hormone replacement therapy. (Moderate) Anecdotal

- **Rifabutin** is predicted to decrease the exposure to ledipasvir. Avoid. (Severe) Theoretical

- **Rifabutin** is predicted to decrease the concentration of lertemovir. (Moderate) Theoretical

- **Rifabutin** is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

- **Lumacaftor** is predicted to decrease the exposure to rifabutin. Adjust dose. (Moderate) Theoretical

- **Macrolides** (*azithromycin*) increase the risk of neutropenia when given with rifabutin. (Severe) Study

- **Macrolides** (*clarithromycin*) increase the risk of uveitis when given with rifabutin. Adjust dose. (Severe) Study

- **Macrolides** (*erythromycin*) are predicted to increase the risk of uveitis when given with rifabutin. Adjust dose. (Severe) Theoretical

- **Rifabutin** is predicted to decrease the efficacy of norethisterone. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

- **Rifabutin** slightly decreases the exposure to rifapentine. Adjust dose. (Severe) Study

- **Rifabutin** is predicted to decrease the exposure to rolipram. Avoid. (Moderate) Theoretical

- **Rifabutin** is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical

- **Rifabutin** is predicted to decrease the exposure to tenofovir alafenamide. Avoid. (Moderate) Theoretical

- **Rifabutin** is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical

- **Rifabutin** decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

- **Rifabutin** is predicted to decrease the concentration of voxpilavir. Avoid. (Severe) Theoretical

### Rifampicin

- **Rifampicin** is predicted to markedly decrease the exposure to abemaciclib. Avoid. (Severe) Study

- **Rifampicin** is predicted to decrease the exposure to abiraterone. Avoid. (Severe) Study

- **Rifampicin** is predicted to decrease the exposure to afatinib. (Moderate) Study

- **Rifampicin** is predicted to decrease the exposure to agomelatin. (Moderate) Theoretical

- **Rifampicin** is predicted to decrease the exposure to aldosterone antagonists (*eplerenone*). Avoid. (Moderate) Theoretical

- **Rifampicin** decreases the exposure to aliskiren. (Moderate) Study

- **Rifampicin** is predicted to decrease the exposure to alprazolam. Adjust dose. (Moderate) Theoretical

- **Rifampicin** transiently increases the exposure to ambrisentan. (Moderate) Study

- **Rifampicin** decreases the exposure to aminophylline. Adjust dose. (Moderate) Study

- **Rifampicin** is predicted to decrease the exposure to anesthetics, local (*ropivacaine*). (Moderate) Theoretical

- **Antacids** decrease the absorption of rifampicin. Rifampicin should be taken 1 hour before anesthetics. (Moderate) Study

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**Rifampicin** is predicted to decrease the exposure to antiarrhythmics (disopyramide, dronedarone). Avoid. (Severe) Study

**Rifampicin** is predicted to decrease the efficacy of antiarrhythmics (propafenone). (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to anticholinesterases, centrally acting (donepezil). (Minor) Study

**Antiarrhythmics** (phenobarbital, primidone) are predicted to decrease the exposure to **rifampicin** and **rifampicin** is predicted to decrease the exposure to antiarrhythmics (phenobarbital, primidone). Use with caution and adjust dose. (Moderate) Study

**Rifampicin** slightly decreases the exposure to antiarrhythmics (brivaracetam). Adjust dose. (Moderate) Study

**Rifampicin** decreases the concentration of **fosphenytoin, phenytoin**. Use with caution and adjust dose. (Moderate) Study

**Rifampicin** markedly increases the clearance of **lamotrigine**. Adjust lamotrigine dose, p. 318. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to antiarrhythmics (pramipexole). Monitor and adjust dose. (Moderate) Study

**Rifampicin** slightly decreases the exposure to antifungals, azoles (fluconazole). Adjust dose. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to antifungals, azoles (econazole). Avoid. (Severe) Study

**Rifampicin** markedly decreases the exposure to antifungals, azoles (itraconazole). Avoid and for 14 days after stopping rifampicin. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to antifungals, azoles (posaconazole). Avoid. (Moderate) Anegetical

**Rifampicin** markedly decreases the exposure to antifungals, azoles (voriconazole). Avoid. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to antihistamines, non-sedating (bilastine). (Moderate) Theoretical

**Rifampicin** increases the clearance of antihistamines, non-sedating (fexofenadine). (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to antimalarials (artemether) with lumefantrine. Avoid. (Severe) Study

**Rifampicin** moderately decreases the exposure to antimalarials (artemether) and antimalarials (atovaquone) slightly increase the exposure to rifampicin. Avoid. (Moderate) Study

**Rifampicin** moderately decreases the exposure to antimalarials (mefloquine). (Severe) Study

**Rifampicin** is predicted to decrease the concentration of antimalarials (piperaquine). Avoid. (Moderate) Theoretical

**Rifampicin** decreases the exposure to antimalarials (quinine). (Severe) Study

**Rifampicin** is predicted to moderately decrease the exposure to apixaban. Use with caution or avoid. (Severe) Study

**Rifampicin** moderately decreases the exposure to apremilast. Avoid. (Severe) Study

**Rifampicin** is predicted to markedly decrease the exposure to aprepitant. Avoid. (Moderate) Study

**Rifampicin** is predicted to moderately decrease the exposure to aripiprazole. Adjust aripiprazole dose, p. 394. (Moderate) Study

**Rifampicin** decreases the exposure to ataluren. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to azithromycin. Avoid or adjust dose. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to bazedoxifene. (Moderate) Theoretical

**Rifampicin** decreases the exposure to bedaquiline. Avoid. (Severe) Study

**Rifampicin** moderately decreases the exposure to beta blockers, non-selective (carvedilol). (Moderate) Study

**Rifampicin** decreases the exposure to beta blockers, non-selective (propranolol). Monitor and adjust dose. (Moderate) Study

**Rifampicin** slightly decreases the exposure to beta blockers, selective (bisoprolol, metoprolol). (Minor) Study

**Rifampicin** moderately decreases the exposure to beta blockers, selective (cefliperol). (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to bictegravir. Avoid. (Moderate) Study

**Rifampicin** slightly decreases the exposure to bortezomib. Avoid. (Severe) Study

**Rifampicin** affects the exposure to bosentan. Avoid. (Severe) Study

**Rifampicin** is predicted to very markedly decrease the exposure to bosutinib. Avoid. (Severe) Study

**Rifampicin** is predicted to decrease the exposure to brigitinib. Avoid. (Severe) Study

**Rifampicin** is predicted to decrease the exposure to bupropion. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to buspirone. Use with caution and adjust dose. (Severe) Study

**Rifampicin** moderately decreases the exposure to cabozantinib. Avoid. (Moderate) Study

**Rifampicin** is predicted to moderately increase the clearance of caffeine citrate. Monitor and adjust dose. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine). Avoid. (Severe) Study

**Rifampicin** moderately decreases the exposure to canagliflozin. Adjust canagliflozin dose, p. 702. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to cannabis extract. Avoid. (Severe) Theoretical

**Rifampicin** is predicted to decrease the exposure to cariprazine. Avoid. (Severe) Theoretical

**Rifampicin** decreases the concentration of caspofungin. Adjust caspofungin dose, p. 392. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to ceritinib. Avoid. (Severe) Study

**Rifampicin** decreases the concentration of chloramphenicol. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to chlor Diazepoxide. (Moderate) Theoretical

**Rifampicin** decreases the concentration of ciclosporin. (Severe) Study

**Rifampicin** is predicted to alter the effects of cilostazol. (Moderate) Theoretical

**Rifampicin** is predicted to decrease the exposure to cinacalcet. Monitor and adjust dose. (Moderate) Study

**Rifampicin** decreases the exposure to clomethiazole. Monitor and adjust dose. (Moderate) Study

**Rifampicin** decreases the exposure to clozapine. (Severe) Anegetical

**Rifampicin** is predicted to decrease the exposure to cobimetinib. Avoid. (Severe) Theoretical

**Rifampicin** is predicted to decrease the efficacy of combined hormonal contraceptives. For FSHR guidance, see Contraceptives, interactions p. 794. (Severe) Study

**Rifampicin** is predicted to decrease the exposure to corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone). Monitor and adjust dose. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to corticosteroids (fluticasone). (Unknown) Theoretical

**Rifampicin** decreases the anticoagulant effect of coumarins. (Severe) Study

**Rifampicin** is predicted to markedly decrease the exposure to crizotinib. Avoid. (Severe) Study

**Rifampicin** is predicted to decrease the exposure to dabigatran. Avoid. (Severe) Study

**Rifampicin** is predicted to decrease the exposure to dabrafenib. Avoid. (Severe) Study

**Rifampicin** decreases the exposure to dapsona. (Moderate) Study

**Rifampicin** is predicted to decrease the exposure to darifenacin. (Moderate) Theoretical
Rifampicin is predicted to decrease the exposure to dasabuvir. Avoid. (Severe) Theoretical

Rifampicin is predicted to markedly decrease the exposure to desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Rifampicin is predicted to decrease the efficacy of desogestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Rifampicin moderately decreases the exposure to diazepam. Avoid. (Moderate) Study

Rifampicin decreases the concentration of digoxin. (Moderate) Study

Rifampicin decreases the exposure to doxycycline. Adjust dose. (Severe) Study

Rifampicin is predicted to decrease the exposure to efavirenz. Adjust dose. (Severe) Study

Rifampicin is predicted to decrease the exposure to elbasvir. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to etravirine. Avoid. (Severe) Theoretical

Rifampicin is predicted to decrease the concentration of everolimus. Avoid or adjust dose. (Severe) Study

Rifampicin moderately decreases the exposure to exemestane. (Moderate) Study

Rifampicin is predicted to decrease the exposure to fexofenadine. Avoid. (Moderate) Study

Rifampicin is predicted to decrease the exposure to fingolimod. (Moderate) Study

Rifampicin is predicted to decrease the exposure to fosaprepitant. Avoid. (Moderate) Theoretical

Rifampicin is predicted to decrease the exposure to gefitinib. Avoid. (Severe) Study

Rifampicin markedly affects the exposure to glecaprevir. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to grazoprevir. Avoid. (Severe) Study

Rifampicin is predicted to decrease the concentration of guanfacine. Adjust guanfacine dose, p. 352. (Moderate) Study

Rifampicin decreases the concentration of haloperidol. Adjust dose. (Moderate) Study

Rifampicin is predicted to moderately to markedly decrease the exposure to HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir). Avoid. (Severe) Study

Rifampicin slightly decreases the exposure to HIV-protease inhibitors (ritonavir). (Severe) Study

Rifampicin is predicted to decrease the exposure to HIV-protease inhibitors (tipranavir). Avoid. (Severe) Study

Rifampicin is predicted to decrease the effects of hormone replacement therapy. (Moderate) Aneccotal

Rifampicin is predicted to decrease the exposure to ibritinib. Avoid or adjust ibritinib dose, p. 983. (Severe) Study

Rifampicin is predicted to decrease the exposure to idelalisib. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to imatinib. Avoid. (Moderate) Study

Rifampicin is predicted to decrease the exposure to irinotecan. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to iron chelators (deferasirox). Monitor serum ferritin and adjust dose. (Moderate) Study

Rifampicin is predicted to decrease the exposure to ivabradine. Adjust dose. (Moderate) Theoretical

Rifampicin is predicted to affect the concentration of lenvatinib. (Severe) Study

Rifampicin is predicted to decrease the efficacy of levonorgestrel. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Theoretical

Rifampicin is predicted to decrease the exposure to linaclotide. (Moderate) Study

Rifampicin slightly decreases the exposure to linezolid. (Moderate) Study

Rifampicin is predicted to decrease the exposure to lorazepam. Monitor and adjust dose. (Moderate) Theoretical

Rifampicin increases the clearance of lorazepam. (Moderate) Study

Rifampicin is predicted to decrease the exposure to luradoline. Avoid. (Moderate) Study

Rifampicin is predicted to decrease the exposure to macitentan. Avoid. (Severe) Study

Rifampicin decreases the concentration of macrolides (clarithromycin). (Severe) Study

Rifampicin is predicted to decrease the exposure to maraviroc. Adjust dose. (Severe) Study

Rifampicin is predicted to decrease the exposure to melatonin. Monitor and adjust dose. (Moderate) Theoretical

Rifampicin is predicted to increase the clearance of mexiteline. Monitor and adjust dose. (Moderate) Study

Rifampicin is predicted to decrease the exposure to midostaurin. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to mirtazapine. Adjust dose. (Moderate) Study

Rifampicin is predicted to decrease the exposure to modafinil. (Moderate) Theoretical

Rifampicin decreases the effects of monoclonal antibodies (brentuximab vedotin). (Severe) Study

Rifampicin is predicted to decrease the exposure to mycophenolate. Monitor and adjust dose. (Severe) Study

Rifampicin is predicted to markedly decrease the exposure to naloxegol. Avoid. (Moderate) Study

Rifampicin is predicted to slightly decrease the exposure to nelargine. Adjust dose. (Moderate) Study

Rifampicin is predicted to decrease the exposure to nelitamib. Avoid. (Severe) Study

Rifampicin decreases the concentration of nelitamib. Avoid. (Severe) Study

Rifampicin is predicted to moderately decrease the exposure to nelitamib. Avoid. (Severe) Study

Rifampicin is predicted to decrease the exposure to nintedanib. (Moderate) Study
Rifampicin – Rifampicin 1525

**Rifampicin** is predicted to decrease the exposure to **nisitidine**. Adjust dose. [Moderate] Theoretical Study

**Rifampicin** increases the clearance of **nitrazepam**, [Moderate] Study

**Rifampicin** is predicted to decrease the efficacy of **norethisterone**. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal

**Rifampicin** moderately decreases the exposure to **NSAIDs**. (celecoxib, diclofenac, etoricoxib). [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to **olanzapine**. Monitor and adjust dose. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to **omacetaxine**. Avoid. [Moderate] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to **ombitasvir**. Avoid. [Severe] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to **ondansetron**. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to opioids (afentanil, fentanyl). [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to opioids (buprenorphine). Monitor and adjust dose. [Moderate] Theoretical Study

**Rifampicin** decreases the exposure to opioids (codeine, morphine). [Moderate] Study

**Rifampicin** decreases the exposure to opioids (methadone). Monitor and adjust dose. [Severe] Study

**Rifampicin** is predicted to moderately decrease the exposure to **osimertinib**. Avoid. [Moderate] Study

**Rifampicin** is predicted to moderately decrease the exposure to osoprenine. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to palbociclib. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **paliperidone**. Monitor and adjust dose. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **panobinostat**. Avoid. [Moderate] Theoretical Study

**Rifampicin** decreases the exposure to **paracetamol**. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to paraprevir (with ritonavir and ombitasvir). Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to pazopanib. Avoid. [Severe] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors (avanafil, tadalaflil). Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to phosphodiesterase type-5 inhibitors ( sildenafil, vardenafl). [Moderate] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to **pitirrimycin**. Monitor and adjust dose. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to pioglitazone. Monitor and adjust dose. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to pirfenidone. Avoid. [Moderate] Theoretical Study

**Rifampicin** is predicted to moderately decrease the exposure to pitholant. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to potolinib. Avoid. [Moderate] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to **praziquantel**. Avoid. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to quetiapine. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to **raltegravir**. Avoid or adjust dose—consult product literature. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to ranolazine. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to reboxetine. [Anecdotal] Study

**Rifampicin** is predicted to decrease the exposure to regorafenib. Avoid. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to **repaglinide**. Monitor blood glucose and adjust dose. [Moderate] Study

**Rifampicin** is predicted to markedly decrease the exposure to **rifociclib**. Avoid. [Severe] Study

**Rifampicin** markedly decreases the exposure to **rilpivirine**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **risperidone**. Adjust dose. [Moderate] Study

**Rifampicin** is predicted to moderately decrease the exposure to **rivaroxaban**. Avoid unless patient can be monitored for signs of thrombosis. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **rosfumilast**. Avoid. [Moderate] Study

**Rifampicin** is predicted to markedly decrease the exposure to **rolapitant**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **roxulitinib**. Monitor and adjust dose. [Moderate] Study

**Rifampicin** is predicted to moderately decrease the exposure to **saxagliptin**. [Moderate] Study

**Rifampicin** moderately decreases the exposure to the active metabolite of **selexipag**. Adjust dose. [Moderate] Study

**Rifampicin** is predicted to decrease the concentration of **sirolimus**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **sofosbuvir**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **sulfinpyrazone**. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to **sunitinib**. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study

**Rifampicin** decreases the concentration of **tacrolimus**. Monitor and adjust dose. [Severe] Study

**Rifampicin** markedly decreases the exposure to **tamoxifen**. [Unknown] Study

**Rifampicin** is predicted to decrease the exposure to **taxanes** (docetaxel, paclitaxel). Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to taxanes (docetaxel). [Severe] Theoretical Study

**Rifampicin** is predicted to decrease the concentration of **teivofovir alafenamide**. Avoid. [Moderate] Theoretical Study

**Rifampicin** decreases the exposure to **terbinafine**. Adjust dose. [Moderate] Study

**Teriflunomide** is predicted to increase the exposure to rifampicin. [Moderate] Theoretical Study

**Rifampicin** decreases the exposure to **tetracyclines** (doxycycline). Monitor and adjust dose. [Moderate] Study

**Rifampicin** is predicted to decrease the exposure to tezacaftor. Avoid. [Severe] Theoretical Study

**Rifampicin** is predicted to decrease the exposure to **theophylline**. Adjust dose. [Moderate] Study

**Rifampicin** is predicted to markedly decrease the exposure to **ticagrelor**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **tivozanib**. [Severe] Study

**Rifampicin** moderately decreases the exposure to **tizanidine**. [Mild] Study

**Rifampicin** is predicted to decrease the exposure to **tobaficitinib**. Avoid. [Severe] Study

**Rifampicin** is predicted to decrease the exposure to **tolvaptan**. Use with caution or avoid depending on indication. [Severe] Study

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Rifampicin — Ritonavir

Rifampicin (continued)
- **Rifampicin** is predicted to decrease the exposure to toremifene. Adjust dose. (Moderate Study)
- **Rifampicin** is predicted to decrease the exposure to telaprevir. Avoid. (Severe) Theoretical
- **Rifampicin** decreases the exposure to trimethoprim. (Moderate) Study
- **Rifampicin** decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal
- **Rifampicin** is predicted to decrease the exposure to vandetanib. Avoid. (Moderate) Study
- **Rifampicin** is predicted to moderately decrease the exposure to velpatavir. Avoid. (Severe) Study
- **Rifampicin** is predicted to decrease the exposure to vemurafenib. Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to venetoclax. Avoid. (Severe) Study
- **Rifampicin** is predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vinidines). (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to vinca alkaloids (vinflunine). Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to vinca alkaloids (vinorelbine). Use with caution or avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to vismodegib. Avoid. (Moderate) Theoretical
- **Rifampicin** potentially increases the risk of nephrotoxicity when given with volatile halogenated anaesthetics (methoxyflurane). Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to voriprazir. Monitor and adjust dose. (Moderate) Study
- **Rifampicin** is predicted to decrease the concentration of voluluaprevir. Avoid. (Severe) Study
- **Rifampicin** moderately decreases the exposure to zolpidem. (Moderate) Study
- **Rifampicin** is predicted to decrease the exposure to zopiclone. Adjust dose. (Moderate) Study

**Rifaximin**
- **Rifaximin** very markedly increases the exposure to rifaximin. (Severe) Study

**Rilpivirine**
- **Antacids** are predicted to decrease the exposure to rilpivirine. Antacids should be taken 2 hours before or 4 hours after rilpivirine. (Severe) Theoretical
- **Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) markedly decrease the exposure to rilpivirine. Avoid. (Severe) Study
- **Antiepileptics** (oxcarbazepine) are predicted to decrease the concentration of rilpivirine. Avoid. (Severe) Theoretical
- **Bozantan** is predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Theoretical
- **Calcium salts** (calcium carbonate) are predicted to slightly decrease the exposure to rilpivirine. Calcium carbonate should be taken 2 hours before or 4 hours after rilpivirine. (Severe) Theoretical
- **Corticosteroids** (dexamethasone) are predicted to decrease the concentration of rilpivirine. Avoid multiple-dose dexamethasone. (Severe) Theoretical
- **Efavirenz** is predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Theoretical
- **Enzalutamide** markedly decreases the exposure to rilpivirine. Avoid. (Severe) Study
- **Estravirine** is predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Theoretical
- **H₂ receptor antagonists** are predicted to decrease the exposure to rilpivirine. H₂ receptor antagonists should be taken 12 hours before or 4 hours after rilpivirine. (Severe) Study
- **Mitotane** markedly decreases the exposure to rilpivirine. Avoid. (Severe) Study
- **Nevirapine** is predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Theoretical
- **Proton pump inhibitors** are predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Study
- **Rifabutin** slightly decreases the exposure to rilpivirine. Adjust dose. (Severe) Study
- **Rifampicin** markedly decreases the exposure to rilpivirine. Avoid. (Severe) Study
- **St John’s Wort** is predicted to decrease the exposure to rilpivirine. Avoid. (Severe) Theoretical

**Riluzole**
- **FOOD AND LIFESTYLE** Charcoal-grilled foods are predicted to decrease the exposure to riluzole.
- **Mexiletine** is predicted to increase the exposure to riluzole. (Moderate) Theoretical
- **Quinolones** (ciprofloxacin) are predicted to increase the exposure to riluzole. (Moderate) Theoretical
- **SSRIs** (fluvoxamine) are predicted to increase the exposure to riluzole. (Moderate) Theoretical

**Riociguat**
- **Study** see TABLE 8 p. 1376 (hypotension)
- **Antacids** slightly decrease the exposure to riociguat. Antacids should be taken 2 hours before or 1 hour after riociguat. (Mild) Study
- **Antifungals, azoles** (itraconazole) are predicted to increase the exposure to riociguat. Avoid. (Moderate) Study
- **Antifungals, azoles** (ketonazole) moderately increase the exposure to riociguat. Avoid. (Moderate) Study
- **Ciclosporin** is predicted to increase the exposure to riociguat. (Moderate) Theoretical
- **HIV-protease inhibitors** (ritonavir) are predicted to increase the exposure to riociguat. Avoid. (Moderate) Theoretical
- **Riociguat** is predicted to increase the risk of hypotension when given with phosphodiesterase type-5 inhibitors. Avoid. (Severe) Theoretical — Also see TABLE 8 p. 1376

**Risedronate** see bisphosphonates

**Risperidone** see TABLE 8 p. 1376 (hypotension), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 11 p. 1377 (CNS depressant effects)
- **Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to risperidone. Adjust dose. (Moderate) Study — Also see TABLE 11 p. 1377
- **Antifungals, azoles** (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study — Also see TABLE 9 p. 1377
- **Buropipron** is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Cinacalcet** is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Cobicistat** is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Risperidone** is predicted to decrease the effects of dopamine receptor agonists. Avoid. (Moderate) Theoretical — Also see TABLE 8 p. 1376 — Also see TABLE 8 p. 1377
- **Enalaprilat** is predicted to decrease the exposure to risperidone. Adjust dose. (Moderate) Study
- **HIV-protease inhibitors** are predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study — Also see TABLE 9 p. 1377
- **Idelalisib** is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Risperidone** is predicted to decrease the effects of levodopa. Avoid or adjust dose. (Severe) Anecdotal — Also see TABLE 8 p. 1376
- **Risperidone** potentially increases the risk of neurotoxicity when given with lithium. (Severe) Anecdotal — Also see TABLE 9 p. 1377
- **Macrolides** (clarithromycin) are predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study — Also see TABLE 9 p. 1377
- **Risperidone** increases the risk of dyskinesias when given with methylphenidate. (Severe) Anecdotal
- **Mitotane** is predicted to decrease the exposure to risperidone. Adjust dose. (Moderate) Study
- **Rifampicin** is predicted to decrease the exposure to risperidone. Adjust dose. (Moderate) Study
- **SSRIs** (fluvoxamine, paroxetine) are predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Terbinafine** is predicted to increase the exposure to risperidone. Adjust dose. (Moderate) Study
- **Ritonavir** see HIV-protease inhibitors
Rituximab → see monoclonal antibodies

Rivaroxaban → see TABLE 3 p. 1375 (anticoagulant effects)

- Antiarrhythmics (dronedarone) are predicted to increase the exposure to rivaroxaban. Avoid. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to rivaroxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- Antifungals, azoles (itraconazole, ketoconazole) are predicted to moderately increase the exposure to rivaroxaban. Avoid. (Severe) Study
- Ciclosporin is predicted to increase the exposure to rivaroxaban. Avoid. (Severe) Theoretical
- Enalapril is predicted to moderately decrease the exposure to rivaroxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- HIV-protease inhibitors (ritonavir) moderately increase the exposure to rivaroxaban. Avoid. (Severe) Study
- Mitotane is predicted to moderately decrease the exposure to rivaroxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- Rifampicin is predicted to moderately decrease the exposure to rivaroxaban. Avoid unless patient can be monitored for signs of thrombosis. (Severe) Study
- Rivastigmine → see anticholinesterases, centrally acting
- Rizatriptan → see TABLE 3 p. 1378 (serotonin syndrome)
- Beta blockers, non-selective (propranolol) slightly to moderately increase the exposure to rizatriptan. Adjust rizatriptan dose and separate administration by at least 2 hours. (Moderate) Study
- Rizatriptan is predicted to increase the risk of vasoconstriction when given with ergotamine. Ergotone should be taken at least 24 hours before or 6 hours after rizatriptan. (Severe) Theoretical
- Moclobemide moderately increases the exposure to rizatriptan. Avoid. (Severe) Study → Also see TABLE 3 p. 1378
- Monoamine-oxidase A and B inhibitors, irreversible are predicted to increase the exposure to rizatriptan. Avoid and for 14 days after stopping the MAOI. (Severe) Theoretical → Also see TABLE 3 p. 1378
- Recuronium → see neuromuscular blocking drugs, non-depolarising
- Aminophylline is predicted to slightly increase the exposure to roflumilast. Avoid. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- Combined hormonal contraceptives are predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- Enalapril is predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- Ity receptor antagonists (cimetidine) slightly increase the exposure to roflumilast. (Moderate) Study
- Mexiletine is predicted to increase the exposure to roflumilast. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to roflumilast. (Moderate) Study
- Quinolones (ciprofloxacin) are predicted to increase the exposure to roflumilast. (Moderate) Theoretical
- Rifampicin is predicted to decrease the exposure to roflumilast. Avoid. (Moderate) Study
- SSRI (fluvoxamine) are predicted to increase the exposure to roflumilast. (Moderate) Study
- Theophylline is predicted to slightly increase the exposure to roflumilast. (Moderate) Theoretical
- Rolipitant is predicted to moderately increase the exposure to beta blockers, selective (metoprolol). (Severe) Study
- Bosentan is predicted to decrease the exposure to rolipitant. Avoid. (Severe) Study
- Rolipitant is predicted to increase the exposure to colchicine. (Moderate) Study
- Rolipitant is predicted to increase the exposure to dabigatran. (Moderate) Study
- Rolipitant slightly increases the exposure to digoxin. (Moderate) Study
- Efavirenz is predicted to decrease the exposure to rolipitant. Avoid. (Severe) Study
- Enalapril is predicted to markedly decrease the exposure to rolipitant. Avoid. (Severe) Study
- Rolipitant is predicted to increase the exposure to irinotecan. Avoid or monitor. (Moderate) Study
- Rolipitant is predicted to increase the exposure to methotrexate. Avoid or monitor. (Moderate) Study
- Mitotane is predicted to markedly decrease the exposure to rolipitant. Avoid. (Severe) Study
- Nevirapine is predicted to decrease the exposure to rolipitant. Avoid. (Severe) Study
- Rolipitant is predicted to increase the exposure to pimozone. (Severe) Study
- Rifabutin is predicted to decrease the exposure to rolipitant. Avoid. (Moderate) Theoretical
- Rifampicin is predicted to markedly decrease the exposure to rolipitant. Avoid. (Severe) Study
- St John's Wort is predicted to decrease the exposure to rolipitant. Avoid. (Severe) Study
- Rolipitant is predicted to increase the exposure to statins (rosuvastatin). Monitor and adjust dose. (Severe) Study
- Rolipitant increases the exposure to sulfasalazine. (Severe) Study
- Rolipitant is predicted to increase the exposure to tamoxifen. (Severe) Study
- Rolipitant is predicted to increase the exposure to topotecan. Avoid or monitor. (Moderate) Study
- Rapinol→ see dopamine receptor antagonists
- Ropivacaine → see anaesthetics, local
- Rosuvastatin → see statins
- Rotavirus vaccine → see live vaccines
- Rotigotine → see dopamine receptor antagonists
- Rucaparib
  - Rucaparib is predicted to increase the exposure to aminophylline. Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to antiepileptics (phenytoin). Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to ciclosporin. Monitor and adjust dose. (Moderate) Study
  - Rucaparib slightly increases the exposure to coumarins (warfarin). Monitor and adjust dose. (Severe) Study
  - Rucaparib is predicted to increase the exposure to ergotamine. Monitor and adjust dose. (Moderate) Study
  - Rucaparib slightly increases the exposure to midazolam. Monitor and adjust dose. (Severe) Study
  - Rucaparib is predicted to increase the exposure to opioids (alfentanil, fentanyl). Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to pimozone. Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to sirolimus. Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to tacrolimus. Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to theophylline. Monitor and adjust dose. (Moderate) Study
  - Rucaparib is predicted to increase the exposure to tizanidine. Monitor and adjust dose. (Moderate) Study
  - Rufinamide → see antiepileptics
  - Rufatadine → see antihistamines, non-sedating
- Ruxolitinib → see TABLE 15 p. 1378 (myelosuppression)
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to ruxolitinib. (Moderate) Theoretical
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to ruxolitinib. Monitor and adjust dose. (Moderate) Study

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Ruxolitinib (continued)

- Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ruxolitinib. Adjust dose and monitor side effects. [Moderate] Study
- Aprepitant is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Bosentan is predicted to decrease the exposure to ruxolitinib. Monitor and adjust dose. [Moderate] Theoretical
- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ruxolitinib. Adjust dose and monitor side effects. [Moderate] Study
- Cobicistat is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Enzalutamide is predicted to increase the exposure to ruxolitinib. [Moderate] Study
- HIV-protease inhibitors are predicted to increase the exposure to ruxolitinib. [Moderate] Study
- Macrolides (clarithromycin) are predicted to increase the exposure to ruxolitinib. [Moderate] Study
- Macrolides (erythromycin) are predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Mitotane is predicted to increase the exposure to ruxolitinib. Adjust dose and monitor side effects. [Moderate] Study
- Nitupitant is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Nevirapine is predicted to increase the exposure to ruxolitinib. Monitor and adjust dose. [Moderate] Theoretical
- Nilotinib is predicted to increase the exposure to ruxolitinib. [Moderate] Theoretical
- Ruxolitinib is predicted to increase the risk of bleeding events when given with coumarins. [Severe] Review
- Selecipag is predicted to increase the exposure to ruxolitinib. Monitor and adjust dose. [Moderate] Study
- Statins are predicted to increase the exposure to ruxolitinib. Adjust dose. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to ruxolitinib. Monitor and adjust dose. [Moderate] Theoretical
- Saxagliptin is predicted to moderately decrease the exposure to saxagliptin. [Moderate] Theoretical
- Selexipag is predicted to increase the exposure to selexipag. [Unknown] Theoretical
- Teriflunomide is predicted to increase the exposure to selexipag. Adjust dose. [Moderate] Study
- Silver sulfadiazine is predicted to inactivate enzymatic debridng agents—concurrent use might not be appropriate.

Selenium

ROUTE-SPECIFIC INFORMATION Interactions do not generally apply to topical use unless specified.

- Oral selenium is predicted to decrease the absorption of eltrombopag. Etaibromopag should be taken 2 hours before or 4 hours after selenium. [Severe] Theoretical

Selexipag

- Antiepileptics (carbamazepine, fosphenytoin, phenytoin) are predicted to decrease the exposure to the active metabolite of selexipag. Adjust dose. [Moderate] Study
- Antiepileptics (valproate) are predicted to increase the exposure to selexipag. [Unknown] Theoretical
- Iron chelators (deferasirox) are predicted to increase the exposure to selexipag. Adjust dose. [Moderate] Study
- Leflunomide is predicted to increase the exposure to selexipag. Adjust dose. [Moderate] Theoretical
- Mitotane is predicted to moderately decrease the exposure to selexipag. Adjust dose. [Moderate] Study
- Sildenafil is predicted to increase the exposure to selexipag. Adjust dose. [Moderate] Study
- Silver sulfadiazine is predicted to inactivate enzymatic debridng agents—concurrent use might not be appropriate.

Simvastatin → see statins
Sirolimus

- Antiarrhythmics (amiodarone) are predicted to increase the concentration of sirolimus. Avoid. [Severe] Anecdotal
- Antiarrhythmics (dronedarone) increase the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Anti-epileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of sirolimus. Avoid. [Severe] Study
- Antifungals, azoles (fluconazole, itraconazole, posaconazole) increase the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of sirolimus. Avoid. [Severe] Study
- Apalutamid is predicted to decrease the exposure to sirolimus. Avoid or monitor. [Moderate] Study
- Aprepitant increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Bosentan is predicted to decrease the concentration of sirolimus and sirolimus potentially increases the concentration of bosentan. Avoid. [Severe] Theoretical
- Brigitinib potentially decreases the concentration of sirolimus. Avoid. [Moderate] Study
- Calcium channel blockers (diltiazem, verapamil) increase the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Ceritinib is predicted to increase the exposure to sirolimus. Avoid. [Severe] Theoretical
- Sirolimus is predicted to affect the efficacy of chenodeoxycholic acid. Monitor and adjust dose. [Moderate] Theoretical
- Ciclosporin moderately increases the exposure to sirolimus. Separate administration by 4 hours. [Severe] Study
- Cobicistat is predicted to increase the concentration of sirolimus. Avoid. [Severe] Study
- Crizotinib increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Doravirine is predicted to decrease the exposure to sirolimus. Monitor sirolimus concentration and adjust dose, p. 846
- Efamolizumab is predicted to decrease the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Erliglustat is predicted to increase the exposure to sirolimus. Adjust dose. [Moderate] Study
- Enalaprilat is predicted to decrease the concentration of sirolimus. Avoid. [Severe] Study
- Grapefruit juice increases the concentration of sirolimus. Avoid. [Severe] Study
- HIV-protease inhibitors are predicted to increase the concentration of sirolimus. Avoid. [Severe] Study
- Idealisib is predicted to increase the concentration of sirolimus. Avoid. [Severe] Study
- Imatinib increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Lapatinib is predicted to increase the exposure to sirolimus. [Moderate] Theoretical
- Leteremor moderately increases the exposure to sirolimus. Monitor and adjust dose. [Severe] Study
- Live vaccines are predicted to increase the risk of generalised infection (possibly life-threatening) when given with sirolimus. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical
- Lumacaftor is predicted to decrease the exposure to sirolimus. Avoid. [Severe] Theoretical
- Macrolides (clarithromycin) are predicted to increase the concentration of sirolimus. Avoid. [Severe] Study
- Macrolides (erythromycin) increase the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Sirolimus is predicted to decrease the efficacy of mifamurtide. Avoid. [Severe] Theoretical
- Mirabegron is predicted to increase the exposure to sirolimus. [Med] Theoretical
- Mitotane is predicted to decrease the concentration of sirolimus. Avoid. [Severe] Study
- Monoclonal antibodies (sarilumab) potentially affect the exposure to sirolimus. Monitor and adjust dose. [Moderate] Theoretical
- Netupitant increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Nevirapine is predicted to decrease the concentration of sirolimus. Monitor and adjust dose. [Moderate] Theoretical
- Nilotinib increases the concentration of sirolimus. Monitor and adjust dose. [Moderate] Study
- Palbociclib is predicted to increase the exposure to sirolimus. Adjust dose. [Moderate] Theoretical
- Pibrentasvir (with glecaprevir) is predicted to increase the exposure to sirolimus. [Moderate] Study
- Pitolisant is predicted to decrease the exposure to sirolimus. Avoid. [Severe] Theoretical
- Ribociclib is predicted to increase the exposure to sirolimus. Use with caution and adjust dose. [Moderate] Theoretical
- Rifampicin is predicted to decrease the concentration of sirolimus. Avoid. [Severe] Study
- Rucaparib is predicted to increase the exposure to sirolimus. Monitor and adjust dose. [Moderate] Study
- St John’s Wort is predicted to decrease the concentration of sirolimus. Monitor and adjust dose. [Severe] Theoretical
- Sirolimus is predicted to decrease the concentration of tacrolimus and tacrolimus increases the exposure to sirolimus. [Severe] Study
- Velpatasvir is predicted to increase the exposure to sirolimus. [Moderate] Study
- Venetoclax is predicted to increase the exposure to sirolimus. Avoid or adjust dose. [Severe] Study

Sodium aurothiomalate

- ACE inhibitors are predicted to increase the risk of hypersensitivity when given with sodium aurothiomalate. Avoid. [Severe] Anecdotal
- Sodium aurothiomalate potentially increases the risk of side-effects when given with penicillamine (in those who have had previous adverse reactions to gold). Avoid. [Severe] Study

Sodium bicarbonate

ROUTE-SPECIFIC INFORMATION

Interactions do not generally apply to topical use unless specified.

- Oral sodium bicarbonate decreases the absorption of antifungals, azoles (ketoconazole). Avoid. [Moderate] Study
- Sodium bicarbonate decreases the concentration of lithium. Avoid. [Severe] Anecdotal
- Sodium bicarbonate is predicted to decrease the efficacy of methenamine. Avoid. [Moderate] Theoretical
- Sodium citrate is predicted to decrease the efficacy of methenamine. Avoid. [Moderate] Theoretical
- Sodium citrate is predicted to increase the risk of side-effects when given with sucralfate. Avoid. [Moderate] Theoretical
- Sodium clodronate → see bisphosphonates
- Sodium feredate → see iron (oral)
- Sodium nitroprusside → see TABLE 8 p. 1376 (hypotension)
- Sodium nitroprusside is predicted to increase the risk of methaemoglobinemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. [Severe] Theoretical
- Sodium nitroprusside is predicted to increase the risk of methaemoglobinemia when given with dapsone. [Severe] Theoretical
- Sodium oxybate → see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)
- Antibiotics (valproate) increase the exposure to sodium oxybate. Adjust sodium oxybate dose, p. 491. [Moderate] Study
- Sodium phenylbutyrate
  - Antibiotics (valproate) potentially decrease the effects of sodium phenylbutyrate. Avoid. [Moderate] Anecdotal
  - Corticosteroids potentially decrease the effects of sodium phenylbutyrate. Avoid. [Moderate] Anecdotal
  - Haloperidol potentially decreases the effects of sodium phenylbutyrate. Avoid. [Moderate] Anecdotal
- Sodium picosulfate → see TABLE 18 p. 1379 (hyponatraemia)
Sodium stibogluconate

- Sodium stibogluconate increases the risk of cardiovascular side-effects when given with amphotericin. Separate administration by 14 days. (Severe) Study

Sofosbuvir

- Sofosbuvir is predicted to increase the risk of severe bradycardia or heart block when given with antithyroid drugs (amiodarone). Refer to specialist literature. (Severe) Anecdotal
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Study
- Antiepileptics (fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- H₂ receptor antagonists potentially decrease the exposure to sofosbuvir. Adjust dose, see ledipasvir with sofosbuvir p. 628, sofosbuvir with velpatasvir p. 629, and sofosbuvir with velpatasvir and voxilaprevir p. 630. (Moderate) Study
- HIV-protecte inhibitors (tipranavir) are predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Proton pump inhibitors potentially decrease the exposure to sofosbuvir. Adjust dose, see ledipasvir with sofosbuvir p. 628, sofosbuvir with velpatasvir p. 629, and sofosbuvir with velpatasvir and voxilaprevir p. 630. (Moderate) Study
- Rifabutin is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Rifampicin is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Modafinil is predicted to decrease the exposure to sofosbuvir. Avoid. (Severe) Theoretical
- Sodium stibogluconate

Solifenacin → see TABLE 10 p. 1377 (antimuscarinics)

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study
- Cobicistat is predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study
- Enalapril is predicted to decrease the exposure to solifenacin. (Moderate) Theoretical
- Enalapril is predicted to decrease the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study
- Idelalisib is predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study
- Macrolides (clarithromycin) are predicted to increase the exposure to solifenacin. Adjust solifenacin p. 779 or tamsulosin with solifenacin p. 786 dose; avoid in hepatic and renal impairment. (Severe) Study
- Mitotane is predicted to decrease the exposure to solifenacin. (Moderate) Theoretical
- Rifampicin is predicted to decrease the exposure to solifenacin. (Moderate) Theoretical
- Somatostatin

Corticosteroids are predicted to decrease the effects of somatropin. (Moderate) Theoretical

Sorafenib → see TABLE 15 p. 1378 (myelosuppression), TABLE 9 p. 1377 (QT-interval prolongation)

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to sorafenib. (Moderate) Theoretical
- Sorafenib increases the anticoagulant effect of coumarins. (Severe) Anecdotal
- Enalapril is predicted to decrease the exposure to sorafenib. (Moderate) Theoretical
- Mitotane is predicted to decrease the exposure to sorafenib. (Moderate) Theoretical → Also see TABLE 15 p. 1378
- Neomycin moderately decreases the exposure to sorafenib. (Moderate) Study
- Sorafenib is predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical
- Rifampicin is predicted to decrease the exposure to sorafenib. (Moderate) Theoretical
- Sotalol → see beta blockers, non-selective
- Spironolactone → see aldosterone antagonists

SSRIs → see TABLE 18 p. 1379 (hyponatraemia), TABLE 13 p. 1378 (serotonin syndrome), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 4 p. 1375 (antiplalet effects)

citalopram - dapoxetine - escitalopram - fluoxetine - fluvoxamine - paroxetine - sertraline

- Fluvoxamine very markedly increases the exposure to agomelatine. Avoid. (Severe) Study
- Fluvoxamine moderately increases the exposure to alprazolam. Adjust dose. (Moderate) Study
- SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to amfetamines. (Severe) Theoretical → Also see TABLE 13 p. 1378
- Fluvoxamine moderately to markedly increases the exposure to aminophylline. Avoid. (Severe) Study
- Fluvoxamine decreases the clearance of anaethetics, local (ropivacaine). Avoid prolonged use. (Moderate) Study
- Fluvoxamine is predicted to increase the exposure to anagrelide. (Moderate) Theoretical → Also see TABLE 4 p. 1375
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to dapoxetine. Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. (Moderate) Theoretical
- Antiarrhythmics (dronedarone) are predicted to increase the exposure to SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). (Severe) Theoretical → Also see TABLE 9 p. 1377
- Fluvoxamine is predicted to increase the exposure to antiarrhythmics (propafenone). Monitor and adjust dose. (Moderate) Study
- SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. (Moderate) Study
- Fluvoxamine is predicted to increase the concentration of paroxetine. (Moderate) Study
- Sertraline potentially increases the risk of toxicity when given with antiepileptics (fosphenytoin, phenytoin). Monitor concentration and adjust dose. (Severe) Anecdotal
- SSRIs (fluoxetine, fluvoxamine) are predicted to increase the concentration of antiarrhythmics (propafenone, phenytoin). Monitor and adjust dose. (Severe) Anecdotal
- Antifungals, azoles (fluconazole, itraconazole, voriconazole) are predicted to increase the exposure to fluconazole. Adjust dose with moderate inhibitors of CYP3A4, p. 821. (Moderate) Theoretical
- Antifungals, azoles (itraconazole, ketocnazole, voriconazole) are predicted to increase the exposure to fluconazole. Avoid moderate inhibitors of CYP3A4 or adjust dapoxetine dose, p. 821. (Severe) Study
- Antifungals, azoles (voriconazole) are predicted to increase the exposure to citalopram. (Severe) Theoretical → Also see TABLE 9 p. 1377
- Antihistamines, sedating (cyproheptadine) potentially decrease the effects of SSRIs. (Moderate) Anecdotal
- Apalutamide is predicted to decrease the exposure to citalopram. Avoid or monitor. (Moderate) Study → Also see TABLE 9 p. 1377
- Aprepitant is predicted to increase the exposure to dapoxetine. Adjust dapoxetine dose with moderate inhibitors of CYP3A4, p. 821. (Moderate) Theoretical
- Aripiprazole is predicted to increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. (Moderate) Study
- Fluvoxamine increases the exposure to asenapine. (Moderate) Study
- Paroxetine moderately increases the exposure to asenapine. (Moderate) Study
- SSRIs (fluoxetine, paroxetine) are predicted to markedly increase the exposure to atomoxetine. Adjust dose. (Severe) Study

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Fluvoxamine is predicted to increase the concentration of beta blockers, non-selective (propranolol). Moderate Study

SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). Moderate Study

Buproprion is predicted to increase the exposure to dapoxtine. Moderate Theoretical

Fluvoxamine markedly decreases the clearance of caffeine citrate. Monitor and adjust dose. Severe Study

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

SSRIs (fluoxetine, fluvoxamine) are predicted to increase the exposure to clozapin. Adjust clozapin dose, p. 232. Moderate Theoretical

SSRIs (fluoxetine, fluvoxamine) are predicted to decrease the efficacy of clonidine. Avoid. Moderate Theoretical

Fluvoxamine is predicted to increase the efficacy of clonidine. Monitor side effects and adjust dose. Moderate Study

Cobicistat is predicted to moderately increase the exposure to dapoxtine. Avoid potent inhibitors of CYP3A4 or adjust dapoxtine dose, p. 821. Moderate Study

Crisitinib is predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

SSRIs (fluoxetine, paroxetine) are predicted to slightly increase the exposure to darifenacin. Mild Study

Fluvoxamine moderately increases the exposure to diazepam. Moderate Study

Fluvoxamine is predicted to increase the exposure to dopamine receptor agonists (ropinirole). Adjust dose. Moderate Study

Fluvoxamine markedly increases the exposure to duloxetine. Avoid. Severe Study Also see TABLE 13 p. 1578

SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to eliglutzat. Avoid or adjust dose—consult product literature. Severe Study

Fluvoxamine is predicted to increase the exposure to eltrobrogop. Moderate Theoretical

Fluvoxamine is predicted to increase the exposure to erlotinib. Monitor side effects and adjust dose. Moderate Theoretical

Fluvoxamine increases the concentration of frovatriptan. Moderate Theoretical Also see TABLE 18 p. 1379

Grapefruit juice moderately increases the exposure to sertraline. Avoid. Moderate Study

H₂ receptor antagonists (cimetidine) slightly increase the exposure to SSRIs (cilastropam, escalopram). Adjust dose. Moderate Study

H₂ receptor antagonists (cimetidine) slightly increase the exposure to SSRIs (paroxetine, sertraline). Moderate Study

Fluoxetine increases the concentration of haloperidol. Adjust dose. Moderate Aneotal

HIV-protease inhibitors are predicted to moderately increase the exposure to dapoxtine. Avoid potent inhibitors of CYP3A4 or adjust dapoxtine dose, p. 821. Severe Study

Idelalisib is predicted to moderately increase the exposure to dapoxtine. Avoid potent inhibitors of CYP3A4 or adjust dapoxtine dose, p. 821. Severe Study

Imatinib is predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

Fluoxetine is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. Unknown Theoretical

Fluvoxamine is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. Moderate Theoretical

Fluvoxamine is predicted to increase the exposure to loxapine. Avoid. Unknown Theoretical

Macrolides (clarithromycin) are predicted to moderately increase the exposure to dapoxtine. Avoid potent inhibitors of CYP3A4 or adjust dapoxtine dose, p. 821. Severe Study

Macrolides (erythromycin) are predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

Fluvoxamine very markedly increases the exposure to melatonin. Avoid. Severe Study

SSRIs (fluoxetine, fluvoxamine, paroxetine) are predicted to increase the exposure to melatonin. Moderate Study

Netupitant is predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

SSRIs potentially increase the risk of prolonged neuromuscular blockade when given with neuromuscular blocking drugs, non-depolarising (mivacurium). Unknown Theoretical

Nilotinib is predicted to increase the exposure to dapoxtine. Adjust dapoxtine dose with moderate inhibitors of CYP3A4, p. 821. Moderate Theoretical

Fluvoxamine moderately increases the exposure to olanzapin. Adjust dose. Severe Aneotal

Paroxetine slightly increases the exposure to procyclidine. Monitor and adjust dose. Moderate Study

Proton pump inhibitors (omeprazole) are predicted to slightly to moderately increase the exposure to SSRIs (cilastropam, escalopram). Monitor and adjust dose. Moderate Study

Fluvoxamine is predicted to increase the exposure to pomalidomide. Adjust pomalidomide dose, p. 941. Moderate Study

Fluvoxamine is predicted to increase the exposure to pipenzylline. Moderate Theoretical

Fluvoxamine is predicted to moderately increase the exposure to pirenidone. Avoid. Moderate Study

SSRIs (fluoxetine, paroxetine) are predicted to moderately increase the exposure to pitolisant. Use with caution and adjust dose. Moderate Study

Fluvoxamine moderately increases the exposure to pomalidomide. Adjust pomalidomide dose, p. 961. Moderate Study

Paroxetine increases the efficacy of opioids (codeine). Moderate Theoretical

SSRIs (fluoxetine, paroxetine) are predicted to decrease the efficacy of opioids (tramadol). Moderate Theoretical

Fluvoxamine is predicted to increase the exposure to pentoxifylline. Moderate Theoretical

Fluvoxamine is predicted to moderately increase the exposure to piropenidone. Avoid. Moderate Study

Fluvoxamine is predicted to moderately increase the exposure to pitolisant. (fluoxetine, paroxetine) are predicted to decrease the exposure to SSRIs (cilastropam, escalopram). Monitor and adjust dose. Moderate Study

Fluvoxamine is predicted to increase the exposure to riluzole. Moderate Theoretical

SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to risperidone. Adjust dose. Moderate Study

Fluvoxamine is predicted to increase the exposure to roflumilast. Moderate Study

SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to SSRIs (cilastropam, escalopram). Monitor and adjust dose. Severe Theoretical

Proton pump inhibitors (omeprazole) slightly to moderately increase the exposure to SSRIs (cilastropam, escalopram). Moderate Study

Fluvoxamine is predicted to increase the exposure to suxamethonium. Unknown Theoretical

SSRIs (fluoxetine, paroxetine) are predicted to decrease the efficacy of tamoxifen. Avoid. Severe Study

Terbinafine is predicted to increase the exposure to fluoxetine. Adjust dose. Moderate Theoretical

Terbinafine moderately increases the exposure to paroxetine. Moderate Study

Terbinafine is predicted to increase the exposure to SSRIs (cilastropam, escalopram, dalopram, escinopram). Adjust dose. Moderate Study

Fluvoxamine very markedly increases the exposure to tiadinol. Avoid. Severe Study

SSRIs (fluoxetine, fluvoxamine) given with a moderate CYP3A4 inhibitor are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. Moderate Study
SSRIs (continued)

- SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to tricyclic antidepressants. Monitor for toxicity and adjust dose. [Severe] Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378
- Fluoxetine increases the exposure to tricyclic antidepressants (amitryptiline, imipramine). Adjust dose. [Severe] Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378
- Fluvoxamine markedly increases the exposure to tricyclic antidepressants (clomipramine). Adjust dose. [Severe] Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378
- SSRIs (fluoxetine, paroxetine) are predicted to increase the exposure to vortioxetine. Monitor and adjust dose. [Moderate] Study → Also see TABLE 13 p. 1378 → Also see TABLE 4 p. 1375
- Fluvoxamine is predicted to increase the exposure to midazolam. Adjust midazolam dose, p. 482. [Severe] Theoretical → Also see TABLE 13 p. 1378

St John’s Wort

- St John’s Wort is predicted to decrease the exposure to abacavir. [Severe] Study
- St John’s Wort is predicted to decrease the concentration of aripiprazole (dronedarone). Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to sertraline (dronedarone). Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to antiepileptics (brivaracetam). [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to antiepileptics (carbamazepine). Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the concentration of antiepileptics (fosphenytoin, phenobarbital, phenytoin). Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to antidepressants (perampanel). Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to antifungals, azoles (isavuconazole). Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to antifungals, azoles (voriconazole). Avoid. [Moderate] Study
- St John’s Wort is predicted to decrease the concentration of antiarrhythmics (piperaquarine). Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to apixaban. Use with caution or avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to aripiprazole. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to aripiprazole. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to axitinib. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to bedaquiline. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to bictegravir. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to bosutinib. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to bosentan. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to brigitinib. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the concentration of aminophylline. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine). Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to cariprazine. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to cisapride. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the concentration of ciclosporin. Avoid. [Moderate] Study
- St John’s Wort is predicted to alter the effects of clozapine. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to cobicistat. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to conivaptan. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the efficacy of combined hormonal contraceptives. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Anecdotal
- St John’s Wort is predicted to decrease the exposure to dabigatran. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to darifenacin. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to dasabuvir. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to dasatinib. [Severe] Study
- St John’s Wort is predicted to decrease the efficacy of desogestrel. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- St John’s Wort is predicted to decrease the concentration of digitoxin. Avoid. [Severe] Anecdotal
- St John’s Wort is predicted to decrease the exposure to dolutegravir. Adjust dose. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to doravirine. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to edoxaban. [Moderate] Study
- St John’s Wort is predicted to decrease the concentration of efavirenz. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to moderately decrease the exposure to elabavir. Avoid. [Severe] Study
- St John’s Wort is predicted to increase the exposure to eliglustat. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the concentration of elvitegravir. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to escorafiban. [Severe] Theoretical
- St John’s Wort is predicted to decrease the effects of ergotamine. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to erlotinib. [Severe] Theoretical
- St John’s Wort is predicted to decrease the efficacy of etonogestrel. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p. 794. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to etravirine. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the concentration of everolimus. Avoid or adjust dose. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to exemestane. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to fosoterodine. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to fingolimod. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to fosaprepitant. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to gefitinib. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to glecaprevir. Avoid. [Severe] Study
- St John’s Wort is predicted to markedly decrease the exposure to grazoprevir. Avoid. [Severe] Study
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- St John’s Wort is predicted to decrease the concentration of guanfacine. Adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to HIV-protease inhibitors. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the efficacy of hormone replacement therapy. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to ibritinib. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to idelalisib. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to imatinib. [Moderate] Study
- St John’s Wort slightly decreases the exposure to irinotecan. Avoid. [Severe] Study
- St John’s Wort decreases the exposure to ivabradine. Avoid. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to ivacaftor. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to lapatinib. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the concentration of letro Mizol. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the efficacy of levonorgestrel. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p.794. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to lurazidone. Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to macitentan. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to macrolides. Avoid. [Severe] Theoretical
- St John’s Wort moderately decreases the exposure to midazolam. Monitor and adjust dose. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to midostaurin. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to nalo norgel. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to netupitant. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the concentration of noretisterone. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to nilotinib. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to nintedanib. [Moderate] Study
- St John’s Wort is predicted to decrease the efficacy of norethisterone. MHRA advises avoid. For FSRH guidance, see Contraceptives, interactions p.794. [Severe] Anecdotal
- St John’s Wort is predicted to decrease the exposure to olaparib. Avoid. [Moderate] Anecdotal
- St John’s Wort is predicted to decrease the exposure to ombitasvir. Avoid. [Severe] Theoretical
- St John’s Wort decreases the exposure to opioids (methadone). Monitor and adjust dose. [Severe] Study → Also see TABLE 13 p.1378
- St John’s Wort moderately decreases the exposure to opioids (oxycodeone). Adjust dose. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to osimertinib. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to os pamemfene. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to paliperidone. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to panobinostat. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to paritaprevir (with ritonavir and ombitasvir). Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to phosphodiesterase type 5 inhibitors. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to pi brentasvir. Avoid. [Severe] Study
- St John’s Wort slightly decreases the exposure to pioglitazone. [Mild] Study
- St John’s Wort is predicted to decrease the exposure to pitolisant. Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to ponatinib. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to quetiapine. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to ranolazine. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to ribociclib. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to rilpivirine. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to rolapitant. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to roxilutinib. Monitor and adjust dose. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the concentration of sirolimus. Monitor and adjust dose. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to sofosbuvir. Avoid. [Severe] Study
- St John’s Wort slightly decreases the exposure to statins (atorvastatin). [Mild] Study
- St John’s Wort moderately decreases the exposure to statins (simvastatin). [Moderate] Study
- St John’s Wort decreases the concentration of tacrolimus. Avoid. [Severe] Theoretical
- St John’s Wort is predicted to decrease the exposure to tenofovir alafenamide. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to tezacaftar. Avoid. [Severe] Theoretical
- St John’s Wort potentially decreases the exposure to theophylline. [Severe] Anecdotal
- St John’s Wort is predicted to decrease the exposure to ticagrelor. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to ti vozanib. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to tofacitinib. [Moderate] Study
- St John’s Wort is predicted to decrease the exposure to tolvaptan. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to topotecan. [Severe] Theoretical
- St John’s Wort decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p.794. [Severe] Anecdotal
- St John’s Wort is predicted to decrease the exposure to vapatasvir. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the exposure to vismodegib. Avoid. [Moderate] Theoretical
- St John’s Wort is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- St John’s Wort slightly to moderately increases the exposure to aliskiren. [Moderate] Study
- Antacids moderately decrease the absorption of rosuvastatin. Separate administration by 2 hours. [Moderate] Study
- Antiarrhythmics (amiodarone) are predicted to increase the risk of rhabdomyolysis when given with atorvastatin. Monitor and adjust dose. [Moderate] Theoretical
- Antiarrhythmics (amiodarone) are predicted to increase the exposure to fluvastatin. [Severe] Theoretical
- Antiarrhythmics (amiodarone) increase the risk of rhabdomyolysis when given with simvastatin. Adjust simvastatin dose, p.205. [Severe] Study

Study p. 794.
Ciclosporin markedly to very markedly increases the exposure to pravastatin. Adjust dose. [Severe] Study

Ciclosporin markedly increases the exposure to statins (rosuvastatin, simvastatin). Avoid. [Severe] Study

Clopaprogrel increases the exposure to rosuvastatin. Adjust rosvastatin dose, p. 204. [Moderate] Study

Cobicistat is predicted to increase the exposure to atorvastatin. Avoid or adjust dose and monitor rhabdomyolysis. [Severe] Study

Cobicistat is predicted to increase the exposure to simvastatin. Avoid. [Severe] Study

Colchicine increases the risk of rhabdomyolysis when given with statins. [Severe] Anecdotal

Statins (fluvastatin, rosuvastatin) increase the anticoagulant effect of coumarins. Monitor INR and adjust dose. [Severe] Study

Crizotinib is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. [Severe] Study

Crizotinib is predicted to increase the exposure to simvastatin. Use with caution and adjust simvastatin dose, p. 205. [Severe] Study

Danazol is predicted to increase the risk of rhabdomyolysis when given with atorvastatin. [Severe] Theoretical

Danazol increases the risk of rhabdomyolysis when given with simvastatin. Avoid. [Severe] Anecdotal

Statins are predicted to increase the risk of rhabdomyolysis when given with daptomycin. [Severe] Theoretical

Dasabuvir increases the exposure to rosuvastatin. Adjust rosuvastatin dose, p. 204. [Moderate] Study

Dasatinib is predicted to increase the exposure to simvastatin. [Moderate] Theoretical

Efavirenz slightly decreases the exposure to atorvastatin. [Mild] Study

Efavirenz moderately decreases the exposure to simvastatin. [Moderate] Study

Efavirenz is predicted to increase the exposure to atorvastatin. Adjust atorvastatin dose, p. 202. [Moderate] Study

Elbasvir is predicted to increase the exposure to fluvastatin. Adjust fluvastatin dose, p. 203. [Unknown] Theoretical

Elbasvir increases the exposure to rosuvastatin. Adjust rosuvastatin dose, p. 204. [Moderate] Study

Elbasvir is predicted to increase the exposure to simvastatin. Adjust simvastatin dose, p. 205. [Unknown] Theoretical

Eltrombopag is predicted to increase the exposure to statins. Monitor and adjust dose. [Moderate] Study

Enzalutamide is predicted to decrease the exposure to simvastatin. [Severe] Study

Ezetimibe potentially increases the risk of rhabdomyolysis when given with statins. [Severe] Anecdotal

Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with pravastatin. Avoid. [Severe] Study

Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with rosvastatin. Adjust rosvastatin dose, p. 204. [Unknown] Theoretical

Fibrates (bezafibrate, ciprofibrate) increase the risk of rhabdomyolysis when given with simvastatin. Adjust simvasatin dose, p. 205. [Unknown] Theoretical

Fibrates (ciprofibrate) increase the risk of rhabdomyolysis when given with atorvastatin. Avoid or adjust dose. [Severe] Study

Fibrates (ciprofibrate) increase the risk of rhabdomyolysis when given with fluvastatin. [Severe] Study

Fibrates (fenofibrate) are predicted to increase the risk of rhabdomyolysis when given with fluvastatin. Adjust fenofibrate dose, p. 199. [Severe] Theoretical

Fibrates (fenofibrate) are predicted to increase the risk of rhabdomyolysis when given with pravastatin. Avoid. [Severe] Theoretical

Fibrates (fenofibrate) increase the risk of rhabdomyolysis when given with rosuvastatin. Adjust fenofibrate and rosuvastatin doses, p. 199, p. 204. [Severe] Anecdotal

Fibrates (gemfibrozil) increase the risk of rhabdomyolysis when given with statins. Avoid. [Severe] Anecdotal

Fibrates (bezafibrate) increase the risk of rhabdomyolysis when given with statins (atorvastatin, fluvastatin). [Severe] Study
Fibrates (fenofibrate) increase the risk of rhabdomyolysis when given with statins (atorvastatin, simvastatin). Adjust fenofibrate dose, p. 199. (Severe) Anecdotal.
Fusidic acid increases the risk of rhabdomyolysis when given with statins. Avoid. (Severe) Anecdotal.
Glecaprevir (with pibrentasvir) marked increases the exposure to atorvastatin. Avoid. (Severe) Study
Glecaprevir (with pibrentasvir) is predicted to increase the exposure to flavuvastatin. (Moderate) Theoretical
Glecaprevir (with pibrentasvir) increases the exposure to pravastatin. Use with caution and adjust pravastatin dose, p. 201. (Moderate) Study
Glecaprevir (with pibrentasvir) increases the exposure to rosuvastatin. Use with caution and adjust rosuvastatin dose, p. 204. (Moderate) Study
Grapefruit juice increases the exposure to atorvastatin. (Moderate) Study
Grapefruit juice increases the exposure to simvastatin. Avoid. (Severe) Study
Grazoprevir increases the exposure to atorvastatin. Adjust atorvastatin dose, p. 202. (Moderate) Study
Grazoprevir is predicted to increase the exposure to flavuvastatin. Adjust flavuvastatin dose, p. 203. (Unknown) Theoretical
Grazoprevir increases the exposure to rosuvastatin. Adjust rosuvastatin dose, p. 204. (Moderate) Study
Grazoprevir is predicted to increase the exposure to simvastatin. Adjust simvastatin dose, p. 205. (Unknown) Theoretical
HIV- protease inhibitors are predicted to increase the exposure to atorvastatin. Avoid or adjust dose and monitor rhabdomyolysis. (Severe) Study
HIV-protease inhibitors slightly to moderately increase the exposure to rosuvastatin. Avoid or adjust dose. (Severe) Study
HIV-protease inhibitors are predicted to increase the exposure to simvastatin. Avoid. (Severe) Study
Idelalisib is predicted to increase the exposure to atorvastatin. Avoid or adjust dose and monitor rhabdomyolysis. (Severe) Study
Idelalisib is predicted to increase the exposure to simvastatin. Avoid. (Severe) Study
Imatinib is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. (Severe) Study
Imatinib is predicted to increase the exposure to simvastatin. Use with caution and adjust simvastatin dose, p. 205. (Severe) Study
Ledipasvir is predicted to increase the exposure to rosuvastatin. Avoid. (Severe) Theoretical
Ledipasvir is predicted to increase the exposure to statins (atorvastatin, flavuvastatin, pravastatin, simvastatin). Monitor and adjust dose. (Moderate) Theoretical
Leflunomide is predicted to increase the exposure to rosuvastatin. Adjust dose. (Moderate) Study → Also see TABLE 1 p. 1375
Leflunomide is predicted to increase the exposure to statins (atorvastatin, flavuvastatin, pravastatin, simvastatin). (Moderate) Study → Also see TABLE 1 p. 1375
Letermovir moderately increases the exposure to atorvastatin. Avoid or adjust atorvastatin dose, p. 202. (Severe) Study
Letermovir is predicted to increase the exposure to flavuvastatin. Monitor and adjust dose. (Moderate) Theoretical
Letermovir is predicted to increase the exposure to pravastatin. Avoid or adjust dose. (Moderate) Theoretical
Letermovir is predicted to increase the exposure to statins (rosuvastatin, simvastatin). Avoid. (Severe) Study
Lomitapide increases the exposure to atorvastatin. Adjust lomitapide dose or separate administration by 12 hours, p. 207. (Moderate) Study → Also see TABLE 1 p. 1375
Lomitapide increases the exposure to simvastatin. Monitor and adjust simvastatin dose, p. 205. (Moderate) Study → Also see TABLE 1 p. 1375
Macrolides (clarithromycin) are predicted to increase the exposure to pravastatin. (Severe) Study
Macrolides (clarithromycin) are predicted to increase the exposure to simvastatin. Avoid. (Severe) Study
Macrolides (erythromycin) are predicted to increase the exposure to atorvastatin. Monitor and adjust dose. (Severe) Study
Macrolides (erythromycin) are predicted to increase the exposure to pravastatin. (Severe) Study
Macrolides (erythromycin) are predicted to increase the exposure to simvastatin. Use with caution and adjust simvastatin dose, p. 205. (Severe) Study
Mitotane is predicted to decrease the exposure to simvastatin. (Severe) Study
Monoclonal antibodies (carilumab) are predicted to decrease the exposure to statins (atorvastatin, simvastatin). (Moderate) Study
Monoclonal antibodies (tocilizumab) are predicted to decrease the exposure to statins (atorvastatin, simvastatin). Monitor and adjust dose. (Moderate) Study
Netupitant is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. (Severe) Study
Netupitant is predicted to increase the exposure to simvastatin. Use with caution and adjust simvastatin dose, p. 205. (Severe) Study
Nevirapine slightly decreases the exposure to atorvastatin. (Unknown) Study
Nevirapine moderately decreases the exposure to simvastatin. (Moderate) Study
Nicotinic acid is predicted to increase the risk of rhabdomyolysis when given with statins. (Severe) Theoretical
Nilotinib is predicted to increase the exposure to atorvastatin. Monitor and adjust dose. (Severe) Study
Nilotinib is predicted to increase the exposure to simvastatin. Use with caution and adjust simvastatin dose, p. 205. (Severe) Study
Osimertinib slightly increases the exposure to rosuvastatin. (Moderate) Study
Paritaprevir (in fixed-dose combination) is predicted to increase the risk of rhabdomyolysis when given with atorvastatin. Avoid. (Severe) Theoretical
Paritaprevir (with ritonavir and ombitasvir) is predicted to increase the exposure to flavuvastatin. Avoid. (Moderate) Theoretical
Paritaprevir (with ritonavir and ombitasvir) increases the exposure to pravastatin. Adjust pravastatin dose, p. 203. (Moderate) Study
Paritaprevir (with ritonavir and ombitasvir) slightly to moderately increases the exposure to rosuvastatin. Adjust rosuvastatin dose, p. 204. (Moderate) Study
Paritaprevir (in fixed-dose combination) is predicted to increase the risk of rhabdomyolysis when given with simvastatin. Avoid. (Severe) Theoretical
Pazopanib is predicted to affect the exposure to atorvastatin. (Moderate) Anecdotal
Pazopanib is predicted to affect the exposure to statins (pravastatin, rosuvastatin, simvastatin). (Moderate) Theoretical
Rosuvastatin is predicted to increase the anticoagulant effect of phenindione. Monitor INR and adjust dose. (Severe) Theoretical
Pibrentasvir (with glecaprevir) markedly increases the exposure to atorvastatin. Avoid. (Severe) Study
Pibrentasvir (with glecaprevir) is predicted to increase the exposure to flavuvastatin. (Moderate) Theoretical
Pibrentasvir (with glecaprevir) is predicted to increase the exposure to rosuvastatin. Use with caution and adjust rosuvastatin dose, p. 204. (Moderate) Study
Pibrentasvir (with glecaprevir) increases the exposure to simvastatin. Avoid. (Moderate) Study
Ranolazine is predicted to increase the exposure to atorvastatin. (Moderate) Theoretical
Ranolazine slightly increases the exposure to simvastatin. Adjust simvastatin dose, p. 205. (Moderate) Study
**Statin** interactions

- **Regorafenib** is predicted to increase the exposure to statins (atorvastatin, fluvastatin, rosuvastatin). [Moderate] Study
- **Ribociclib** (high-dose) is predicted to increase the exposure to simvastatin. Avoid. [Theoretical]
- **Ribociclib** is predicted to increase the exposure to statins (pravastatin, rosuvastatin). [Moderate] Study
- **Rifampicin** markedly decreases the exposure to atorvastatin. Atorvastatin should be taken at the same time as rifampicin, p. 202, 582. [Moderate] Study
- **Rifampicin** moderately decreases the exposure to fluvastatin. Monitor and adjust dose. [Moderate] Study
- **Rifampicin** very markedly decreases the exposure to simvastatin. [Severe] Study
- **Rolapitant** is predicted to increase the exposure to atorvastatin, fluvastatin, rosuvastatin. Avoid. [Moderate] Study
- **Sacubitril** is predicted to increase the exposure to statins. [Severe] Study
- **St John's Wort** slightly decreases the exposure to atorvastatin. [Moderate] Study
- **St John's Wort** moderately decreases the exposure to simvastatin. [Moderate] Study
- **Fluvastatin** slightly increases the exposure to sulfonyleureas (glibenclamide). [Mild] Study
- **Tedizolid** is predicted to increase the exposure to statins (atorvastatin, fluvastatin, rosuvastatin). Avoid. [Moderate] Study
- **Teriflunomide** moderately increases the exposure to rosuvastatin. Adjust rosuvastatin dose, p. 204. [Moderate] Study
- **Teriflunomide** is predicted to increase the exposure to statins (atorvastatin, fluvastatin, pravastatin, simvastatin). [Moderate] Study
- **Ticagrelor** slightly increases the exposure to simvastatin. Adjust simvastatin dose, p. 205. [Moderate] Study
- **Tivozanib** is predicted to decrease the exposure to rosvastatin. Avoid. [Moderate] Study
- **Velpatasvir** is predicted to increase the exposure to atorvastatin. Avoid. [Severe] Study
- **Velpatasvir** increases the exposure to rosuvastatin. Adjust rosvastatin dose and monitor side effects, p. 204. [Severe] Study
- **Velpatasvir** is predicted to increase the exposure to simvastatin. Monitor side effects and adjust dose. [Severe] Theoretical
- **Venetoclax** is predicted to increase the exposure to atorvastatin. [Moderate] Study
- **Venetoclax** is predicted to increase the exposure to statins (fluvastatin, pravastatin, rosuvastatin, simvastatin). [Moderate] Theoretical
- **Voxilaprevir** is predicted to increase the exposure to atorvastatin. Avoid. [Moderate] Theoretical
- **Voxilaprevir** (with sofosbuvir and velpatasvir) moderately increases the exposure to pravastatin. Monitor and adjust pravastatin dose, p. 203. [Moderate] Study
- **Voxilaprevir** (with sofosbuvir and velpatasvir) markedly increases the exposure to rosvastatin. Avoid. [Severe] Study
- **Voxilaprevir** (with sofosbuvir and velpatasvir) is predicted to increase the exposure to statins (fluvastatin, simvastatin). Avoid. [Moderate] Theoretical

**Stavudine**

- See TABLE 12 (p. 1378 (peripheral neuropathy))
- **Didanosine** increases the risk of toxicity when given with stavudine. Avoid. [Severe] Study
- **Isoniazid** is predicted to increase the risk of peripheral neuropathy when given with stavudine. Avoid. [Severe] Study
- **Ribavirin** increases the risk of toxicity when given with stavudine. Avoid. [Severe] Study
- **Zidovudine** is predicted to decrease the efficacy of stavudine. Avoid. [Severe] Theoretical

**Streptokinase**

- See TABLE 3 (p. 1375 (anticoagulant effects))
- **Streptokinase** is predicted to increase the risk of anaemia.

**Streptozocin**

- See TABLE 1 (p. 1375 (hepatotoxicity)), TABLE 2 (p. 1375 (nephrotoxicity))
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with streptozocin. Public Health England advises avoid (refer to Green Book). [Severe] Theoretical

**Sucrafate**

- **Sucrafate** is predicted to decrease the exposure to bictegravir. Avoid. [Moderate] Theoretical
- **Sucrafate** potentially decreases the effects of coumarins (warfarin). Separate administration by 2 hours. [Moderate] Study
- **Sucrafate** decreases the absorption of digoxin. Separate administration by 2 hours. [Severe] Anecdotal
- **Sucrafate** decreases the absorption of dolasetron. Separate administration by 2 hours. [Moderate] Study
- **Sucrafate** increases the risk of blocked enteral or nasogastric tubes when given with enteral feeds. Separate administration by 1 hour. [Moderate] Study
- **Potassium citrate** increases the risk of side-effects when given with sucralfate. Avoid. [Moderate] Theoretical
- **Sucrafate** decreases the exposure to quinolones. Separate administration by 2 hours. [Moderate] Study
- **Sucrafate** potentially decreases the absorption of theophylline. Separate administration by at least 2 hours. [Moderate] Study
- **Sucrafate** decreases the absorption of thyroid hormones (levothyroxine). Separate administration by at least 4 hours. [Moderate] Study
- **Sucrafate** is predicted to decrease the absorption of tricyclic antidepressants. [Moderate] Study
- **Sufentanil** → see opioids
- **Sugammadex**
  - **Sugammadex** is predicted to decrease the exposure to oral combined hormonal contraceptives. Refer to patient information leaflet for missed pill advice. [Severe] Theoretical
  - **Sugammadex** is predicted to decrease the exposure to desogestrel. Refer to patient information leaflet for missed pill advice. [Severe] Theoretical
  - **Sugammadex** is predicted to decrease the efficacy of etonogestrel. Use additional contraceptive precautions. [Severe] Theoretical
  - **Sugammadex** is predicted to decrease the exposure to levonorgestrel. Use additional contraceptive precautions. [Severe] Theoretical
- **Sulfamethoxazole** → see sulfonamides
- **Sulfadiazine** → see sulfonamides
- **Sulfadimethoxine** → see sulfonamides
- **Sulfasalazine** → see sulfonamides
- **Sulfadiazine** → see sulfonamides
- **Sulfadimethoxine** → see sulfonamides
- **Sulfamethoxazole** → see sulfonamides
- **Sulfasalazine** (hepatotoxicity), TABLE 15 p. 1378 (myelosuppression)
  - **Antifungals, azoles (Isavuconazole)** are predicted to increase the exposure to sulfasalazine. [Moderate] Theoretical
- **Sulfasalazine** decreases the concentration of digoxin. [Moderate] Study
- **Sulfasalazine** is predicted to decrease the absorption of folates. [Moderate] Study
- **Leffunomide** is predicted to increase the exposure to sulfasalazine. [Moderate] Study → Also see TABLE 1 p. 1375 → Also see TABLE 15 p. 1378
- **Regorafenib** is predicted to increase the exposure to sulfasalazine. [Moderate] Study → Also see TABLE 15 p. 1378
- **Rolapitant** increases the exposure to sulfasalazine. [Severe] Study
- **Tedizolid** is predicted to increase the exposure to sulfasalazine. Avoid. [Moderate] Study
- **Teriflunomide** is predicted to increase the exposure to sulfasalazine. [Moderate] Study
**Sulphasalazine — Sunitinib 1537**

- **Velpatasvir** is predicted to increase the exposure to sulphasalazine. [Moderate] Theoretical
- **Venetoclax** is predicted to increase the exposure to sulphasalazine. [Moderate] Theoretical
- **Voxilaprevir** is predicted to increase the concentration of sulphasalazine. Avoid. [Severe] Theoretical

Sulfonamides → see TABLE 15 p. 1378 (myelosuppression)

sulfadiazine - sulfadizone - sulfamethoxazole

- **Sulfonamides** potentially increase the risk of methaemoglobinemia when given with topical anaesthetics, local (prilocaine). Use with caution or avoid. [Severe] Anecdotal
- **Sulfadiazine** is predicted to increase the concentration of antiepileptics (fosphenytoin). Monitor and adjust dose. [Moderate] Study
- **Sulfadiazine** increases the concentration of antiepileptics (phenytoin). Monitor and adjust dose. [Moderate] Study
- **Antimalarials (pyrimethamine)** increase the risk of side-effects when given with sulfonamides. [Severe] Study → Also see TABLE 15 p. 1378
- **Sulfadiazine** is predicted to increase the anticoagulant effect of coumarins. [Severe] Theoretical
- **Sulfamethoxazole** increases the anticoagulant effect of coumarins. [Severe] Study
- **Sulfonamides** are predicted to increase the risk of methaemoglobinemia when given with dapson. [Severe] Theoretical
- **Sulfonamides** are predicted to increase the exposure to methotrexate. Use with caution or avoid. [Severe] Theoretical → Also see TABLE 15 p. 1378
- **Potassium aminobenzoate** is predicted to affect the efficacy of sulfonamides. Avoid. [Severe] Theoretical
- **Sulfonamides** are predicted to increase the exposure to sulfonylureas. [Moderate] Study
- **Sulfonamides** are predicted to increase the effects of thiopental. [Moderate] Theoretical

**Sulfonylureas** → see TABLE 14 p. 1378 (antidiabetic drugs)

- **Glibenclamide** - glipizide - glimepiride - gliclizide - tolbutamide
  - **Antihyperglycaemics (amidodarone)** are predicted to increase the exposure to sulfonylureas. Use with caution and adjust dose. [Moderate] Study
  - **Antifungals, azoles (fluconazole, miconazole)** are predicted to increase the exposure to sulfonylureas. Use with caution and adjust dose. [Moderate] Study
  - **Antifungals, azoles (voriconazole)** are predicted to increase the concentration of sulfonylureas. Use with caution and adjust dose. [Moderate] Study
  - **Bosentan** increases the risk of hepatotoxicity when given with glibenclamide. Avoid. [Severe] Study
  - **Cephalosporins (ceftriaxone)** are predicted to increase the concentration of glibenclamide. [Moderate] Theoretical
  - **Cefepine** is predicted to increase the exposure to glimepiride. [Moderate] Theoretical
  - **Chloramphenicol** is predicted to increase the exposure to sulfonylureas. [Severe] Study
  - **Fibrates** are predicted to increase the risk of hypoglycaemia when given with sulfonylureas. [Moderate] Theoretical
  - **Leflunomide** is predicted to increase the exposure to glibenclamide. [Moderate] Study
  - **Letermovir** is predicted to increase the concentration of glibenclamide. [Moderate] Theoretical
  - **Macrolides (clarithromycin)** are predicted to slightly increase the exposure to sulfonylureas. [Moderate] Theoretical
  - **Rifampicin** is predicted to decrease the exposure to sulfonylureas. [Moderate] Study
  - **Statins (fluvastatin)** slightly increase the exposure to glibenclamide. [Mild] Study
  - **Sulfonamides** are predicted to increase the exposure to sulfonylureas. [Moderate] Study
  - **Teriflunomide** is predicted to increase the exposure to glibenclamide. [Moderate] Study
  - **Venetoclax** is predicted to increase the exposure to glibenclamide. [Moderate] Theoretical

Sulindac → see NSAIDs

**Sulpiride** → see TABLE 8 p. 1376 (hypotension), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 11 p. 1377 (CNS depressant effects)
- **Antacids** decrease the absorption of sulpiride. Separate administration by 2 hours. [Moderate] Study
- **Sulpiride** is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical → Also see TABLE 8 p. 1376 → Also see TABLE 9 p. 1377
- **Sulpiride** is predicted to decrease the effects of levodopa. Avoid. [Severe] Theoretical → Also see TABLE 8 p. 1376
- **Sulpiride** potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → Also see TABLE 9 p. 1377
- **Sucralfate** decreases the absorption of sulpiride. Separate administration by 2 hours. [Moderate] Study

**Sumatriptan** → see TABLE 13 p. 1378 (serotonin syndrome)
- **Sumatriptan** increases the risk of vasodistension when given with ergotamine. Ergotamine should be taken at least 24 hours before or 6 hours after sumatriptan. [Severe] Study
- **Moclobemide** moderately increases the exposure to sumatriptan. Avoid. [Moderate] Study → Also see TABLE 13 p. 1378
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the exposure to sumatriptan. Avoid and for 14 days after stopping the MAOI. [Severe] Theoretical → Also see TABLE 13 p. 1378

**Sunitinib** → see TABLE 15 p. 1378 (myelosuppression), TABLE 9 p. 1377 (QT-interval prolongation)
- **Antihymetics (dronedarone)** are predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study
- **Antifungals, azoles (fluconazole, isavuconazole, posaconazole)** are predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 9 p. 1377
- **Aprepitant** is predicted to increase the exposure to sunitinib. [Moderate] Theoretical
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to sunitinib. [Moderate] Theoretical
- **Cobicistat** is predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study
- **Sunitinib** is predicted to increase the risk of bleeding events when given with coumarins. [Severe] Theoretical
- **Crizotinib** is predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378 → Also see TABLE 9 p. 1377
- **Elbasvir** is predicted to increase the concentration of sunitinib. Use with caution and adjust dose. [Moderate] Theoretical
- **Enzalutamide** is predicted to decrease the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study
- **Grapefruit juice** is predicted to increase the exposure to sunitinib. Avoid. [Moderate] Theoretical
- **Grazoprevir** is predicted to increase the concentration of sunitinib. Use with caution and adjust dose. [Moderate] Theoretical
- **HIV-protase inhibitors** are predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 9 p. 1377
- **Idelalisib** is predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 15 p. 1378
- **Imatinib** is predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 15 p. 1378
- **Macrolides (clarithromycin)** are predicted to slightly increase the exposure to sunitinib. Avoid or adjust sunitinib dose, p. 999. [Moderate] Study → Also see TABLE 9 p. 1377
- **Macrolides (erythromycin)** are predicted to increase the exposure to sunitinib. [Moderate] Theoretical → Also see TABLE 9 p. 1377

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Sunitinib — Sympathomimetics, vasoconstrictor

- **Opicapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropic. (Severe) Theoretical
- **Tolcapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropic. (Moderate) Theoretical

**Sympathomimetics, vasoconstrictor**
- adrenaline/epinephrine, -ephrine, -isometheptene, -metaraminol, -midodrine, -noradrenaline/norepinephrine, -phenylephrine, -pseudoephedrine, -xylometazoline

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

- **Ephedrine** increases the risk of side-effects when given with aminophylline. Avoid in children. (Moderate) Study
- **Sympathomimetics, vasoconstrictor** are predicted to decrease the effects of apraclonidine. Avoid. (Severe) Theoretical
- **Atropine** increases the risk of severe hypertension when given with phenylephrine. (Severe) Study
- **Beta blockers, non-selective** are predicted to increase the risk of hypertension and bradycardia when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Severe) Study
- **Beta blockers, selective** are predicted to increase the risk of hypertension and bradycardia when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Severe) Study
- **Isometheptene** potentially increases the risk of side-effects when given with dopamine receptor agonists (bromocriptine). Avoid. (Severe) Anecdotal
- **Entacapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Moderate) Study
- **Ergometrine** is predicted to increase the risk of peripheral vasoconstriction when given with noradrenaline/norepinephrine. (Severe) Anecdotal
- **Guanethidine** increases the effects of metaraminol. (Severe) Anecdotal
- **Guanethidine** increases the effects of phenylephrine. (Severe) Study
- **Guanethidine** is predicted to increase the effects of sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Moderate) Study
- **Pseudoephedrine** increases the risk of elevated blood pressure when given with linezolid. Avoid. (Severe) Study
- **Sympathomimetics, vasoconstrictor (adrenaline/epinephrine, phenylephrine, isometheptene, noradrenaline/norepinephrine, phenylephrine) are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. (Severe) Theoretical
- **Mianserin** decreases the effects of ephedrine. (Severe) Anecdotal
- **Moclobemide** is predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, vasoconstrictor (ephedrine, isometheptene, phenylephrine, pseudoephedrine). Avoid. (Severe) Study
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, vasoconstrictor. Avoid and for 14 days after stopping the MAOI. (Severe) Study
- **Monoamine-oxidase B inhibitors** are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, inotropic. Avoid. (Severe) Anecdotal
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropic. (Severe) Theoretical
- **Ephedrine** increases the risk of side-effects when given with theophylline. Avoid in children. (Moderate) Study
- **Tolcapone** is predicted to increase the effects of sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine). (Moderate) Theoretical
- **Tricyclic antidepressants** are predicted to decrease the effects of ephedrine. Avoid. (Severe) Study

**Sympathomimetics, inotropic**
- **dobutamine - dopamine**
- **Sympathomimetics, inotropic** are predicted to decrease the effects of apraclonidine. Avoid. (Severe) Theoretical
- **Beta blockers, non-selective** increase the risk of hypertension and bradycardia when given with dobutamine. (Severe) Theoretical
- **Beta blockers, selective** increase the risk of hypertension and bradycardia when given with dobutamine. (Moderate) Theoretical
- **Entacapone** is predicted to increase the risk of cardiovascular side-effects when given with sympathomimetics, inotropic. (Moderate) Theoretical
- **Ergometrine** potentially increases the risk of peripheral vasoconstriction when given with dopamine. Avoid. (Severe) Anecdotal
- **Guanethidine** is predicted to increase the effects of dopamine. (Severe) Theoretical
- **Sympathomimetics, inotropic** are predicted to increase the risk of elevated blood pressure when given with linezolid. Avoid. (Severe) Theoretical
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, vasoconstrictor. Avoid and for 14 days after stopping the MAOI. (Severe) Study
- **Monoamine-oxidase B inhibitors** are predicted to increase the risk of a hypertensive crisis when given with sympathomimetics, inotropic. Avoid. (Severe) Anecdotal

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.
**Tricyclic antidepressants** increase the effects of sympathomimetics, vasoconstrictor

**Talcacitol** → see vitamin D substances

**Tacrolimus** → see TABLE 2 p. 1375 (nephrotoxicity), TABLE 16 p. 1379 (increased serum potassium)

- Pomelo and pomegranate juices might greatly increase the concentration of tacrolimus.
- Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

**Alcohol (beverage)** increases the risk of facial flushing and skin irritation when given with topical tacrolimus. (Moderate) Study

**Antirheumatics (amiodarone)** are predicted to increase the concentration of tacrolimus. (Severe) Study

**Antifungals, azoles** (fluconazole, itasuconazole, posaconazole) are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Antifungals, azoles** (itraconazole, ketoconazole, voriconazole) are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Antifungals, azoles** (miconazole) are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Aprepitant** is predicted to increase the concentration of tacrolimus. (Severe) Study

**Bosentan** is predicted to decrease the concentration of tacrolimus and tacrolimus potentially increases the concentration of bosentan. Avoid. (Severe) Theoretical

**Brigatinib** potentially decreases the concentration of tacrolimus. Avoid. (Moderate) Theoretical

- Calcium channel blockers (diltiazem, verapamil) are predicted to increase the concentration of tacrolimus. (Severe) Study

- Calcium channel blockers (nicardipine) potentially increase the concentration of tacrolimus. Monitor concentration and adjust dose. (Severe) Anecdotal

**Ceritinib** is predicted to increase the exposure to tacrolimus. Avoid. (Severe) Theoretical

**Chloramphenicol** increases the concentration of tacrolimus. (Severe) Study

**Ciclosporin** increases the concentration of tacrolimus. Avoid. (Severe) Study → Also see TABLE 2 p. 1375 → Also see TABLE 16 p. 1379

**Cobicistat** is predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Crizotinib** is predicted to increase the concentration of tacrolimus. (Severe) Study

**Tacrolimus** is predicted to increase the exposure to dabigatran. Avoid. (Severe) Theoretical

**Danzol** potentially increases the concentration of tacrolimus. (Severe) Anecdotal

**Doravirine** is predicted to decrease the exposure to tacrolimus. Monitor tacrolimus concentration and adjust dose, p. 841. (Moderate) Theoretical

**Efavirenz** is predicted to decrease the concentration of tacrolimus. Monitor and adjust dose. (Moderate) Theoretical

**Enalapril** decreases the concentration of tacrolimus. Monitor and adjust dose. (Moderate) Theoretical

**Gliclazide** (with gliclazide) slightly increases the exposure to tacrolimus. Monitor and adjust dose. (Severe) Study

**Grapefruit juice** greatly increases the concentration of tacrolimus. Avoid. (Severe) Study

**Grazoprevir** increases the exposure to tacrolimus. (Moderate) Study

**HIV-protase inhibitors** are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Idelalisib** is predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Imatinib** is predicted to increase the concentration of tacrolimus. (Severe) Study

**Letermovir** moderately increases the exposure to tacrolimus. Monitor and adjust dose. (Severe) Study

**Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with tacrolimus. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical

**Tacrolimus** is predicted to increase the exposure to lonafacta. Separate administration by 12 hours. (Moderate) Theoretical

**Lumacaftor** is predicted to decrease the exposure to tacrolimus. Avoid. (Severe) Theoretical

**Macrolides** (clarithromycin) are predicted to increase the concentration of tacrolimus. Monitor and adjust dose. (Severe) Study

**Macrolides** (erythromycin) are predicted to increase the concentration of tacrolimus. (Severe) Study

**Tacrolimus** is predicted to affect the efficacy of mifamurtide. Avoid. (Severe) Theoretical

**Mitotane** decreases the concentration of tacrolimus. Monitor and adjust dose. (Severe) Theoretical

**Nilotinib** is predicted to increase the concentration of tacrolimus. (Severe) Study

**Palbociclib** is predicted to increase the exposure to tacrolimus. Adjust dose. (Moderate) Theoretical

**Ponatinib** (with ponatinib) slightly increases the exposure to tacrolimus. Monitor and adjust dose. (Severe) Study

**Ponatinib** is predicted to decrease the exposure to tacrolimus. Avoid. (Severe) Theoretical

**Ponilozan** increases the concentration of tacrolimus. Adjust dose. (Severe) Anecdotal

**Ranolazine** increases the concentration of tacrolimus. Adjust dose. (Severe) Theoretical

**Ranolazine** increases the concentration of tacrolimus. Adjust dose. (Severe) Theoretical

**Rucaparib** is predicted to increase the exposure to tacrolimus. Use with caution and adjust dose. (Moderate) Theoretical

**Ribociclib** is predicted to increase the exposure to tacrolimus. (Severe) Study

**Sirolimus** is predicted to decrease the concentration of tacrolimus and tacrolimus increases the exposure to sirolimus. (Severe) Study

**St John’s Wort** decreases the concentration of tacrolimus. Avoid. (Severe) Study

**Tacrolimus** increases the exposure to tofacitinib. Avoid. (Severe) Study

**Tacrolimus** potentially increases the risk of serotonin syndrome when given with venlafaxine. (Severe) Anecdotal

**Tadalafil** → see phosphodiesterase type-5 inhibitors

**Tamoxifen** → see TABLE 5 p. 1375 (stromboembrilism)

- Bupropion is predicted to decrease the efficacy of tamoxifen. Avoid. (Severe) Study

**Cinacalcet** is predicted to decrease the efficacy of tamoxifen. Avoid. (Severe) Study

**Tamoxifen** increases the anticoagulant effect of coumarins. (Severe) Study

**Rifaximin** markedly decreases the exposure to tamoxifen. (Unknown) Study

**Rolipram** is predicted to increase the exposure to tamoxifen. (Severe) Study

**Terbinafine** is predicted to decrease the efficacy of tamoxifen. Avoid. (Severe) Study

**Tamulosin** → see alpha blockers

**Taperadol** → see opioids

**Taxanes** → see TABLE 15 p. 1378 (myelosuppression), TABLE 12 p. 1378 (peripheral neuropathy)

- cabazitaxel · docetaxel · pacli taxel
### Table 15: Interactions

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leflunomide</td>
<td>Avoid.</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Avoid.</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Adjust dose.</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Avoid. Study</td>
</tr>
<tr>
<td>Eliglustat</td>
<td>Decrease exposure to docetaxel.</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>Decrease exposure to paclitaxel.</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>Decrease exposure to taxanes (cabazitaxel, paclitaxel).</td>
</tr>
<tr>
<td>Tegafur</td>
<td>Decrease exposure to imatinib.</td>
</tr>
<tr>
<td>Tegafur</td>
<td>Increased risk of toxicity when given with tegafur.</td>
</tr>
<tr>
<td>Tegafur</td>
<td>Increased risk of generalised infection (possibly life-threatening) when given with taxanes (docetaxel, paclitaxel).</td>
</tr>
</tbody>
</table>

Public Health England advises avoid (refer to Green Book).
Methotrexate is predicted to increase the risk of toxicity when given with tegafur. **Severe** Theoretical

Telcoplanin

**GENERAL INFORMATION** If other nephrotoxic or neurotoxic drugs are given, monitor renal and auditory function on prolonged administration.

Telavancin → see Table 2 p. 1375 (nephrotoxicity), Table 19 p. 1379 (ototoxicity), Table 9 p. 1377 (QT interval prolongation)

Telbivudine

- Interferons (interferon alfa) are predicted to increase the risk of peripheral neuropathy when given with telbivudine. Avoid. **Severe** Theoretical
- Interferons (peginterferon alfa) increase the risk of peripheral neuropathy when given with telbivudine. Avoid. **Severe** Study

Telmisartan → see angiotensin-II receptor antagonists

Telotristat ethyl

- Telotristat ethyl is predicted to decrease the exposure to doravirine. Avoid or adjust doravirine dose, p. 644. **Severe** Theoretical
- Telotristat ethyl decreases the exposure to midazolam. **Moderate** Study
- Octreotide (short-acting) decreases the exposure to telotristat ethyl. Telotristat ethyl should be taken at least 30 minutes before octreotide. **Moderate** Study

Temazepam → see Table 11 p. 1377 (CNS depressant effects)

Temocillin → see penicillins

Temozolomide → see alkylating agents

Tensirolimus is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Study  
Also see Table 15 p. 1378

Tenofovir disoproxil is predicted to increase the concentration of tenofovir disoproxil. Avoid or adjust dose. **Moderate** Study  
Also see Table 2 p. 1375

Tenofvir alafenamide is predicted to increase the concentration of tenofvir alafenamide. **Moderate** Theoretical  
Also see Table 2

Tenovir is predicted to increase the concentration of tenofovir disoproxil. **Moderate** Theoretical

Tenecteplase → see Table 3 p. 1375 (anticoagulant effects)

Tenofvir alafenamide is predicted to increase the concentration of tenofovir alafenamide. **Moderate** Theoretical

Ciclosporin is predicted to increase the exposure to tenofovir alafenamide. **Moderate** Theoretical

Eltrombopag is predicted to increase the exposure to tenofovir alafenamide. **Moderate** Theoretical

HIV-protease inhibitors (atazanavir, darunavir, lopinavir) increase the risk of tenofovir alafenamide. Avoid or adjust dose. **Moderate** Study

Ritonavir is predicted to increase the concentration of tenofovir alafenamide. **Moderate** Theoretical

St John's Wort is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Theoretical

Terbinafine

- Terbinafine is predicted to markedly increase the exposure to alafenamide. **Avoid.** Theoretical
- Terbinafine is predicted to markedly increase the exposure to alafenamide. **Theoretical**  
Also see Table 2

Metisa lign is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Study  
Also see Table 15 p. 1378

Netupitant is predicted to increase the concentration of temsirolimus. **Moderate** Theoretical

Nevirapine is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Theoretical

Nilotinib is predicted to increase the concentration of temsirolimus. **Moderate** Theoretical  
Also see Table 15 p. 1378

Pitolisant is predicted to decrease the exposure to temsirolimus. Avoid. **Severe** Theoretical

Rifampicin is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Study

St John's Wort is predicted to decrease the concentration of temsirolimus. Avoid. **Severe** Theoretical

Tenoxicam → see NSAIDs

Terazosin is predicted to increase the exposure to tenofovir disoproxil. **Moderate** Theoretical

Also see Appendix 1

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind.

Tobafinafine is predicted to increase the exposure to anticholinesterases, centrally acting (galantamine). Monitor and adjust dose. **Moderate** Study

Tobafinafine is predicted to moderately increase the exposure to aripiprazole. Adjust aripiprazole dose, p. 395. **Moderate** Study

Tobafinafine is predicted to markedly increase the exposure to atomoxetine. Adjust dose. **Severe** Study

Tobafinafine is predicted to increase the exposure to beta blockers, selective (metoprolol, nebivolol). **Moderate** Study

Terbinafine interactions
Terbinafine – Tetracyclines

**Terbinafine (continued)**

- **Terbinafine** is predicted to slightly increase the exposure to **darifenacin**. **[Rid] Study**
- **Terbinafine** is predicted to increase the exposure to **elaglufast**. Avoid or adjust dose—consult product literature. **[Severe] Study**
- **Terbinafine** is predicted to increase the exposure to **mesiloxine**. **[Moderate] Study**
- **Terbinafine** is predicted to decrease the efficacy of **opioids** **[codeine]**. **[Moderate] Theoretical**
- **Terbinafine** is predicted to decrease the efficacy of **opioids** **[tramadol]**. **[Severe] Study**
- **Terbinafine** is predicted to moderately increase the exposure to **pitolisant**. Use with caution and adjust dose. **[Moderate] Study**
- **Rifampicin** decreases the exposure to **terbinafine**. Adjust dose. **[Moderate] Study**
- **Terbinafine** is predicted to increase the exposure to **risperidone**. Adjust dose. **[Moderate] Study**
- **Terbinafine** is predicted to increase the exposure to SSRIs (**citalopram**, **dapoxetine**, **escitalopram**, **fluvoxamine**, **sertraline**). **[Moderate] Study**
- **Terbinafine** is predicted to increase the exposure to **SSRIs** (**paroxetine**). **[Moderate] Study**
- **Terbinafine** is predicted to decrease the efficacy of **tamoxifen**. **[Moderate] Study**
- **Terbinafine** is predicted to increase the exposure to **tricyclic antidepressants**. Monitor for toxicity and adjust dose. **[Severe] Study**
- **Terbinafine** is predicted to increase the exposure to **voroxetine**. Monitor and adjust dose. **[Moderate] Study**

Tertubalutine → see beta agonists

**Teriflunomide**

- **Teriflunomide** is predicted to increase the exposure to **adefovir**. **[Moderate] Study**
- **Teriflunomide** is predicted to decrease the exposure to **agomelatine**. **[Moderate] Theoretical**
- **Teriflunomide** decreases the exposure to **aminophylline**. Adjust dose. **[Moderate] Study**
- **Teriflunomide** is predicted to decrease the exposure to **anaesthetics, local** (**ropivacaine**). **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **anthracyclines** (**daunorubicin**, **doxorubicin**, **mitoxantrone**). **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **antihistamines, non-sedating** (**fexofenadine**). **[Moderate] Study**
- **Teriflunomide** potentially increases the exposure to **baricitinib**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **bosentan**. **[Moderate] Study**
- **Teriflunomide** is predicted to moderately increase the clearance of **caffeine citrate**. Monitor and adjust dose. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **clozapine**. **[Moderate] Theoretical**
- **Teriflunomide** affects the anticoagulant effect of **coumarins**. **[Severe] Study**
- **Teriflunomide** is predicted to decrease the exposure to **duloxetine**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **ganciclovir**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **H2 receptor antagonists** (**cimetidine**, **famotidine**). **[Moderate] Study**
- **Teriflunomide** is predicted to increase the concentration of **intermivir**. **[Moderate] Study**
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with **teriflunomide**. **Public Health England advises avoid** (refer to **Green Book**). **[Severe] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **loop diuretics** (**furosemide**). **[Moderate] Study**
- **Teriflunomide** is predicted to decrease the exposure to **melatonin**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **methotrexate**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the clearance of **mesiloxine**. Monitor and adjust dose. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **montelukast**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **nateglinide**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to NSAID. **[Moderate] Study**
- **Teriflunomide** is predicted to decrease the exposure to **non-stereoidal anti-inflammatory drugs** (**NSAID**). **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **olanzapine**. Monitor and adjust dose. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **oseltamivir**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **penicillins** (**benzylpenicillin**). **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **pioglitazone**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **quinolones** (**ciprofloxacin**). **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **rapaglinide**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **rosuvastatin**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **sulfasalazine**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **sulfonylureas** (**glibenclamide**). **[Moderate] Study**
- **Teriflunomide** is predicted to increase the concentration of **taxanes** (**paclitaxel**). **[Severe] Anecdotal**
- **Teriflunomide** is predicted to increase the exposure to **tegafur**. **[Severe] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **tenofovir alafenamide**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to increase the exposure to **tenofovir disoproxil**. **[Moderate] Theoretical**
- **Teriflunomide** is predicted to decrease the exposure to **theophylline**. Adjust dose. **[Moderate] Study**
- **Teriflunomide** moderately decreases the exposure to **tizanidine**. **[Rid] Study**
- **Teriflunomide** is predicted to increase the exposure to **topotecan**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **trandolapril**. **[Severe] Study**
- **Teriflunomide** is predicted to increase the exposure to **tizanidine**. **[Rid] Study**
- **Teriflunomide** is predicted to increase the exposure to **topotecan**. **[Moderate] Study**
- **Teriflunomide** is predicted to increase the exposure to **tizanidine**. **[Rid] Study**

Tetanus immunoglobulin → see immunoglobulins

Tetrabenazine → see TABLE 9 p. 1377 (QT-interval prolongation)

Tetrabenazine is predicted to decrease the effects of **levodopa**. **Use with caution or avoid**. **[Moderate] Theoretical**

Tetrabenazine is predicted to increase the risk of CNS toxicity when given with **monoamine-oxidase A and B inhibitors**, **irreversible**. **Avoid and for 14 days after stopping the MAOI**. **[Severe] Theoretical**

**Tetracaine** → see anaesthetics, local

Tetracyclines → see tetracyclines

**ROUTE-SPECIFIC INFORMATION**  Interactions do not generally apply to topical use of **oxytetracycline** unless specified.

- **ACE inhibitors** (**quinapril**) (tablet) decrease the absorption of oral **tetracycline**. **Avoid**. **[Moderate] Study**
- **Antacids** decrease the absorption of **tetracyclines**. Separated administration by 2 to 3 hours. **[Moderate] Study**
- **Antiepileptics** (**carbamazepine**, **fosphenytoin**, **phenobarbital**, **phenytoin, primidone**) decrease the exposure to **doxycycline**. **Monitor and adjust dose**. **[Moderate] Study** → Also see TABLE 1 p. 1375
**Tetracyclines – Theophylline**

- **Tetracyclines** decrease the concentration of antimalarials (atovaquone). (Moderate) Study
- **Calcium salts** (calcium carbonate) are predicted to decrease the absorption of tetracyclines. Separate administration by 2 to 3 hours. (Moderate) Theoretical
- **Tetracyclines** increase the risk of bleeding events when given with **coumarins**. (Moderate) Anecdotal
- **Dairy products** decrease the exposure to tetracyclines (demeclocycline, oxytetracycline, tetracycline). Avoid. (Moderate) Study
- **Enalapril** decreases the exposure to doxycycline. Monitor and adjust dose. (Moderate) Study
- **Iron** (oral) decreases the absorption of tetracyclines. Tetracyclines should be taken 2 to 3 hours after iron (oral). (Moderate) Study
- **Kazeln** is predicted to decrease the absorption of tetracyclines. (Moderate) Theoretical
- **Lanthanum** is predicted to decrease the absorption of tetracyclines. Separate administration by 2 hours. (Moderate) Theoretical
- **Mitotane** decreases the exposure to doxycycline. Monitor and adjust dose. (Moderate) Study
- **Retinoids** (acitretin, alitretinoin, isotretinoin, tretinoin) increase the risk of benign intracranial hypertension when given with tetracyclines. Avoid. (Severe) Anecdotal
- **Rifampicin** decreases the exposure to doxycycline. Monitor and adjust dose. (Moderate) Study
- **Oral zinc** is predicted to decrease the absorption of tetracyclines. Separate administration by 2 to 3 hours. (Moderate) Theoretical

### Tezacaftor

**FOOD AND LIFESTYLE**Avoid bitter (Seville) oranges as they are predicted to increase the exposure to tezacaftor.

- **Antiarhythmics** (dronedarone) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Antiepileptics** (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical
- **Antifungals, azoles** (fluconazole, itraconazole, posaconazole) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Antifungals, azoles** (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Aripiprazole** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Calcium channel blockers** (diltiazem, verapamil) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Cobicistat** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Ciritinib** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Enalapril** is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical
- **Grapefruit juice** is predicted to increase the exposure to tezacaftor. Avoid. (Severe) Study
- **HIV-protease inhibitors** are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Idelalisib** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Imatinib** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Macrolides** (clarithromycin) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Macrolides** (erythromycin) are predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Mitotane** is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical
- **Netupitant** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Nilotinib** is predicted to increase the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Rifabutin** is predicted to increase the exposure to tezacaftor. Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical
- **St John’s Wort** is predicted to decrease the exposure to tezacaftor. Avoid. (Severe) Theoretical

### Thalidomide

- **Thalidomide** is predicted to increase the concentration of theophylline when given with thalidomide. Avoid. (Severe) Theoretical
- **Hormone replacement therapy** is predicted to increase the risk of venous thromboembolism when given with thalidomide. Avoid. (Severe) Theoretical

### Theophylline

- **Theophylline** decreases the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with potent inhibitors of CYP3A4. (Severe) Study
- **Theophylline** decreases the exposure to tezacaftor. Adjust tezacaftor with ivacaftor p. 295 dose with moderate inhibitors of CYP3A4. (Severe) Study
- **Theophylline** decreases clearance and increased doses of theophylline are therefore required; dose adjustments are likely to be necessary if smoking started or stopped during treatment.

- **Acclovir** is predicted to increase the exposure to theophylline. Monitor and adjust dose. (Severe) Theoretical
- **Theophylline** decreases the efficacy of antiarrhythmics (adenosine). Separate administration by 24 hours. (Moderate) Study
- **Antiepileptics** (carbamazepine) potentially increase the clearance of theophylline and theophylline decreases the exposure to antiepileptics (carbamazepine). Adjust dose. (Moderate) Anecdotal
- **Antiepileptics** (fosphenytoin, phenytoin) are predicted to decrease the exposure to theophylline. Adjust dose. (Moderate) Study
- **Antiepileptics** (phenobarbital, primidone) are predicted to increase the clearance of theophylline. Adjust dose. (Moderate) Theoretical
- **Antiepileptics** (stiripentol) are predicted to increase the exposure to theophylline. Avoid. (Moderate) Theoretical
- **Beta blockers, non-selective** are predicted to increase the risk of bronchospasm when given with theophylline. Avoid. (Severe) Theoretical
- **Beta blockers, selective** are predicted to increase the risk of bronchospasm when given with theophylline. Avoid. (Severe) Theoretical
- **Caffeine citrate** decreases the clearance of theophylline. (Moderate) Study
- **Combined hormonal contraceptives** are predicted to increase the exposure to theophylline. Monitor and adjust dose. (Moderate) Study
- **Theophylline** increases the risk of agitation when given with doxapram. (Moderate) Study
- **Enteral feeds** decrease the exposure to theophylline. (Moderate) Study
- **Esketamine** is predicted to increase the risk of seizures when given with theophylline. Avoid. (Severe) Theoretical
- **H2 receptor antagonists** (cimetidine) increase the concentration of theophylline. Adjust dose. (Severe) Study
- **HIV-protease inhibitors** (ritonavir) are predicted to decrease the exposure to theophylline. Adjust dose. (Moderate) Study
- **Iron chelators** (deferasirox) increase the exposure to theophylline. Avoid. (Moderate) Study

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Theophylline (continued)

- Isoniazid is predicted to affect the clearance of theophylline. [Severe] Anecdotal
- Lefunomide is predicted to decrease the exposure to theophylline. Adjust dose. [Moderate] Anecdotal
- Theophylline is predicted to decrease the concentration of lithium. Monitor concentration and adjust dose. [Moderate] Anecdotal
- Macrolides (azithromycin, clarithromycin) are predicted to increase the exposure to theophylline. Adjust dose. [Moderate] Anecdotal
- Macrolides (erythromycin) decrease the clearance of theophylline and theophylline potentially decreases the clearance of macrolides (erythromycin). Adjust dose. [Severe] Study
- Methotrexate decreases the clearance of theophylline. [Moderate] Study
- Mexiletine is predicted to increase the exposure to theophylline. Monitor and adjust dose. [Moderate] Theoretical
- Monoclonal antibodies (blinatumomab) are predicted to transiently increase the exposure to theophylline. Monitor and adjust dose. [Moderate] Theoretical
- Monoclonal antibodies (sarilumab) potentially affect the exposure to theophylline. Monitor and adjust dose. [Moderate] Theoretical
- Nefazodone (ciprofloxacin) are predicted to increase the exposure to theophylline. Monitor and adjust dose. [Moderate] Theoretical
- Rifampicin is predicted to decrease the exposure to theophylline. Adjust dose. [Moderate] Study
- Theophylline is predicted to slightly increase the exposure to roflumilast. Avoid. [Moderate] Theoretical
- Rucaparib is predicted to increase the exposure to theophylline. [Severe] Theoretical
- SSRI (fluvoxamine) moderately to markedly increase the exposure to theophylline. Avoid. [Severe] Study
- St John’s Wort potentially decreases the exposure to theophylline. [Severe] Anecdotal
- Sucralfate potentially decreases the absorption of theophylline. Separate administration by at least 2 hours. [Moderate] Study
- Sympathomimetics, vasoconstrictor (ephedrine) increase the risk of side-effects when given with theophylline. Avoid in children. [Moderate] Study
- Teriflunomide is predicted to decrease the exposure to theophylline. Adjust dose. [Moderate] Study
- Valaciclovir is predicted to increase the exposure to theophylline. [Severe] Theoretical

Thiazide diuretics

- Thiazide diuretics increase the risk of hypercalcaemia when given with vitamin D substances. [Moderate] Theoretical
- Thipental [see TABLE 8 p. 1376 (hypotension), TABLE 11 p. 1377 (CNS depressant effects)]
- Sulfonamides are predicted to increase the effects of thipental. [Moderate] Theoretical
- Tricyclic antidepressants increase the risk of cardiac arrhythmias and hypotension when given with thipental. [Moderate] Study [Also see TABLE 8 p. 1376]
- Thiotepa → see alkylating agents

Thyroid hormones

- levothyroxine - liothyronine

- Antacids are predicted to decrease the absorption of levothyroxine. Separate administration by at least 4 hours. [Moderate] Anecdotal
- Antiarrhythmics (amiodarone) are predicted to increase the risk of thyroid dysfunction when given with thyroid hormones. Avoid. [Moderate] Study
- Antiarrhythmics (carbamazepine, fosphenytoin, phenytoin) are predicted to increase the risk of hypothyroidism when given with thyroid hormones. [Moderate] Study
- Antiarrhythmics (phenobarbital, primidone) are predicted to decrease the effects of thyroid hormones. [Moderate] Theoretical
- Apalutamide potentially decreases the exposure to levothyroxine. [Rid] Theoretical
- Oral calcium salts are predicted to decrease the absorption of levothyroxine. Separate administration by at least 4 hours. [Moderate] Anecdotal
- Thyroid hormones are predicted to affect the concentration of digoxin. Monitor and adjust dose. [Moderate] Theoretical
- HIV-protease inhibitors (ritonavir) decrease the concentration of levothyroxine. MHRA advises monitor TSH for at least one month after starting or stopping ritonavir. [Moderate] Anecdotal
- Oral hormone replacement therapy is predicted to decrease the effects of thyroid hormones. [Moderate] Theoretical
- Iron (oral) decreases the absorption of levothyroxine. Separate administration by at least 4 hours. [Moderate] Study
- Lanthanum decreases the absorption of thyroid hormones. Separate administration by 2 hours. [Moderate] Study
- Thyroid hormones are predicted to affect the absorption of thiopental. Monitor and adjust dose. [Moderate] Study
- Tricyclic antidepressants increase the risk of cardiac arrhythmias and hypotension when given with thipental. [Moderate] Study [Also see TABLE 8 p. 1376]
- Ticagrelor [see ticagrelor]

Tiagabine → see antiepileptics

Tiaiprofenic acid → see NSAIDs

Tibolone → see TABLE 5 p. 1375 (thromboembolism)

Ticagrelor → see TABLE 4 p. 1375 (antiplatelet effects)

- Antiarrhythmics (amiodarone) are predicted to increase the exposure to ticagrelor. Use with caution or avoid. [Severe] Study
- Antiarrhythmics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to markedly decrease the exposure to ticagrelor. Avoid. [Severe] Study
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to markedly increase the exposure to ticagrelor.

- Avantant is predicted to decrease the exposure to ticagrelor. Monitor and adjust dose. [Moderate] Study
- Bosentan is predicted to decrease the exposure to ticagrelor. [Moderate] Theoretical
- Ciclosporin is predicted to increase the exposure to ticagrelor. Use with caution or avoid. [Severe] Study
- Cobimetinib is predicted to markedly increase the exposure to ticagrelor. Avoid. [Severe] Study
- Cobicistat is predicted to markedly increase the exposure to ticagrelor. Avoid. [Severe] Study
- Cisplatin is predicted to decrease the exposure to ticagrelor. Monitor and adjust dose. [Moderate] Study
- Enalapril is predicted to decrease the exposure to ticagrelor. Avoid. [Severe] Theoretical
- Efavirenz is predicted to decrease the exposure to ticagrelor. Avoid. [Severe] Study
- Fenofibrate is predicted to decrease the exposure to ticagrelor. Avoid. [Severe] Study
- Fluticasone increases the concentration of digoxin. [Moderate] Study
- Fosphenytoin is predicted to decrease the exposure to ticagrelor. Avoid. [Severe] Study
- Grapefruit juice moderately increases the exposure to ticagrelor. [Moderate] Study
- Lisinopril is predicted to decrease the exposure to ticagrelor. Monitor and adjust dose. [Moderate] Study
- Lipid lowering substances (atorvastatin, rosuvastatin) are predicted to decrease the exposure to ticagrelor. Avoid. [Severe] Study
- Lisinopril is predicted to decrease the exposure to ticagrelor. Monitor and adjust dose. [Moderate] Study
- Mexiletine is predicted to increase the risk of hypokalaemia when given with thiazide diuretics. [Severe] Theoretical
- Mexiletine is predicted to increase the risk of hyperglycaemia when given with toremifene. [Severe] Theoretical
- Metolazone moderately increases the exposure to ticagrelor. [Moderate] Anecdotal
HIV-protease inhibitors are predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Idelalisib is predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Ticagrelor is predicted to increase the exposure to lomitapide. Separate administration by 12 hours. (Moderate) Theoretical

Macrolides (azithromycin) are predicted to increase the exposure to ticagrelor. Use with caution or avoid. (Severe) Study

Macrolides (clarithromycin) are predicted to markedly increase the exposure to ticagrelor. Avoid. (Severe) Study

Methotrexate is predicted to markedly decrease the exposure to ticagrelor. Avoid. (Severe) Study

Mexiletine is predicted to decrease the exposure to ticagrelor. Avoid. (Moderate) Study

Obeticholic acid is predicted to increase the exposure to tizanidine. (Severe) Theoretical

Quinolones (ciprofloxacin) increase the exposure to tizanidine. Avoid. (Moderate) Study

Rifaximin moderately decreases the exposure to tizanidine. (Moderate) Study

Rucaparib is predicted to increase the exposure to tizanidine. Monitor and adjust dose. (Moderate) Study

SSRIs (fluvoxamine) very markedly increase the exposure to tizanidine. Avoid. (Severe) Study

Teriflunomide moderately decreases the exposure to tizanidine. (Moderate) Study

Tobramycin → see aminoglycosides

Tolctazumab → see monoclonal antibodies

Tofacitinib

Antithrombin (dronedaron) given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Antiprotease inhibitors (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Aprepitant given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Bosantan is predicted to decrease the exposure to tofacitinib. Avoid. (Moderate) Study

Calcium channel blockers (diltiazem, verapamil) given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Ciclosporin increases the exposure to tofacitinib. Avoid. (Severe) Study

Cobicistat is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Crisotinib given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Efavirenz is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Enalapril is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Enalaprilat is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Ezetimibe is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Idelalisib is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Imatinib given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Itraconazole, ketoconazole, voriconazole are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Live vaccines potentially increase the risk of generalised infection (possibly life-threatening) when given with tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Macrolides (clarithromycin) are predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Netupitant given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Nilotinib given with a potent CYP2C19 inhibitor is predicted to increase the exposure to tofacitinib. Adjust tofacitinib dose, p. 1105. (Moderate) Study

Rifampicin is predicted to decrease the exposure to tofacitinib. Avoid. (Severe) Study

Tofacitinib

A1
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Tofacitinib (continued)
▶ SSRIs (fluoxetine, fluvoxamine) given with a moderate CYP3A4
inhibitor are predicted to increase the exposure to tofacitinib.
Adjust tofacitinib dose, p. 1105. o Study
▶ St John’s Wort is predicted to decrease the exposure to
tofacitinib. o Study
▶ Tacrolimus increases the exposure to tofacitinib. Avoid. r
Study

Tolbutamide → see sulfonylureas
Tolcapone
▶ Tolcapone increases the exposure to levodopa. Monitor and
adjust dose. o Study
▶ Tolcapone is predicted to increase the effects of monoamineoxidase A and B inhibitors, irreversible. Avoid. r Theoretical
▶ Tolcapone is predicted to increase the risk of cardiovascular
side-effects when given with sympathomimetics, inotropic.

▶
▶

▶

▶

▶

o Theoretical
▶

Tolcapone is predicted to increase the effects of
sympathomimetics, vasoconstrictor (adrenaline/epinephrine,
noradrenaline/norepinephrine). o Theoretical
Tolfenamic acid → see NSAIDs
Tolterodine → see TABLE 9 p. 1377 (QT-interval prolongation), TABLE 10

▶
▶

r Study
▶

Interactions | Appendix 1

▶

Antiarrhythmics (dronedarone) are predicted to increase the
exposure to tolterodine. n Theoretical → Also see TABLE 9

▶

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Antifungals, azoles (fluconazole, isavuconazole, posaconazole)
are predicted to increase the exposure to tolterodine. n
Theoretical → Also see TABLE 9 p. 1377
▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to tolterodine. Avoid.
r Study → Also see TABLE 9 p. 1377
▶ Aprepitant is predicted to increase the exposure to tolterodine.
▶

▶

▶

▶

n Theoretical

▶
▶
▶
▶
▶
▶
▶

Calcium channel blockers (diltiazem, verapamil) are predicted to
increase the exposure to tolterodine. n Theoretical
Cobicistat is predicted to increase the exposure to tolterodine.
Avoid. r Study
Crizotinib is predicted to increase the exposure to tolterodine.
n Theoretical → Also see TABLE 9 p. 1377
Eliglustat is predicted to increase the exposure to tolterodine.
Adjust dose. o Theoretical
HIV-protease inhibitors are predicted to increase the exposure
to tolterodine. Avoid. r Study → Also see TABLE 9 p. 1377
Idelalisib is predicted to increase the exposure to tolterodine.
Avoid. r Study
Imatinib is predicted to increase the exposure to tolterodine.

▶

Macrolides (clarithromycin) are predicted to increase the
exposure to tolterodine. Avoid. r Study → Also see TABLE 9
Macrolides (erythromycin) are predicted to increase the
exposure to tolterodine. n Theoretical → Also see TABLE 9

Netupitant is predicted to increase the exposure to tolterodine.

▶

▶

▶

n Theoretical
▶

Nilotinib is predicted to increase the exposure to tolterodine.
n Theoretical → Also see TABLE 9 p. 1377
Tolvaptan → see TABLE 16 p. 1379 (increased serum potassium)
GENERAL INFORMATION Avoid concurrent use of drugs that
increase serum-sodium concentrations.
▶

Antiarrhythmics (dronedarone) are predicted to increase the
exposure to tolvaptan. Manufacturer advises caution or adjust
tolvaptan dose with moderate inhibitors of CYP3A4, p. 669.
o Study

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital,
phenytoin, primidone) are predicted to decrease the exposure
to tolvaptan. Use with caution or avoid depending on
indication. r Study
▶ Antifungals, azoles (fluconazole, isavuconazole, posaconazole)
are predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
▶ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are
predicted to increase the exposure to tolvaptan. Manufacturer
▶

Mitotane is predicted to decrease the exposure to tolvaptan.
Use with caution or avoid depending on indication. r
Study

▶

p. 1377
▶

Macrolides (erythromycin) are predicted to increase the
exposure to tolvaptan. Manufacturer advises caution or adjust
tolvaptan dose with moderate inhibitors of CYP3A4, p. 669.
o Study

▶

p. 1377
▶

HIV-protease inhibitors are predicted to increase the exposure
to tolvaptan. Manufacturer advises caution or adjust tolvaptan
dose with potent inhibitors of CYP3A4, p. 669. r Study
Idelalisib is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
potent inhibitors of CYP3A4, p. 669. r Study
Imatinib is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
Tolvaptan is predicted to increase the exposure to lomitapide.
Separate administration by 12 hours. o Theoretical
Macrolides (clarithromycin) are predicted to increase the
exposure to tolvaptan. Manufacturer advises caution or adjust
tolvaptan dose with potent inhibitors of CYP3A4, p. 669. r
Study

▶

n Theoretical

▶

Grapefruit juice increases the exposure to tolvaptan. Avoid.
o Study

p. 1377 (antimuscarinics)

A1

advises caution or adjust tolvaptan dose with potent inhibitors
of CYP3A4, p. 669. r Study
Apalutamide is predicted to decrease the exposure to
tolvaptan. Avoid or monitor. o Study
Aprepitant is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
Calcium channel blockers (diltiazem, verapamil) are predicted to
increase the exposure to tolvaptan. Manufacturer advises
caution or adjust tolvaptan dose with moderate inhibitors of
CYP3A4, p. 669. o Study
Cobicistat is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
potent inhibitors of CYP3A4, p. 669. r Study
Crizotinib is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
Tolvaptan increases the concentration of digoxin. n Study
Enzalutamide is predicted to decrease the exposure to
tolvaptan. Use with caution or avoid depending on indication.

Netupitant is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
Nilotinib is predicted to increase the exposure to tolvaptan.
Manufacturer advises caution or adjust tolvaptan dose with
moderate inhibitors of CYP3A4, p. 669. o Study
Quinolones (ciprofloxacin) are predicted to increase the
exposure to tolvaptan. Use with caution and adjust tolvaptan
dose, p. 669. o Theoretical
Rifampicin is predicted to decrease the exposure to tolvaptan.
Use with caution or avoid depending on indication. r
Study

▶

St John’s Wort is predicted to decrease the exposure to
tolvaptan. Avoid. o Theoretical
Topiramate → see antiepileptics
Topotecan → see TABLE 15 p. 1378 (myelosuppression)
▶ Antiarrhythmics (amiodarone, dronedarone) are predicted to
increase the exposure to topotecan. r Study
▶ Antiepileptics (fosphenytoin, phenytoin) increase the clearance
of topotecan. o Study
▶ Antifungals, azoles (isavuconazole) are predicted to increase the
exposure to topotecan. o Theoretical
▶ Antifungals, azoles (itraconazole, ketoconazole) are predicted to
increase the exposure to topotecan. r Study
▶ Calcium channel blockers (verapamil) are predicted to increase
the exposure to topotecan. r Study
▶ Ceritinib is predicted to increase the exposure to topotecan.
o Theoretical → Also see TABLE 15 p. 1378
▶ Ciclosporin is predicted to increase the exposure to topotecan.
r Study

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Topotecan — Trazodone 1547

- **Eliglustat** is predicted to increase the exposure to topotecan. Adjust dose. (Moderate) Study
- **HIV-protease inhibitors (lopinavir, ritonavir, saquinavir)** are predicted to increase the exposure to topotecan. (Severe) Study
- **Lapatinib** is predicted to increase the exposure to topotecan. (Severe) Study
- **Leflunomide** is predicted to increase the exposure to topotecan. (Moderate) Study Also see TABLE 15 p. 1378
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with topotecan. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- **Macrolides** are predicted to increase the exposure to topotecan. (Severe) Study
- **Mirabegron** is predicted to increase the exposure to topotecan. (Moderate) Study
- **Paritaprevir** (with ritonavir andombitasvir) is predicted to increase the exposure to topotecan. (Moderate) Study
- **Pibrentasvir** (with glecaprevir) is predicted to increase the exposure to topotecan. (Moderate) Study
- **Pitolisant** is predicted to decrease the exposure to topotecan. (Mild) Theoretical
- **Ranolazine** is predicted to increase the exposure to topotecan. (Severe) Study
- **Regorafenib** is predicted to increase the exposure to topotecan. (Moderate) Study Also see TABLE 15 p. 1378
- **Rolapitant** is predicted to increase the exposure to topotecan. Avoid or monitor. (Moderate) Study
- **St John’s Wort** is predicted to decrease the exposure to topotecan. (Severe) Theoretical
- **Tedizolid** is predicted to increase the exposure to topotecan. (Moderate) Study
- **Venetoclax** is predicted to increase the concentration of topotecan. (Moderate) Study
- **Vemurafenib** is predicted to increase the exposure to topotecan. (Severe) Study
- **Voxilaprevir** is predicted to increase the concentration of topotecan. (Moderate) Theoretical
- **Torasemide** → see loop diuretics
- **Toremifene** → see loop diuretics

(See interval prolongation)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to toremifene. Adjust dose. (Moderate) Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to toremifene. Adjust dose. (Moderate) Study
- **Cobicistat** is predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical Also see TABLE 1 p. 1375
- **Enzalutamide** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **HIV-protease inhibitors** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Idelalisib** is predicted to increase the exposure to toremifene. Avoid. (Severe) Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with toremifene. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Mitoxantrone** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **Tramadol** → see opioids

**Trametinib**

- **Antihypertensives (amiodarone, dronedarone)** are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Antifungals, azoles (itraconazole, ketoconazole) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Calcium channel blockers (verapamil) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Ciclosporin** is predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Ranolazine** is predicted to decrease the concentration of trametinib. (Moderate) Theoretical
- **Torasemide** → see loop diuretics

(See interval prolongation)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to toremifene. Adjust dose. (Moderate) Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to toremifene. Adjust dose. (Moderate) Study
- **Cobicistat** is predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical Also see TABLE 1 p. 1375
- **Enzalutamide** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **HIV-protease inhibitors** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Idelalisib** is predicted to increase the exposure to toremifene. Avoid. (Severe) Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with toremifene. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Mitoxantrone** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical

(A1)

- **Trametinib**

- **Antihypertensives (amiodarone, dronedarone)** are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Antifungals, azoles (itraconazole, ketoconazole) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Calcium channel blockers (verapamil) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Ciclosporin** is predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **HIV-protease inhibitors (lopinavir, ritonavir, saquinavir) are predicted to increase the concentration of trametinib. (Moderate) Theoretical
- **Ranolazine** is predicted to decrease the concentration of trametinib. (Moderate) Theoretical
- **Torasemide** → see loop diuretics

(See interval prolongation)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to toremifene. Adjust dose. (Moderate) Study
- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to toremifene. Adjust dose. (Moderate) Study
- **Cobicistat** is predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical Also see TABLE 1 p. 1375
- **Enzalutamide** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **HIV-protease inhibitors** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Idelalisib** is predicted to increase the exposure to toremifene. Avoid. (Severe) Theoretical
- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with toremifene. Public Health England advises avoid (refer to Green Book). (Severe) Theoretical
- **Macrolides (clarithromycin)** are predicted to increase the exposure to toremifene. Avoid or adjust dose. (Severe) Theoretical
- **Mitoxantrone** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical
- **Rifampicin** is predicted to decrease the exposure to toremifene. Avoid. (Severe) Theoretical

(A1)
Trazodone (continued)

**Imatinib** is predicted to increase the exposure to trazodone. (Moderate) Theoretical

**Macrolides (clarithromycin)** are predicted to moderately increase the exposure to trazodone. Avoid or adjust dose. (Moderate) Study

**Macrolides (erythromycin)** are predicted to increase the exposure to trazodone. (Moderate) Theoretical

**Netupitant** is predicted to increase the exposure to trazodone. (Moderate) Theoretical

**Nilotinib** is predicted to increase the exposure to trazodone. (Moderate) Theoretical

**Tree pollen extract**

**General information** Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline might be ineffective in case of a hypersensitivity reaction) or ACE inhibitors (risk of severe anaphylactoid reactions).

**Tresufan** → see alkylating agents

**Tretinoin** → see retinoids

**Triamcinolone** → see corticosteroids

**Tramadol** → see potassium-sparing diuretics

**Tricyclic antidepressants**

**Tricyclic antidepressants** → see TABLE 18 p. 1379 (hypotension), TABLE 13 p. 1376 (serotonin syndrome), TABLE 9 p. 1377 (QT-interval prolongation), TABLE 10 p. 1377 (antimuscarinics)

**amitriptyline • clomipramine • dosulepin • doxepin • imipramine • lofepramine • nortriptyline • trimipramine**

**Tropicamide**

**ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions of topical doxepin should be borne in mind.

**Antiarrhythmics (dronedarone)** are predicted to increase the exposure to tricyclic antidepressants. Avoid. (Severe) Theoretical → Also see TABLE 9 p. 1377

**Antiarrhythmics (propafenone)** are predicted to increase the concentration of tricyclic antidepressants. (Moderate) Theoretical → Also see TABLE 10 p. 1377

**Antiepileptics (carbamazepine)** decrease the exposure to tricyclic antidepressants. Adjust dose. (Moderate) Study → Also see TABLE 16 p. 1376

**Antiepileptics (phenobarbital, primidone)** are predicted to decrease the exposure to tricyclic antidepressants. (Moderate) Study

**Tricyclic antidepressants** (clomipramine, imipramine) potentially increase the risk of overheating and dehydration when given with antiepileptics (zonisamide). Avoid in children. (Severe) Theoretical

**Bupropion** is predicted to increase the exposure to tricyclic antidepressants. Monitor for toxicity and adjust dose. (Severe) Study

**Cinacalcet** is predicted to increase the exposure to tricyclic antidepressants. Monitor for toxicity and adjust dose. (Severe) Study

**Tricyclic antidepressants** decrease the antihypertensive effects of clonidine. Monitor and adjust dose. (Moderate) Aneautal → Also see TABLE 8 p. 1376

**Cobicistat** is predicted to slightly increase the exposure to tricyclic antidepressants. (Small) Study

**Darifenacin** is predicted to increase the exposure to tricyclic antidepressants. (Moderate) Theoretical → Also see TABLE 10 p. 1377

**Eliglustat** is predicted to increase the exposure to nortriptyline. Adjust dose. (Moderate) Theoretical

**Tricyclic antidepressants** are predicted to decrease the antihypertensive effects of guanethidine. (Moderate) Study → Also see TABLE 8 p. 1376

**H₂ receptor antagonists (cimetidine)** increase the exposure to tricyclic antidepressants. (Moderate) Study

**HIV-protease inhibitors (ritonavir, tipranavir)** are predicted to increase the exposure to tricyclic antidepressants. (Moderate) Theoretical

**Tricyclic antidepressants** potentially increase the risk of neurotoxicity when given with lithium. (Severe) Aneautal → Also see TABLE 13 p. 1378 → Also see TABLE 9 p. 1377

**Amiodipine** decreases the effects of metyrapone. Avoid. (Moderate) Theoretical

**Tricyclic antidepressants** are predicted to increase the risk of severe toxic reaction when given with moclobemide. Avoid. (Severe) Theoretical → Also see TABLE 13 p. 1378

**Tricyclic antidepressants** are predicted to increase the risk of severe toxic reaction when given with monoamine-oxidase A and B inhibitors, irreversible. Avoid and for 14 days after stopping the MAO. (Severe) Theoretical → Also see TABLE 8 p. 1376 → Also see TABLE 13 p. 1378

**Tricyclic antidepressants** are predicted to decrease the effects of moxonidine. Avoid. (Moderate) Theoretical → Also see TABLE 8 p. 1376

**Tricyclic antidepressants** are predicted to decrease the efficacy of pitolisant. (Small) Theoretical

**SSRIs (fluoxetine, paroxetine)** are predicted to increase the exposure to tricyclic antidepressants. Monitor for toxicity and adjust dose. (Severe) Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378

**SSRIs (fluvoxamine)** markedly increase the exposure to clomipramine. Adjust dose. (Severe) Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378

**SSRIs (fluvoxamine)** increase the exposure to tricyclic antidepressants (amitriptyline, imipramine). Adjust dose. (Severe) Study → Also see TABLE 18 p. 1379 → Also see TABLE 13 p. 1378

**Sucralfate** is predicted to decrease the absorption of tricyclic antidepressants. (Moderate) Study

**Tricyclic antidepressants** increase the effects of sympathomimetics, vasoconstrictor (adrenaline/epinephrine, noradrenaline/norepinephrine, phenylephrine). Avoid. (Severe) Study

**Tricyclic antidepressants** are predicted to decrease the effects of sympathomimetics, vasoconstrictor (ephedrine). Avoid. (Severe) Study

**Tricyclic antidepressants** are predicted to decrease the effects of dopamine receptor agonists. Avoid. (Severe) Study

**Tricyclic antidepressants** increase the risk of cardiac arrhythmias and hypotension when given with thiopental. (Moderate) Study → Also see TABLE 8 p. 1376

**Trientine**

**Trientine** potentially decreases the absorption of iron (oral). (Moderate) Theoretical

**Trientine** potentially decreases the absorption of zinc. (Moderate) Theoretical

**Trifluoperazine** → see phenothiazines

**Trimethaphenylid** → see TABLE 10 p. 1377 (antimuscarinics)

**Trimethoprim** → see TABLE 18 p. 1379 (hypotension), TABLE 2 p. 1375 (nephrotoxicity), TABLE 16 p. 1379 (increased serum potassium)

**Trimethoprim** increases the concentration of antiepileptics (fosphephenylvin, phenytoin). (Moderate) Study

**Antimalarials (pyrimethamine)** increase the risk of side-effects when given with trimethoprim. (Severe) Study

**Trimethoprim** is predicted to increase the anticoagulant effect of coumarins. (Severe) Study

**Dapsone** increases the exposure to trimethoprim and trimethoprim increases the exposure to dapsone. (Severe) Study

**Trimethoprim** increases the concentration of digoxin. (Moderate) Study

**Trimethoprim** is predicted to increase the exposure to dopamine receptor agonists (pramipexole), Adjust dose. (Moderate) Study

**Trimethoprim** slightly increases the exposure to lamivudine. (Small) Study

**Trimethoprim** is predicted to increase the risk of side-effects when given with methotrexate. Avoid. (Severe) Theoretical → Also see TABLE 2 p. 1375

**Trimethoprim** slightly increases the exposure to repaglinide. Avoid or monitor blood glucose. (Moderate) Study

**Rifampicin** decreases the exposure to trimethoprim. (Moderate) Study

**Trimethoprim** is predicted to decrease the efficacy of sapropterin. (Moderate) Theoretical

**Trimethoprim** → see TABLE 10 p. 1377 (antimuscarinics)
Trospium → see TABLE 10 p. 1377 (antimuscarinis)

Trosporane → see TABLE 13 p. 1378 (serotonin syndrome)

▸ Trosporane greatly decreases the concentration of levodopa. (Moderate) Study

▸ Trosporane increases the risk of side-effects when given with monoamine-oxidase A and B inhibitors, irreversible. (Severe) Anecdotal → Also see TABLE 13 p. 1378

Typhoid vaccine, oral → see live vaccines

Ulipristal

▸ Antihistamines (dronedaron) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Antiepileptics (carbamazepine, eslicarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate) decrease the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Antifungals, azoles (fluconazole, isavuconazole, posaconazole) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Anecdotal

▸ Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

▸ Aprepitant decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Bosantan decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Cobisistat is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

▸ Ulipristal is predicted to decrease the efficacy of combined hormonal contraceptives. Avoid. (Severe) Theoretical

▸ Crizotinib is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Ulipristal is predicted to decrease the efficacy of desogestrel. Avoid. (Severe) Theoretical

▸ Efavirenz decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Enalaprilat is predicted to markedly decrease the exposure to ulipristal. Avoid and for 4 weeks after stopping ulipristal. (Severe) Theoretical

▸ Ulipristal is predicted to decrease the efficacy of etonogestrel. Avoid. (Severe) Theoretical

▸ Fosaprepitant decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Grapefruit juice is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Griseofulvin potentially decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

▸ HIV-protease inhibitors (ritonavir) decrease the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Idelalisib is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Severe) Study

▸ Imatinib is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Ulipristal is predicted to decrease the efficacy of levonorgestrel. Avoid. (Severe) Theoretical

▸ Lumacaftor is predicted to decrease the efficacy of ulipristal. Use additional contraceptive precautions. (Severe) Theoretical

▸ Macrolides (erythromycin) are predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Modafinil decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Netupitant is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Nevirapine decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Nilotinib is predicted to increase the exposure to ulipristal. Avoid if used for uterine fibroids. (Moderate) Study

▸ Ulipristal is predicted to decrease the efficacy of norethisterone. Avoid. (Severe) Theoretical

▸ Rifabutin decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ Rifampicin decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

▸ St John's Wort decreases the efficacy of ulipristal. For FSRH guidance, see Contraceptives, interactions p. 794. (Severe) Anecdotal

Umedilidium → see TABLE 10 p. 1377 (antimuscarinis)

Urokinase → see TABLE 3 p. 1375 (anticoagulant effects)

Ursodeoxycholic acid

▸ Antacids are predicted to decrease the absorption of ursodeoxycholic acid. Separate administration by 2 hours. (Moderate) Theoretical

▸ Ursodeoxycholic acid affects the concentration of ciclosporin. Use with caution and adjust dose. (Severe) Anecdotal

▸ Fibrates are predicted to decrease the efficacy of ursodeoxycholic acid. Avoid. (Severe) Theoretical

▸ Ustekinumab → see monoclonal antibodies

▸ Valaciclovir → see TABLE 2 p. 1375 (nephrotoxicity)

▸ Valaciclovir is predicted to increase the exposure to aminophylline. (Severe) Anecdotal

▸ Mycophenolate is predicted to increase the risk of haematological toxicity when given with valaciclovir. (Moderate) Theoretical

▸ Valaciclovir is predicted to increase the exposure to theophylline. (Severe) Theoretical

▸ Valganciclovir → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity)

▸ Valganciclovir is predicted to increase the risk of seizures when given with carbapenem (imipenem). Avoid. (Severe) Anecdotal

▸ Valganciclovir is predicted to increase the exposure to didanosine. (Moderate) Study

▸ Mycophenolate is predicted to increase the risk of haematological toxicity when given with valganciclovir. (Moderate) Theoretical

▸ Mycophenolate is predicted to increase the exposure to theophylline. (Severe) Theoretical

▸ Valganciclovir is predicted to increase the exposure to theophylline. (Severe) Theoretical

▸ Valproate → see antiepileptics

▸ Valtsartan → see angiotensin-II receptor antagonists

▸ Vancomycin → see TABLE 2 p. 1375 (nephrotoxicity), TABLE 19 p. 1379 (ototoxicity)

▸ Vandetanib → see TABLE 9 p. 1377 (QT-interval prolongation)

▸ Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to vandetanib. Avoid. (Moderate) Study

▸ Vandetanib is predicted to increase the risk of bleeding events when given with coumarins. (Severe) Theoretical

▸ Vandetanib slightly increases the exposure to digoxin. Monitor ECG and adjust dose. (Moderate) Study

▸ Vandetanib is predicted to increase the exposure to dopamine receptor agonists (pramipexole). Adjust dose. (Moderate) Study

▸ Enalaprilat is predicted to decrease the exposure to vandetanib. Avoid. (Moderate) Study

▸ Vandetanib increases the exposure to metformin. Monitor and adjust dose. (Moderate) Study

▸ Mitotane is predicted to decrease the exposure to vandetanib. Avoid. (Moderate) Study

▸ Vandetanib is predicted to increase the risk of bleeding events when given with phenindione. (Severe) Theoretical
Vandetanib (continued)

- **Rifampicin** is predicted to decrease the exposure to vandetanib. Avoid. [Moderate] Study

 Vandetanib

- **Vardenafil** → see phosphodiesterase type-5 inhibitors

 Varicella-zoster immunoglobulin → see immunoglobulins

 Varicella-zoster vaccine → see live vaccines

 Vedolizumab → see monoclonal antibodies

 **Velpatasvir**

- **Velpatasvir** is predicted to increase the exposure to aliskiren. [Severe] Theoretical

- **Antacids** are predicted to decrease the concentration of velpatasvir. Separate administration by 4 hours. [Moderate] Theoretical

- **Antihypertensives (ami洛dare) are predicted to increase the concentration of velpatasvir. Avoid or monitor. [Moderate] Theoretical

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to moderately decrease the exposure to velpatasvir. Avoid. [Severe] Study

- **Bosentan** is predicted to decrease the exposure to velpatasvir. Avoid. [Moderate] Theoretical

- **Calcium salts (calcium carbonate) are predicted to decrease the concentration of velpatasvir. Separate administration by 4 hours. [Moderate] Anecdotal

- **Velpatasvir** is predicted to increase the exposure to colchicine. [Severe] Theoretical

- **Velpatasvir** increases the exposure to dabigatran. Avoid. [Severe] Study

- **Velpatasvir** is predicted to increase the exposure to digoxin. [Severe] Study

- **Velpatasvir** is predicted to increase the exposure to edoxaban. [Severe] Theoretical

- **Efavirenz** is predicted to decrease the exposure to velpatasvir. Avoid. [Moderate] Theoretical

- **Enzalutamide** is predicted to moderately decrease the exposure to velpatasvir. Avoid. [Severe] Study

- **H2 receptor antagonists are predicted to decrease the concentration of velpatasvir. Adjust dose, see sofosbuvir with velpatasvir p. 69. [Moderate] Study

- **HIV protease inhibitors (tipranavir) are predicted to increase the exposure to velpatasvir. [Severe] Theoretical

- **Velpatasvir** is predicted to increase the exposure to lopinavir. [Severe] Theoretical

- **Mirtazapine is predicted to moderately decrease the exposure to velpatasvir. Avoid. [Severe] Study

- **Modafinil is predicted to decrease the exposure to velpatasvir. Avoid. [Severe] Theoretical

- **Nevirapine** is predicted to decrease the exposure to velpatasvir. Avoid. [Moderate] Theoretical

- **Proton pump inhibitors are predicted to decrease the concentration of velpatasvir. Adjust dose, see sofosbuvir with velpatasvir p. 69. [Moderate] Study

- **Rifampicin is predicted to moderately decrease the exposure to velpatasvir. Avoid. [Severe] Study

- **Velpatasvir** is predicted to increase the exposure to sirolimus. [Severe] Theoretical

- **St John’s Wort is predicted to decrease the exposure to velpatasvir. Avoid. [Moderate] Theoretical

- **Velpatasvir** is predicted to increase the exposure to statins (atorvastatin). Avoid. [Severe] Study

- **Velpatasvir** increases the exposure to statins (rosuvastatin). Adjust rosuvastatin dose and monitor side effects, p. 204. [Severe] Study

- **Velpatasvir** is predicted to increase the exposure to statins (simvastatin). Monitor side effects and adjust dose. [Severe] Theoretical

- **Velpatasvir** is predicted to increase the exposure to sulfasalazine. [Moderate] Theoretical

- **Velpatasvir** is predicted to increase the exposure to taxanes (paclitaxel). [Severe] Theoretical

- **Velpatasvir** is predicted to increase the exposure to tenofovir disoproxil. [Severe] Study

- **Velpatasvir** is predicted to increase the exposure to topotecan. [Severe] Theoretical

- **Vemurafenib** → see Table 9 p. 1377 (QT-interval prolongation)

- **Vemurafenib** is predicted to increase the exposure to afatinib. Separate administration by 12 hours. [Moderate] Study

- **Vemurafenib** is predicted to increase the exposure to aliskiren. Use with caution and adjust dose. [Moderate] Theoretical

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to vemurafenib. Avoid. [Severe] Theoretical

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole) are predicted to increase the exposure to vemurafenib. [Severe] Theoretical → Also see Table 9 p. 1377

- **Vemurafenib is predicted to increase the exposure to beta blockers, non-selective (nadolol). [Moderate] Study

- **Vemurafenib is predicted to increase the exposure to bictegravir. Use with caution or avoid. [Moderate] Theoretical

- **Cobicistat is predicted to increase the exposure to vemurafenib. [Severe] Theoretical

- **Vemurafenib is predicted to increase the exposure to colchicine. Avoid or adjust colchicine dose, p. 120. [Severe] Theoretical

- **Vemurafenib increases the exposure to dabigatran. Use with caution and adjust dose. [Severe] Theoretical

- **Vemurafenib is predicted to slightly increase the exposure to edoxaban. [Severe] Theoretical

- **Enzalutamide is predicted to decrease the exposure to vemurafenib. Avoid. [Severe] Theoretical

- **Vemurafenib is predicted to increase the exposure to erlotinib. [Moderate] Theoretical

- **Vemurafenib is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical → Also see Table 9 p. 1377

- **Idelalisib is predicted to increase the exposure to vemurafenib. [Severe] Theoretical

- **Macrolides (clarithromycin) are predicted to increase the exposure to vemurafenib. [Severe] Theoretical → Also see Table 9 p. 1377

- **Mitotane is predicted to decrease the exposure to vemurafenib. Avoid. [Severe] Study

- **Vemurafenib is predicted to increase the exposure to nilotinib. [Moderate] Study

- **Vemurafenib is predicted to increase the exposure to panobinostat. Adjust dose. [Moderate] Theoretical → Also see Table 9 p. 1377

- **Vemurafenib is predicted to increase the exposure to pibrentasvir. [Moderate] Theoretical

- **Rifampicin is predicted to decrease the exposure to vemurafenib. Avoid. [Severe] Theoretical

- **Vemurafenib is predicted to increase the exposure to ticagrelor. Use with caution or avoid. [Severe] Study

- **Vemurafenib is predicted to increase the exposure to topotecan. [Severe] Study

- **Vemurafenib is predicted to increase the concentration of trametinib. [Moderate] Theoretical

- **Vemurafenib is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical

**Venetoclax**

*FOOD AND LIFESTYLE* Avoid Seville (bitter orange) and star fruit as they might increase the exposure to venetoclax.

- **Antihypertensives (ami洛dare) are predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical

- **Antihypertensives (dronedarone) are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study

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<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole)</td>
<td>are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to statins (atorvastatin). [Moderate] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to rivaroxaban. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to sulfinpyrazone. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to sulfonylureas (glibenclamide). [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to topotecan. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to venlafaxine. [Moderate] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to warfarin. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to bosantan. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Calcium channel blockers (diltiazem, verapamil)</td>
<td>are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>is predicted to increase the exposure to everolimus. Avoid or adjust dose. [Severe] Study</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>HIV-protease inhibitors</td>
<td>are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>potentially decreases the efficacy of live vaccines. Avoid. [Severe] Theoretical</td>
</tr>
<tr>
<td>Idenalisib</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Verapamil</td>
<td>is predicted to increase the exposure to dabigatran. Avoid or adjust dose. [Severe] Study</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Enalaprilamide</td>
<td>is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to everolimus. Avoid or adjust dose. [Severe] Study</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>HIV-protease inhibitors</td>
<td>are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>potentially decreases the efficacy of live vaccines. Avoid. [Severe] Theoretical</td>
</tr>
<tr>
<td>Macrolides (clarithromycin, erythromycin)</td>
<td>are predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>is predicted to increase the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or adjust dose—consult product literature. [Severe] Study</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to regapinide. [Moderate] Theoretical</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to sirolimus. Avoid or adjust dose. [Severe] Study</td>
</tr>
<tr>
<td>St John’s Wort</td>
<td>is predicted to decrease the exposure to venetoclax. Avoid. [Severe] Study</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to statins (fluvastatin, pravastatin, rosvastatin, simvastatin). [Moderate] Theoretical</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>is predicted to increase the exposure to sulfinpyrazone. [Moderate] Theoretical</td>
</tr>
</tbody>
</table>

Venetoclax – Vinca alkaloids 1551

Venetoclax is predicted to increase the exposure to sulfonylureas (glibenclamide). [Moderate] Theoretical

Venetoclax is predicted to increase the exposure to topotecan. [Moderate] Theoretical

Venetoclax is predicted to increase the exposure to venetoclax. Avoid or monitor for toxicity. [Severe] Theoretical

Venlafaxine – see Table 1. p. 1378 (serotonin syndrome, Table 9 p. 1377 (QT-interval prolongation), Table 11 p. 1377 (CNS depressant effects), Table 4 p. 1375 (antiplatelet effects)

Antifungals, azoles (itraconazole, ketoconazole, posaconazole, voriconazole) are predicted to increase the exposure to venlafaxine. [Moderate] Study

Also see Table 9 p. 1377

Cobicistat is predicted to increase the exposure to venlafaxine. [Moderate] Study

Hy receptor antagonists (cimetidine) slightly increase the exposure to venlafaxine. [Mild] Study

Venlafaxine slightly increases the exposure to haloperidol. [Severe] Study → Also see Table 9 p. 1377 → Also see Table 11 p. 1377

HIV-protease inhibitors are predicted to increase the exposure to venlafaxine. [Moderate] Study → Also see Table 9 p. 1377

Idelalisib is predicted to increase the exposure to venlafaxine. [Moderate] Study

Macrolides (clarithromycin) are predicted to increase the exposure to venlafaxine. [Moderate] Study

Verapamil is predicted to increase the exposure to pitolisant. Use with caution and adjust dose. [Mild] Theoretical

Tacrolimus potentially increases the risk of serotonin syndrome when given with venlafaxine. [Severe] Anecdotal

Venetoclax is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical

Also see Table 9 p. 1377

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to vinflunine. Avoid. [Severe] Theoretical → Also see Table 12 p. 1378

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to vinorelbine. Use with caution or avoid. [Severe] Theoretical → Also see Table 12 p. 1378

Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vindesine). [Severe] Theoretical → Also see Table 1 p. 1375 → Also see Table 12 p. 1378

Antifungals, azoles (fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole) are predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical → Also see Table 1 p. 1375 → Also see Table 9 p. 1377

Antifungals, azoles (miconazole) are predicted to increase the concentration of vinca alkaloids. Use with caution and adjust dose. [Moderate] Theoretical

Aprepitant is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical

Asparaginase potentially increases the risk of neurotoxicity when given with vincristine. Vincristine should be taken 5 to 24 hours before asparaginase. [Severe] Anecdotal → Also see Table 1 p. 1375 → Also see Table 15 p. 1378

Calcium channel blockers (diltiazem, verapamil) are predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical

Cobicistat is predicted to increase the exposure to vinca alkaloids. [Severe] Theoretical

Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole potentially increase the risk of serotonin syndrome when given with venlafaxine. [Severe] Theoretical

Also see Appendix 1
### Vinca alkaloids – Vortioxetine

**Vinca alkaloids** (continued)

- **Crisantaspase** potentially increases the risk of neurotoxicity when given with vincristine. Vincristine should be taken 3 to 24 hours before crisantaspase. **(Severe) Anecdotal** → Also see TABLE 15. p. 1378

- **Crisantaspase** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Enzalutamide** is predicted to decrease the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- **Enzalutamide** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Vismodegib** is predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vindeosine). **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- **Enzalutamide** is predicted to decrease the exposure to vinflunine. Avoid. **(Severe) Theoretical**

- **Enzalutamide** is predicted to decrease the exposure to vinorelbine. Use with caution or avoid. **(Severe) Theoretical**

- **Enzalutamide** is predicted to decrease the exposure to vinorelbine. Avoid. **(Severe) Theoretical**

- **HIV-protase inhibitors** are predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- **Iralisib** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Imatinib** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Live vaccines** are predicted to increase the risk of generalised infection (possibly life-threatening) when given with vinca alkaloids. Public Health England advises avoid (refer to Green Book). **(Severe) Theoretical**

- **Macrolides (clarithromycin, erythromycin)** are predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 9 p. 1377

- **Mitotane** is predicted to decrease the exposure to vinflunine. Avoid. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Mitotane** is predicted to decrease the exposure to vinorelbine. Use with caution or avoid. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Netupitant** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical**

- **Nilotinib** is predicted to increase the exposure to vinca alkaloids. **(Severe) Theoretical** → Also see TABLE 15. p. 1378 → Also see TABLE 9 p. 1377

- **Pegaspargase** potentially increases the risk of neurotoxicity when given with vincristine. Vincristine should be taken 3 to 24 hours before pegaspargase. **(Severe) Anecdotal** → Also see TABLE 1 p. 1375 → Also see TABLE 15. p. 1378

- **Rifampicin** is predicted to decrease the exposure to vinca alkaloids (vinblastine, vincristine, vindeosine). **(Severe) Theoretical**

- **Rifampicin** is predicted to decrease the exposure to vinflunine. Avoid. **(Severe) Theoretical**

- **Rifampicin** is predicted to decrease the exposure to vinorelbine. Avoid. **(Severe) Theoretical** → Also see TABLE 15. p. 1378

- **Vincristine** → see vinca alkaloids

- **Vindesine** → see vinca alkaloids

- **Vinorelbine** → see vinca alkaloids

- **Vismodegib** → see vinca alkaloids

- **Vismodegib** → see TABLE 15. p. 1378 (myelosuppression)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to vismodegib. Avoid. **(Moderate) Theoretical**

- **Enzalutamide** is predicted to decrease the exposure to vismodegib. Avoid. **(Moderate) Theoretical**

- **Mitotane** is predicted to decrease the exposure to vismodegib. Avoid. **(Moderate) Theoretical** → Also see TABLE 15. p. 1378

- **Rifampicin** is predicted to decrease the exposure to vismodegib. Avoid. **(Moderate) Theoretical**

- **St John’s Wort** is predicted to decrease the exposure to vismodegib. Avoid. **(Moderate) Theoretical**

- **Vitamin A**

  - **Retinoids (tretinoin)** are predicted to increase the risk of vitamin A toxicity when given with vitamin A. Adjust dose. **(Moderate) Theoretical**

  - **Retinoids (tretinoin)** are predicted to increase the risk of vitamin A toxicity when given with vitamin A. Avoid. **(Severe) Study**

- **Vitamin D substances**

  - **Alfacalcidol** - **calcipotriol** - **calcitriol** - **colecalciferol** - **dihydrotachysterol** - **ergocalciferol** - **paricalcitol** - **licalcalcitol**

- **ROUTE-SPECIFIC INFORMATION** Since systemic absorption can follow topical application, the possibility of interactions with topical calcitriol should be borne in mind.

- **Antiepileptics (carbamazepine)** are predicted to decrease the effects of vitamin D substances. **(Moderate) Study**

- **Antiepileptics (fosphenytoin, phenytoin)** decrease the effects of vitamin D substances. **(Moderate) Study**

- **Antiepileptics (phenobarbital, primidone)** are predicted to decrease the effects of vitamin D substances. **(Moderate) Theoretical**

- **Antifungals, azoles ( clotrimazole, ketoconazole)** are predicted to decrease the exposure to colecalciferol. **(Moderate) Theoretical**

- **Antifungals, azoles (itraconazole, ketoconazole, voriconazole)** are predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Cobicistat** is predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Vitamin D substances are predicted to increase the risk of toxicity when given with digoxin. **(Severe) Theoretical**

- **HIV-protase inhibitors are predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Idelalisib** is predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Macrolides (clarithromycin)** are predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Vinca alkaloids** are predicted to increase the exposure to paricalcitol. **(Moderate) Study**

- **Thiazide diuretics increase the risk of hypercalcaemia when given with vitamin D substances. **(Moderate) Theoretical**

- **Vitamin E substances**

  - **alpha tocopherol** - **alpha tocopheryl acetate**

  - **Vitamin E substances affect the exposure to ciclosporin. **(Moderate) Study**

- **Volatile halogenated anaesthetics** → see TABLE 8. p. 1376

- **(Hypotension), TABLE 11 p. 1377 (CNS depressant effects)**

  - desflurane - isoflurane - methoxyflurane - sevoflurane

  - **Antiepileptics (phenobarbital, primidone)** potentially increase the risk of nephrotoxicity when given with methoxyflurane. Avoid. **(Severe) Theoretical** → Also see TABLE 11. p. 1377

  - **Isoniazid** potentially increases the risk of nephrotoxicity when given with methoxyflurane. Avoid. **(Severe) Theoretical**

  - **Rifampicin** potentially increases the risk of nephrotoxicity when given with methoxyflurane. Avoid. **(Severe) Theoretical**

- **Vincristine** → see TABLE 13 p. 1378 (serotonin syndrome), TABLE 4 p. 1375 (antiplatelet effects)

- **Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)** are predicted to decrease the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**

- **Bupropion** is predicted to increase the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study** → Also see TABLE 13 p. 1378

- **Cinacalcet** is predicted to increase the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**

- **Enzalutamide** is predicted to decrease the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**

- **Mitotane** is predicted to decrease the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**

- **St John’s Wort** is predicted to decrease the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**

- **SSRIs (fluoxetine, paroxetine)** are predicted to increase the exposure to vortioxetine. Monitor and adjust dose. **(Moderate) Study**
Voxilaprevir

- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Study
- Antiepileptics (oxcarbazepine) are predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Bosantan is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Ciclosporin increases the concentration of voxilaprevir. Avoid. [Severe] Study
- Combined hormonal contraceptives (containing ethinylestradiol) are predicted to increase the risk of increased ALT concentrations when given with voxilaprevir (with sofosbuvir and velpatasvir). Avoid. [Severe] Study
- Voxilaprevir (with sofosbuvir and velpatasvir) increases the concentration of dabigatran. Avoid. [Severe] Study
- Voxilaprevir (with sofosbuvir and velpatasvir) is predicted to increase the exposure to digoxin. Monitor and adjust dose. [Severe] Theoretical
- Voxilaprevir (with sofosbuvir and velpatasvir) is predicted to increase the concentration of edoxaban. Avoid. [Severe] Theoretical
- Efavirenz is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Enalaprilat is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Study
- HIV-protease inhibitors (atazanavir) boosted with ritonavir) increase the concentration of voxelaprevir. Avoid. [Severe] Study
- HIV-protease inhibitors (lopinavir) boosted with ritonavir) are predicted to increase the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- HIV-protease inhibitors (tipranavir) boosted with ritonavir) are predicted to increase the concentration of voxilaprevir. [Severe] Theoretical
- Mitotane is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Study
- Modafinil is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Nevirapine is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Proton pump inhibitors are predicted to decrease the exposure to voxilaprevir. Adjust dose, see sofosbuvir with velpatasvir and voxilaprevir p. 630. [Moderate] Study
- Rifabutin is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Rifampicin is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Study
- St John’s Wort is predicted to decrease the concentration of voxilaprevir. Avoid. [Severe] Theoretical
- Voxilaprevir is predicted to increase the exposure to statins (atorvastatin). Avoid. [Moderate] Theoretical
- Voxilaprevir (with sofosbuvir and velpatasvir) is predicted to increase the exposure to statins (fluvasatin, simvasatin). Avoid. [Moderate] Theoretical
- Voxilaprevir (with sofosbuvir and velpatasvir) is predicted to increase the exposure to statins (pravastatin). Monitor and adjust pravastatin dose. [Moderate] Study
- Voxilaprevir (with sofosbuvir and velpatasvir) markedly increases the exposure to statins (rosuvastatin). Avoid. [Severe] Study
- Voxilaprevir is predicted to increase the concentration of sulfasalazine. Avoid. [Severe] Theoretical
- Voxilaprevir (with sofosbuvir and velpatasvir) potentially increases the concentration of tenofovir disoproxil. [Severe] Study
- Voxilaprevir is predicted to increase the concentration of topotecan. Avoid. [Severe] Theoretical
- Warfarin → see coumarins

Additional information

General information

- Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline might be ineffective in case of a hypersensitivity reaction) or ACE inhibitors (risk of severe anaphylactoid reactions).
- Xipamide → see thiazide diuretics
- Xylometazoline → see sympathomimetics, vasoconstrictor

Yellow fever vaccine, live → see live vaccines

Zidovudine → see TABLE 15 p. 1378 (myelosuppression), TABLE 2 p. 1375 (nephrotoxicity)
- Antiepileptics (valproate) slightly increase the exposure to zidovudine. [Moderate] Study
- Antifungals, azoles (fluconazole) slightly increase the exposure to zidovudine. [Moderate] Study
- Antimalarials (pyrimethamine) are predicted to increase the risk of side-effects when given with zidovudine. [Severe] Theoretical → Also see TABLE 15 p. 1378
- Zidovudine increases the risk of haematological toxicity when given with aspirin (high-dose). [Severe] Study
- Zidovudine increases the risk of toxicity when given with lamivudine. [Severe] Aneocdal
- Leflunomide is predicted to increase the exposure to zidovudine. [Moderate] Theoretical → Also see TABLE 15 p. 1378
- Macrolides (clarithromycin) decrease the absorption of zidovudine. Separate administration by at least 2 hours. [Moderate] Study
- Nevirapine is predicted to decrease the concentration of zidovudine. Refer to specialist literature. [Severe] Theoretical
- Zidovudine increases the risk of haematological toxicity when given with NS-5AIs. [Severe] Study → Also see TABLE 2 p. 1375
- Ribavirin increases the risk of anaemia and/or leucopenia when given with zidovudine. Avoid. [Severe] Study
- Zidovudine is predicted to decrease the efficacy of stavudine. Avoid. [Severe] Theoretical
- Teriflunomide is predicted to increase the exposure to zidovudine. [Moderate] Theoretical

Zinc

ROUTE-SPECIFIC INFORMATION

- Interactions do not generally apply to topical use unless specified.

- Oral zinc decreases the absorption of oral bisphosphonates (alendronic acid). Zinc should be taken at least 30 minutes before alendronic acid. [Moderate] Study
- Oral zinc is predicted to decrease the absorption of oral bisphosphonates (ibandronic acid). Avoid zinc for at least 6 hours before or 1 hour after ibandronic acid. [Moderate] Theoretical
- Oral zinc decreases the absorption of oral bisphosphonates (risendronate). Separate administration by at least 2 hours. [Moderate] Study
- Oral zinc decreases the absorption of oral bisphosphonates (sodium clodronate). Avoid zinc for 2 hours before or 1 hour after sodium clodronate. [Moderate] Study
- Oral calcium salts decrease the absorption of zinc. [Moderate] Study
- Oral zinc is predicted to decrease the absorption of etorofibram. Etorofibram should be taken 2 hours before or 4 hours after zinc. [Severe] Theoretical
- Zinc is predicted to decrease the efficacy of iron (oral) and iron (oral) is predicted to decrease the efficacy of zinc. [Moderate] Study
- Zinc is predicted to decrease the absorption of penicillin. [Mild] Theoretical
- Zinc is predicted to decrease the exposure to quinolones. Separate administration by 2 hours. [Moderate] Study
- Oral zinc is predicted to decrease the absorption of tetracyclines. Separate administration by 2 to 3 hours. [Moderate] Theoretical
- Trientine potentially decreases the absorption of zinc. [Moderate] Theoretical
- Zoledronic acid → see bisphosphonates

Zolmitriptan → see TABLE 13 p. 1378 (serotonin syndrome)
- Combined hormonal contraceptives are predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Moderate] Study
- H2 receptor antagonists (cimetidine) slightly increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Mild] Study

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Zolmitriptan (continued)

- **Mexiteline** is predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Moderate] Theoretical
- **Moclubemide** slightly increases the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Moderate] Study → Also see TABLE 13 p. 1378
- **Monoamine-oxidase A and B inhibitors, irreversible** are predicted to increase the exposure to zolmitriptan. [Severe] Theoretical → Also see TABLE 13 p. 1378
- **Quinolones** (ciprofloxacin) are predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Moderate] Theoretical
- **SSRI (fluvoxamine)** are predicted to increase the exposure to zolmitriptan. Adjust zolmitriptan dose, p. 482. [Severe] Theoretical → Also see TABLE 13 p. 1378
- **Zopiclone** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Zolpidem** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Calcium channel blockers (diltiazem, verapamil)** are predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Cobicistat** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Theoretical
- **Crizotinib** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Enzalutamide** is predicted to decrease the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **HIV-protease inhibitors** are predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Theoretical
- **Idelalisib** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Theoretical
- **Imatinib** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Macrolides (clarithromycin)** are predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Theoretical
- **Macrolides (erythromycin)** are predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Mitotane** is predicted to decrease the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Netupitant** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Nilotinib** is predicted to increase the exposure to zolmitriptan. Adjust dose. [Moderate] Study
- **Rifampicin** is predicted to decrease the exposure to zolmitriptan. Adjust dose. [Moderate] Study

Zuclopenthixol

- **Zuclopenthixol** is predicted to decrease the effects of dopamine receptor agonists. Avoid. [Moderate] Theoretical → Also see TABLE 8 p. 1376 → Also see TABLE 9 p. 1377
- **Zuclopenthixol** is predicted to decrease the effects of levodopa. Avoid or monitor worsening parkinsonian symptoms. [Severe] Theoretical → Also see TABLE 8 p. 1376
- **Zuclopenthixol** potentially increases the risk of neurotoxicity when given with lithium. [Severe] Anecdotal → Also see TABLE 9 p. 1377
Appendix 2
Borderline substances

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In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances (ACBS) advises as to the circumstances in which such substances may be regarded as drugs. Prescriptions issued in accordance with the Committee's advice and endorsed ‘ACBS’ will normally not be investigated.

Information
General Practitioners are reminded that the ACBS recommends products on the basis that they may be regarded as drugs for the management of specified conditions. Doctors should satisfy themselves that the products can safely be prescribed, that patients are adequately monitored and that, where necessary, expert hospital supervision is available.

Foods which may be prescribed on FP10, GP10 (Scotland), or WP10 (Wales)
All the food products listed in this appendix have ACBS approval. The clinical condition for which the product has been approved is included with each entry.

Note Foods included in this appendix may contain cariogenic sugars and patients should be advised to take appropriate oral hygiene measures.

Enteral feeds and supplements
For most enteral feeds and nutritional supplements, the main source of carbohydrate is either maltodextrin or glucose syrup; other carbohydrate sources are listed in the relevant table, below. Feeds containing residual lactose (less than 1 g lactose/100 mL formula) are described as ‘clinically lactose-free’ or ‘lactose-free’ by some manufacturers. The presence of lactose (including residual lactose) in feeds is indicated in the relevant table, below. The primary sources of protein or amino acids are included with each product entry. The fat or oil content is derived from a variety of sources such as vegetables, soya bean, corn, palm nuts, and seeds; where the fat content is derived from animal or fish sources, this information is included in the relevant table, below. The presence of medium chain triglycerides (MCT) is also noted where the quantity exceeds 30% of the fat content.

Enteral feeds and nutritional supplements can contain varying amounts of vitamins, minerals, and trace elements—the manufacturer’s product literature should be consulted for more detailed information. Feeds containing vitamin K may affect the INR in patients receiving warfarin. The suitability of food products for patients requiring a vegan, kosher, halal, or other compliant diet should be confirmed with individual manufacturers.

Note Feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be avoided in children unless recommended by an appropriate specialist or dietician.

Nutritional values
Nutritional values of products vary with flavour and pack size—consult product literature.

Other conditions for which ACBS products can be prescribed
This is a list of clinical conditions for which the ACBS has approved toilet preparations.

Dermatitis, Eczema and Pruritus
Aveeno® Cream; Aveeno® Lotion; E45® Emollient Bath Oil; E45® Emollient Wash Cream

Disfiguring skin lesions (birthmarks, mutilating lesions, scars, vitiligo)
Covermark® classic foundation and finishing powder; Dermacolor® Camouflage cream and fixing powder; Keromask® finishing powder and masking cream; Veil® Cover cream and Finishing Powder. (Cleansing Creams, Cleansing Milks, and Cleansing Lotions are excluded).

Disinfectants (antiseptics)
May be prescribed on an FP10 only when ordered in such quantities and with such directions as are appropriate for the treatment of patients, but not if ordered for general hygienic purposes.

Dried mouth (xerostomia)
For patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome.

AS Saliva Orthana®, Biotène Oralbalance®, Glandosane®, Saliveze®
Photodermatoses (skin protection in)

*LA Roche-Posay Anthelios*® XL SPF 50+ cream; *Sunsense® Ultra* (Ego) SPF 50+; *Uvistat® Lipscreen* SPF 50, *Uvistat® Suncream* SPF 30 and 50

**Standard ACBS indications:** Disease-related malnutrition, intractable malabsorption, pre-operative preparation of malnourished patients, dysphagia, proven inflammatory bowel disease, following total gastrectomy, short-bowel syndrome, bowel fistula

Prices quoted in Appendix 2 are basic NHS net prices; for further information see Prices in BNF.
### Table 1 Enteral feeds (non-disease specific)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1500 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13 g (sugars 0.9 g)</td>
<td>3.4 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years</td>
<td>Fresubin 1500 Complete liquid: 1.5 litre = £14.58</td>
</tr>
<tr>
<td>Fresubin® Original (Fresenius Kabi Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13.8 g (sugars 3.5 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin Feed in flexible pack contains fish oil and fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin Original drink: blackcurrant, nut, peach, chocolate, vanilla 200 ml = £2.36; Fresubin Original tube feed liquid: 500 ml = £4.57; 1000 ml = £9.07; 1500 ml = £13.60</td>
</tr>
<tr>
<td>Fresubin® Original Fibre (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g cows’ milk soya</td>
<td>13 g (sugars 0.9 g)</td>
<td>3.4 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years</td>
<td>Fresubin Original Fibre liquid: 500 ml = £5.18; 1000 ml = £10.34</td>
</tr>
<tr>
<td>Jevity® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>449 kJ (107 kcal)</td>
<td>4 g caseinates</td>
<td>14.1 g (sugars 0.47 g)</td>
<td>3.47 g</td>
<td>1.76 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula. Not suitable for child under 2 years</td>
<td>Jevity liquid: 500 ml = £5.83; 1000 ml = £10.99; 1500 ml = £16.45</td>
</tr>
<tr>
<td>Nutrison® (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Nutrison liquid: 500 ml = £5.39; 1000 ml = £9.47; 1500 ml = £14.20</td>
</tr>
<tr>
<td>Nutrison® Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula</td>
<td>Nutrison Multi Fibre liquid: 500 ml = £5.83; 500 ml = £5.47; 1000 ml = £10.97; 1500 ml = £16.43</td>
</tr>
<tr>
<td>Osmolite® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>424 kJ (100 kcal)</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 0.63 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Osmolite liquid: 500 ml = £5.40; 1000 ml = £9.48; 1500 ml = £14.22</td>
</tr>
</tbody>
</table>
### SOYA PROTEIN FORMULA

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® Soya Fibre (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.8 g soya protein</td>
<td>13.3 g (sugars 4.1 g)</td>
<td>3.6 g</td>
<td>2 g</td>
<td>Gluten-free Lactose-free Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1557; also cows' milk protein intolerance, lactose intolerance</td>
<td>Fresubin Soya Fibre liquid: 500 ml = £5.35</td>
</tr>
<tr>
<td>Nutrison® Soya (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Borderline substances standard ACBS indications p. 1557; also cows' milk protein and lactose intolerance</td>
<td>Nutrison Soya liquid: 500 ml = £5.82; 1000 ml = £11.66</td>
</tr>
<tr>
<td>Nutrison® Soya Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 0.7 g)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula; also cows' milk protein and lactose intolerance</td>
<td>Nutrison Soya Multi Fibre liquid: 1.5 litre = £19.39</td>
</tr>
</tbody>
</table>

### PEPTIDE-BASED FORMULA

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison Peptisorb® (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>425 kJ (100 kcal)</td>
<td>4 g whey protein hydrolysate</td>
<td>17.6 g (sugars 1.7 g)</td>
<td>1.7 g (MCT 47 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Nutrison Peptisorb liquid: 500 ml = £7.72; 500 ml = £8.49; 1000 ml = £15.30</td>
</tr>
<tr>
<td>Peptamen® (Nestle Health Science)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4 g whey peptides</td>
<td>12.7 g (sugars 0.48 g)</td>
<td>3.7 g (MCT 70 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Peptamen liquid: vanilla 800 ml = £13.04; unflavoured 500 ml = £7.33; 1000 ml = £13.76</td>
</tr>
<tr>
<td>Survivem® OPD (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>4.5 g whey protein hydrolysate</td>
<td>14.3 g (sugars 1.1 g)</td>
<td>2.8 g (MCT 51 %)</td>
<td>0.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Borderline substances standard ACBS indications p. 1557; also growth failure</td>
<td>Survivem OPD: liquid 500 ml = £7.64; 800 ml = £13.56; 1000 ml = £15.28; HN liquid 500 ml = £7.36</td>
</tr>
</tbody>
</table>

### Enteral feeds: Less than 1 kcal/mL and less than 5 g protein/100 mL

**AMINO ACID FORMULA (ESSENTIAL AND NON-ESSENTIAL AMINO ACIDS)**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
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<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental 028® Extra (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>360 kJ (86 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11 g (sugars 4.7 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra liquid: summer fruits, orange &amp; pineapple, grapefruit 250 ml = £3.99</td>
</tr>
<tr>
<td></td>
<td>Standard dilution (20 %) of powder (sip or tube feed) per 100 mL</td>
<td>374 kJ (89 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11.8 g (sugars 1.8 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra powder: plain, banana, orange 100 gram = £7.75</td>
</tr>
</tbody>
</table>

Powder provides protein equivalent 12.5 g, carbohydrate 59 g, fat 17.45 g, energy 1871 kJ (443 kcal)/100 g. To flavour unflavoured products, see Modjul® Flavour System p. 1576.
**Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL**

**Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
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<th>Energy</th>
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<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fresubin® 2250 Complete</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows' milk</td>
<td>18.8 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin 2250 Complete liquid: 1.5 litre = £16.28</td>
</tr>
<tr>
<td><strong>Fresubin® Energy</strong></td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows' milk</td>
<td>18.8 g (sugars)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin Energy liquid: unflavoured 200 ml = £1.40; blackcurrant, tropical fruits, strawberry, chocolate, lemon, vanilla, cappuccino, banana 200 ml = £1.10</td>
</tr>
<tr>
<td><strong>Fresubin® Energy Fibre</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows' milk</td>
<td>18.8 g (sugars 1.4 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin Energy Fibre liquid: banana, caramel, cherry, chocolate, strawberry 200 ml = £2.20</td>
</tr>
<tr>
<td><strong>Fresubin® HP Energy</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>7.5 g cows' milk</td>
<td>17 g (sugars 1.7 g)</td>
<td>5.8 g (MCT 57 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD and haemodialysis</td>
<td>Fresubin HP Energy liquid: 500 ml = £7.51; 1000 ml = £11.42</td>
</tr>
<tr>
<td><strong>Jevity® 1.5 kcal</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>573 kJ (142 kcal)</td>
<td>4.8 g cows' milk</td>
<td>12.5 g (sugars 1.5 g)</td>
<td>4.9 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Jevity 1.5kcal liquid: 500 ml = £6.98; 1000 ml = £13.15; 1500 ml = £20.29</td>
</tr>
<tr>
<td><strong>Nutrison® Energy</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows' milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Nutrison Energy liquid: 500 ml = £5.87; 500 ml = £6.28; 1000 ml = £11.82; 1500 ml = £17.68</td>
</tr>
<tr>
<td><strong>Nutrison® Multi Fibre</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows' milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Nutrison Energy Multi Fibre liquid: 500 ml = £6.57; 500 ml = £6.97; 1000 ml = £13.12; 1500 ml = £20.25</td>
</tr>
<tr>
<td><strong>Osmolite® 1.5 kcal</strong></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows' milk</td>
<td>20 g (sugars 4.9 g)</td>
<td>5 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Osmolite 1.5kcal tube feed liquid: 500 ml = £6.28; 1000 ml = £11.84; 1500 ml = £17.71</td>
</tr>
<tr>
<td><strong>Resource® Energy</strong></td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows' milk</td>
<td>21 g (sugars 5.2 g)</td>
<td>5 g</td>
<td>less than 0.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Resource Energy liquid: apricot, banana, chocolate, coffee, strawberry &amp; raspberry, vanilla 800 ml = £8.24</td>
</tr>
</tbody>
</table>

**Borderline substances standard**

**ACBS indications p.**

<table>
<thead>
<tr>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 litre = £16.28</td>
</tr>
<tr>
<td>unflavoured 200 ml = £1.40; blackcurrant, tropical fruits, strawberry, chocolate, lemon, vanilla, cappuccino, banana 200 ml = £1.10</td>
</tr>
<tr>
<td>banana, caramel, cherry, chocolate, strawberry 200 ml = £2.20</td>
</tr>
<tr>
<td>1.5 litre = £16.28</td>
</tr>
<tr>
<td>1.5kcal liquid: 500 ml = £6.98; 1000 ml = £13.15; 1500 ml = £20.29</td>
</tr>
<tr>
<td>500 ml = £5.87; 500 ml = £6.28; 1000 ml = £11.82; 1500 ml = £17.68</td>
</tr>
<tr>
<td>500 ml = £6.57; 500 ml = £6.97; 1000 ml = £13.12; 1500 ml = £20.25</td>
</tr>
<tr>
<td>Resource Energy liquid: apricot, banana, chocolate, coffee, strawberry &amp; raspberry, vanilla 800 ml = £8.24</td>
</tr>
</tbody>
</table>
### Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1-6 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
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<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1000 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>12.5 g (sugars 1.1 g)</td>
<td>3.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin 1000 Complete liquid: 1 litre = £11.73</td>
</tr>
<tr>
<td>Fresubin® 1200 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin 1200 Complete liquid: 1 litre = £14.93</td>
</tr>
<tr>
<td>Fresubin® 1800 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fresubin 1800 Complete liquid: 1.5 litre = £14.93</td>
</tr>
<tr>
<td>Jevity® Plus (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>514 kJ (122 kcal)</td>
<td>5.5 g caseinates soy isolates</td>
<td>15.1 g (sugars 0.89 g)</td>
<td>3.93 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Jevity Plus liquid: 500 ml = £6.99; 1000 ml = £12.73; 1500 ml = £19.03</td>
</tr>
<tr>
<td>Jevity® Plus HP (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>551 kJ (131 kcal)</td>
<td>8.13 g cows’ milk soy isolates</td>
<td>14.2 g (sugars 0.95 g)</td>
<td>4.33 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>Jevity Plus HP gluten free liquid: 500 ml = £6.85</td>
</tr>
<tr>
<td>Jevity® Promote (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>434 kJ (103 kcal)</td>
<td>5.55 g caseinates soy isolates</td>
<td>12 g (sugars 0.67 g)</td>
<td>3.32 g</td>
<td>1.7 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td>Jevity Promote liquid: 1 litre = £12.18</td>
</tr>
<tr>
<td>Nutrison® 800 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>345 kJ (83 kcal)</td>
<td>5.5 g cows’ milk pea protein soy protein</td>
<td>8.8 g (sugars 0.60 g)</td>
<td>2.5 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula Not suitable for child under 6 years; not recommended for child 6-12 years</td>
<td>Nutrison 800 Complete Multi Fibre liquid: 1 litre = £11.47</td>
</tr>
<tr>
<td>Nutrison® 1000 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>11.3 g (sugars 0.70 g)</td>
<td>3.7 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease related malnutrition in patients with low energy and/or low fluid requirements</td>
<td>Nutrison 1000 Complete Multi Fibre liquid: 1 litre = £12.17</td>
</tr>
<tr>
<td>Nutrison® 1200 Complete Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>505 kJ (120 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>15 g (sugars 1.2 g)</td>
<td>4.3 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula</td>
<td>Nutrison 1200 Complete Multi Fibre liquid: 1500 ml = £19.33; 1000 ml = £12.87</td>
</tr>
</tbody>
</table>
### Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1-6 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison® MCT (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5 g cows’ milk</td>
<td>12.6 g (sugars 1 g)</td>
<td>3.3 g (MCT 61%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Nutrison MCT liquid: 1000 mL = £10.96</td>
</tr>
<tr>
<td>Nutrison® Protein Plus (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>525 kJ (125 kcal)</td>
<td>6.3 g cows’ milk</td>
<td>14.2 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Nutrison Protein Plus liquid: 1 litre = £11.25</td>
</tr>
<tr>
<td>Nutrison® Protein Plus Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>535 kJ (128 kcal)</td>
<td>6.3 g cows’ milk</td>
<td>14.1 g (sugars 1.0 g)</td>
<td>4.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>For use as dietary management of disease related malnutrition.</td>
<td>Nutrison Protein Plus Multifibre liquid: 1 litre = £12.54</td>
</tr>
<tr>
<td>Osmolite® Plus (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>508 kJ (121 kcal)</td>
<td>5.55 g caseinates</td>
<td>15.8 g (sugars 0.73 g)</td>
<td>3.93 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Not suitable for child under 10 years</td>
</tr>
<tr>
<td>Peptamen® HN (Nestle Health Science)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>556 kJ (133 kcal)</td>
<td>6.6 g whey protein hydrolysates</td>
<td>15.6 g (sugars 1.4 g)</td>
<td>4.9 g (MCT 70%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Hydrolysed with pork trypsin</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 3 years</td>
<td>Peptamen HN liquid: 500 mL = £7.89</td>
</tr>
<tr>
<td>Perative® (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>552 kJ (131 kcal)</td>
<td>6.7 g caseinate whey protein hydrolysates</td>
<td>17.7 g (sugars 0.66 g)</td>
<td>3.7 g (MCT 42%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Not suitable for child under 5 years</td>
</tr>
</tbody>
</table>

### Enteral feeds: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Twocal (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>836 kJ (200 kcal)</td>
<td>8.4 g cows’ milk</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also haemodialysis and CAPD</td>
<td>Ensure TwoCal liquid: banana, neutral, strawberry, vanilla 200 mL = £2.22</td>
</tr>
<tr>
<td>TwoCal® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>837 kJ (200 kcal)</td>
<td>8.4 g cows’ milk caseinates</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Adults with or at risk of disease-related malnutrition, catabolic or fluid-restricted patients, and other patients requiring a 2 kcal/mL feed</td>
<td>TwoCal liquid: 1 litre = £17.20; 200 mL = £3.19</td>
</tr>
</tbody>
</table>

### Table 2 Nutritional supplements (non-disease specific)

Nutritional supplements: less than 5 g protein/100 mL

Nutritional supplements: 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; use with caution in child 1-5 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>423 kJ (100 kcal)</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 3.93 g)</td>
<td>3.36 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Ensure liquid: chocolate, coffee, vanilla 250 mL = £2.39</td>
</tr>
</tbody>
</table>
### Nutritional supplements: More than 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in children under 1 year unless otherwise stated; use with caution in children 1-5 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Juice (Abbott Laboratories Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>638 kJ (150 kcal)</td>
<td>4.8 g whey protein isolate</td>
<td>32.7 g (sugars 9.4 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Ensure Plus Juice liquid: assorted 880 ml = no price available; apple, fruit punch, lemon &amp; lime, orange, peach, strawberry 220 ml = £1.37</td>
</tr>
<tr>
<td>Fortijuce® (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>640 kJ (150 kcal)</td>
<td>4.0 g cows' milk</td>
<td>33.5 g (sugars 13.1 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Fortijuce Starter Pack liquid: 800 ml = £8.08; Fortijuce liquid: ‘assorted 800 ml = no price available; apple, blackcurrant, forest fruits, lemon, orange, strawberry, tropical 200 ml = £2.02</td>
</tr>
<tr>
<td>Fresubin® Jucy Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>4 g whey protein</td>
<td>33.5 g (sugars 8 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis</td>
<td>Fresubin Jucy drink: apple, blackcurrant, cherry, orange, pineapple 800 ml = £8.04</td>
</tr>
</tbody>
</table>

### Nutritional supplements: 5 g (or more) protein/100 mL

Not suitable for children under 1 year; use with caution in children under 6 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altraplen Protein® (Nualtra Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>10 g cows' milk soya protein</td>
<td>15 g (sugars 4.6 g)</td>
<td>5.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Altraplen Protein Starter Pack liquid: 400 ml = £3.18; Altraplen Protein liquid: strawberry, vanilla 800 ml = £6.59</td>
</tr>
<tr>
<td>Ensure® Plus Advance (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>631 kJ (150 kcal)</td>
<td>9.1 g cows' milk soya protein isolate whey protein concentrate</td>
<td>16.8 g (sugars 6.8 g)</td>
<td>4.8 g</td>
<td>0.75 g</td>
<td>Gluten-free Residual lactose</td>
<td>Frail elderly people (this is defined as older than 65 years with BMI less than or equal to 23 kg/m² where clinical assessment and nutritional screening show the individual to be at risk of undernutrition). Not suitable as the sole source of nutrition.</td>
<td>Ensure Plus Advance liquid: banana, chocolate, coffee, strawberry, vanilla 200 ml = £2.08</td>
</tr>
<tr>
<td>Ensure® Plus Commence (Abbott Laboratories Ltd)</td>
<td>Starter pack (5-10 day's supply), contains Ensure® Plus Commence (various flavours), 1 pack (10 × 200ml) = £11.10</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ensure® Plus Fibre (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>652 kJ (155 kcal)</td>
<td>6.25 g cows' milk soya protein isolate</td>
<td>20.2 g (sugars 5.5 g)</td>
<td>4.92 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis.</td>
<td>Ensure Plus Fibre liquid: banana, chocolate, raspberry, strawberry, vanilla 200 ml = £2.14</td>
</tr>
<tr>
<td>Ensure® Plus Milkshake style (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows' milk soya protein isolate</td>
<td>20.2 g (sugars 6.89 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis</td>
<td>Ensure Plus milkshake style liquid: banana, chocolate, coffee, fruits of the forest, neutral, peach, raspberry, strawberry, vanilla, 200 ml = £1.11</td>
</tr>
</tbody>
</table>
### Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ensure® Plus Savoury</strong> (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed per 100 mL)</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk soy protein isolate</td>
<td>20.2 g (sugars 1.13 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis.</td>
<td>Ensure Plus savoury liquid: 200 ml = £1.11</td>
</tr>
<tr>
<td><strong>Ensure® Plus Yoghurt style</strong> (Abbott Laboratories Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk</td>
<td>20.2 g (sugars 11.7 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis</td>
<td>Ensure Plus yoghurt style liquid: orchard peach, strawberry swirl 200 ml = £1.11</td>
</tr>
<tr>
<td><strong>Fortisip® Bottle</strong> (Nutricia Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.4 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Fortisip Bottle: banana, caramel, chocolate, neutral, orange, strawberry, tropical fruit, vanilla 200 ml = £1.12</td>
</tr>
<tr>
<td><strong>Fortisip® Range</strong> (Nutricia Ltd)</td>
<td>Starter pack contains 4 x Fortisip® Bottle, 4 x Fortijuice®, 2 x Fortisip® Yoghurt Style, 1 pack (10 x 200ml) = £20.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fortisip® Yoghurt Style</strong> (Nutricia Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.7 g (sugars 10.6 g)</td>
<td>5.8 g</td>
<td>0.2 g</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 3 years</td>
<td>Fortisip Yoghurt Style liquid: raspberry, vanilla &amp; lemon 200 ml = £2.22</td>
</tr>
<tr>
<td><strong>Fresubin® Protein Energy Drink</strong> (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows’ milk</td>
<td>12.4 g (sugars 6.4 g)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis.</td>
<td>Fresubin Protein Energy drink: cappuccino, chocolate, tropical fruits, vanilla, wild strawberry 200 ml = £2.15</td>
</tr>
<tr>
<td><strong>Fresubin® Thickened</strong> (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed per 100 mL)</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows’ milk</td>
<td>12 g (sugars 7.3 g)</td>
<td>6.7 g</td>
<td>0.83 g</td>
<td>Gluten-free Residual lactose</td>
<td>Dysphagia or disease-related malnutrition.</td>
<td>Fresubin Thickened Stage 1 syrup: vanilla, wild strawberry 800 ml = £9.40; Fresubin Thickened Stage 2 custard: vanilla, wild strawberry 800 ml = £9.40</td>
</tr>
<tr>
<td><strong>Fresubin® YouCrème</strong> (Fresenius Kabi Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>630 kJ (150 kcal)</td>
<td>7.5 g whey protein</td>
<td>19.5 g (sugars 16.8 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Dysphagia, or presence or risk of malnutrition Not suitable for child under 3 years</td>
<td>Fresubin YouCrème dessert: apricot-peach, biscuit, lemon, raspberry, wild strawberry 500 gram = £8.44</td>
</tr>
</tbody>
</table>

### Nutritional supplements: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
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<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ensure® Plus Crème</strong> (Abbott Laboratories Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>574 kJ (137 kcal)</td>
<td>5.68 g cow’s milk soy protein isolates</td>
<td>18.4 g (sugars 12.4 g)</td>
<td>4.47 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains soya</td>
<td>Borderline substances standard ACBS indications p. 1557; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Ensure Plus Crème: banana, chocolate, neutral, vanilla 500 gram = £8.00</td>
</tr>
<tr>
<td><strong>Nutilis® Fruit Dessert Level 4</strong> (Nutricia Ltd)</td>
<td>Semi-Solid per 100 g</td>
<td>560 kJ (133 kcal)</td>
<td>7 g whey isolate</td>
<td>16.7 g (sugars 11.3 g)</td>
<td>4 g</td>
<td>2.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 except bowel fistula; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Nutilis Fruit Dessert Level 4: strawberry, apple 450 gram = £7.35</td>
</tr>
</tbody>
</table>
### Oral Impact®

**Nestle Health Science**

<table>
<thead>
<tr>
<th>Standard dilution of powder (74 g in 250 mL water) (sip feed) per 100 mL</th>
<th>425 kJ (101 kcal)</th>
<th>5.6 g cows’ milk</th>
<th>13.4 g (sugars 7.4 g)</th>
<th>2.8 g</th>
<th>1 g</th>
<th>Residual lactose Contains fish oil</th>
</tr>
</thead>
</table>

**Powder provides:** protein 16.8 g, carbohydrate 40.2 g, fat 8.3 g, fibre 3 g, energy 1276 kJ (303 kcal)/74 g.

**Pre-operative nutritional supplement for malnourished patients or patients at risk of malnourishment**

**Not suitable for children under 3 years; use with caution in children 3-5 years.**

**Oral Impact oral powder sachets:** citrus, tropical 5 sachet = £18.20

### Renapro Shot®

**Stanningley Pharma Ltd**

<table>
<thead>
<tr>
<th>Standard dilution of powder (Nestle Health Science)</th>
<th>583 kJ (137 kcal)</th>
<th>33 g</th>
<th>2.0 g (fructose 2.0 g)</th>
<th>0.1 g</th>
<th>Nil</th>
<th>Gluten-free</th>
</tr>
</thead>
</table>

**Powder provides:** protein 25.5 g, carbohydrate 3.3 g, fat 2.1 g, fibre 0.2 g, energy 1065 kJ (250 kcal) 250 mL whole milk.

**For the dietary management of dialysis patients with biochemically proven hypoproteinaemia on the recommendation of a specialist dietician.**

**Renapro Shot oral powder saline 60 ml bottles:** 30 bottle = £76.80

### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

**Not suitable for use in children under 3 years unless otherwise stated; use with caution in children 3-6 years.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altraplen® Compact (Nualtra Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1008 kJ (240 kcal)</td>
<td>9.6 g cows’ milk soya protein</td>
<td>28.8 g (sugars 11.3 g)</td>
<td>9.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Altraplen Compact Starter Pack liquid: 500 mL = £5.80; Altraplen Compact liquid: banana, hazel chocolate, strawberry, vanilla 500 mL = £5.32</td>
</tr>
<tr>
<td>Complan® Shake (Nutricia Ltd)</td>
<td>Powder per 57 g</td>
<td>1065.9 kJ (253.7 kcal)</td>
<td>8.8 g cows’ milk</td>
<td>35.6 g (sugars 18.8 g)</td>
<td>8.4 g</td>
<td>Trace</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Complan Shake Starter Pack sachets: 5 sachet = £4.39; Complan Shake oral powder 57 g sachets: banana, chocolate, milk, strawberry, vanilla 4 sachet = £2.80</td>
</tr>
<tr>
<td>Ensure® Compact (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>1008 kJ (240 kcal)</td>
<td>10.2 g cows’ milk</td>
<td>28.8 g (sugars 6.2 g)</td>
<td>9.35 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>As a sole source of nutrition or as a nutritional supplement for the dietary management of patients with, or at risk of developing, disease-related malnutrition.</td>
<td>Ensure Compact liquid: banana, cafe latte, strawberry, vanilla 500 mL = £5.32</td>
</tr>
<tr>
<td>Ensure® Shake (Abbott Laboratories Ltd)</td>
<td>Powder per 100 g</td>
<td>1852 kJ (443 kcal)</td>
<td>17.8 g cows’ milk whey protein concentrate</td>
<td>59 g (sugars 33.7 g)</td>
<td>15.1 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557</td>
<td>Ensure Shake oral powder 57 g sachets: banana, chocolate, strawberry, vanilla 7 sachet = £4.20</td>
</tr>
<tr>
<td>Foodlink® Complete (Nualtra Ltd)</td>
<td>Powder per 100 g</td>
<td>1869 kJ (444 kcal)</td>
<td>21 g cows’ milk soya protein</td>
<td>56 g (sugars 43 g)</td>
<td>15 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free Contains soya</td>
<td>Borderline substances standard ACBS indications p. 1557 Not to be prescribed for any child under one year; use with caution for young children up to five years of age.</td>
<td>Foodlink Complete powder: banana, chocolate, natural, strawberry, vanilla 1596 gram = £15.40</td>
</tr>
</tbody>
</table>

Recommended serving = the contents of a 57-g sachet in 200 mL full cream milk provides: protein 19 g, carbohydrate 41 g, fat 16 g, energy 161 kJ (383 kcal).
### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foodlink® Complete with Fibre (Nualtra Ltd)</td>
<td>Powder per 100 g</td>
<td>1779 kJ (423 kcal)</td>
<td>19 g cows' milk, soya protein</td>
<td>52 g (sugars 40 g)</td>
<td>14 g</td>
<td>7.2 g</td>
<td>Contains lactose</td>
<td>Gluten-free</td>
<td>Borderline substances standard ACBS indications p. 1557; Not to be prescribed for any child under one year; use with caution for young children up to five years of age.</td>
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<td></td>
<td>Foodlink Complete powder with fibre 63 g sachets: banana, chocolate, natural, strawberry, vanilla 7 sachet = £4.97; Foodlink Complete powder with fibre Starter Pack: 5 sachet = £3.55</td>
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<tr>
<td></td>
<td>Semi-solid per 100 g</td>
<td>675 kJ (160 kcal)</td>
<td>9.5 g cows' milk</td>
<td>29.7 g (sugars 15 g)</td>
<td>9.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Residual lactose</td>
<td>Forticreme Complete dessert: banana, chocolate, forest fruits, vanilla 500 gram = £7.84</td>
</tr>
<tr>
<td>Forticreme® Complete (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>9.4 g cows' milk</td>
<td>25.2 g (sugars 13.9 g)</td>
<td>10.4 g</td>
<td>3.6 g</td>
<td>Residual lactose</td>
<td>Residual lactose</td>
<td>Fortisip Compact liquid: apricot, banana, chocolate, forest fruits, mocha, strawberry, vanilla 500 ml = £5.32</td>
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</tr>
<tr>
<td>Fortisip® Compact Fibre (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>14.4 g cows' milk</td>
<td>24.4 g (sugars 13.3 g)</td>
<td>9.4 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Residual lactose</td>
<td>Fortisip Compact Protein Starter Pack liquid: 750 ml = £12.00; Fortisip Compact Protein liquid: banana, berries, ginger, hot tropical mango, mocha, neutral, peach &amp; strawberry, vanilla 500 ml = £8.00</td>
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<tr>
<td>Fortisip® Extra (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>675 kJ (160 kcal)</td>
<td>10 g cows' milk</td>
<td>18.1 g (sugars 9 g)</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Gluten-free</td>
<td>Fortisip Extra liquid: strawberry, vanilla 200 ml = £2.30</td>
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<tr>
<td>Fresubin® 2 kcal Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>10 g cows' milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Residual lactose</td>
<td>Fresubin 2kcal drink: apricot-peach, cappuccino, fruits of the forest, neutral, toffee 200 ml = £2.17</td>
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</tr>
<tr>
<td>Fresubin® 2 kcal Fibre Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>10 g cows' milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>1.6 g</td>
<td>Residual lactose</td>
<td>Residual lactose</td>
<td>Fresubin 2kcal Fibre drink: apricot-peach, cappuccino, chocolate, lemon, neutral 200 ml = £2.17</td>
</tr>
</tbody>
</table>

Recommended serving - the contents of a 63 g sachet in 200 mL full cream milk provides: protein 19 g, carbohydrate 42 g, fat 16 g, fibre 4.5 g, energy 1667 kJ (397 kcal).
### Table 3 Specialised formulas

**Specialised formulas: Infant and child see BNF for children**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alicalm®</strong></td>
<td>Liquid (sip feed)</td>
<td>836 kJ</td>
<td>9 g cows' milk</td>
<td>21.4 g</td>
<td>8.7 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 6 years; use with caution in child 6-10 years.</td>
<td>Resource Fibre 2.0 liquid: apricot, coffee, neutral, strawberry, summer fruit, vanilla 200 ml = £2.02</td>
</tr>
<tr>
<td><strong>Forticare®</strong></td>
<td>Liquid (sip feed)</td>
<td>675 kJ</td>
<td>9 g cows' milk</td>
<td>19.1 g</td>
<td>5.3 g</td>
<td>2.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement in patients with lung cancer undergoing chemotherapy, or with pancreatic cancer Not suitable in child under 3 years</td>
<td>Forticare liquid: cappuccino, orange &amp; lemon, peach &amp; ginger 500 ml = £9.75</td>
</tr>
<tr>
<td><strong>Renilon® 7.5</strong></td>
<td>Liquid (sip feed)</td>
<td>840 kJ</td>
<td>7.5 g cows' milk</td>
<td>20 g</td>
<td>10 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 6 years; use with caution in child 6-10 years.</td>
<td>Renilon 7.5 liquid: apricot, caramel 500 ml = £9.47</td>
</tr>
<tr>
<td><strong>Nutilis® Complete Drink Level 3</strong></td>
<td>Liquid (pre-thickened)</td>
<td>1010 kJ</td>
<td>9.6 g cows' milk</td>
<td>29.1 g</td>
<td>9.3 g</td>
<td>3.2 g</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Nutilis Complete Drink Level 3 liquid: chocolate, lemon tea, mango &amp; passionfruit, strawberry, vanilla 500 ml = £8.84</td>
</tr>
<tr>
<td><strong>Nutilis® Complete Crème Level 3</strong></td>
<td>Semi-solid</td>
<td>1030 kJ</td>
<td>10 g cows' milk, soya protein</td>
<td>18.8 g</td>
<td>7.2 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Nutilis Complete Creme Level 3 custard: chocolate, strawberry, vanilla 500 gram = £8.69</td>
</tr>
<tr>
<td><strong>Fresubin® Powder Extra</strong></td>
<td>Powder per 100 g</td>
<td>1764 kJ</td>
<td>17.5 g cows' milk, whey protein</td>
<td>63 g</td>
<td>10.9 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Borderline substances standard ACBS indications p. 1557 Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
<td>Fresubin Powder Extra oral powder 62g sachets: chocolate, neutral, strawberry, vanilla 7 sachet = £4.90</td>
</tr>
</tbody>
</table>

**Specialised formulas for specific clinical conditions**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alicalm®</strong></td>
<td>Standard dilution</td>
<td>567 kJ</td>
<td>4.5 g caseinate whey</td>
<td>17.4 g</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Crohn's disease Not suitable for child under 1 year; use as nutritional supplement only in children 1-6 years.</td>
<td>Alicalm oral powder: 400 gram = £23.29</td>
</tr>
</tbody>
</table>

**Powder 62 g reconstituted with 200 ml whole milk provides:** protein 17.7 g, carbohydrate 48.5 g, fat 14.8 g, energy 1658 kJ (397 kcal).
### Specialised formulas for specific clinical conditions (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparon® Junior</td>
<td>Standard dilution</td>
<td>363 kJ</td>
<td>2 g</td>
<td>11.6 g</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Contains lactose; Electrolytes/100 mL: Na+ 0.56 mmol K+ 1.9 mmol Ca2+ 2.3 mmol P+ 1.6 mmol</td>
<td>Enteral feed or nutritional supplement for children</td>
<td>Heparon Junior powder: 400 gram = £23.47</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>(18%) of powder per 100 mL</td>
<td>(86 kcal)</td>
<td>cows’ milk</td>
<td>(sugars 2.9 g)</td>
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<tr>
<td>Powder provides: protein 11.1 g, carbohydrate 64.2 g, fat 19.9 g, energy 2016 kJ (480 kcal)/100 g.</td>
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<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>KetoCal® (Nutricia Ltd)</td>
<td>Standard dilution</td>
<td>602 kJ</td>
<td>3.1 g</td>
<td>0.6 g</td>
<td>14.6 g</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na+ 4.3 mmol K+ 4.1 mmol Ca2+ 2.15 mmol P+ 2.77 mmol</td>
<td>Enteral feed or nutritional supplement as part of keto</td>
<td>KetoCal 4:1 powder: vanilla, unflavoured 300 gram = £33.04</td>
</tr>
<tr>
<td></td>
<td>(20%) of powder per 100 mL</td>
<td>(146 kcal)</td>
<td>cows’ milk with additional amino acids</td>
<td>(sugars 0.12 g)</td>
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<tr>
<td>Powder provides: protein 15.25 g, carbohydrate 3 g, fat 73 g, energy 3011 kJ (730 kcal)/100 g.</td>
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<tr>
<th>Product</th>
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<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>KetoCal® 3:1</td>
<td>Standard dilution</td>
<td>276 kJ</td>
<td>1.5 g</td>
<td>0.68 g</td>
<td>6.4 g</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na+ 1.3 mmol K+ 2.4 mmol Ca2+ 2 mmol P+ 1.7 mmol</td>
<td>Enteral feed or nutritional supplement as part of keto</td>
<td>KetoCal 3:1 powder: 300 gram = £31.98</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>(9.5%) of powder per 100 mL</td>
<td>(66 kcal)</td>
<td></td>
<td>(sugars 0.57 g)</td>
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<tr>
<td>Powder provides: protein 15.3 g, carbohydrate 7.2 g, fat 67.7 g, energy 2927 kJ (699 kcal)/100 g.</td>
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<tr>
<th>Product</th>
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<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>KetoCal® 4:1 LQ</td>
<td>Liquid (sip or tube feed)</td>
<td>620 kJ</td>
<td>3.09 g</td>
<td>0.61 g</td>
<td>14.8 g</td>
<td>1.12 g</td>
<td>Residual lactose; Electrolytes/100 mL: Na+ 4.5 mmol K+ 4.7 mmol Ca2+ 2.4 mmol P+ 3.1 mmol</td>
<td>Enteral feed or nutritional supplement as part of keto</td>
<td>KetoCal 4:1 LQ liquid: unflavoured 200 ml = £4.71; vanilla 200 ml = £4.71</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>per 100 mL</td>
<td>(150 kcal)</td>
<td>casein and whey with additional amino acids</td>
<td>(sugars 0.23 g)</td>
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</tr>
<tr>
<td>Powder provides: protein 15.3 g, carbohydrate 7.2 g, fat 67.7 g, energy 2927 kJ (699 kcal)/100 g.</td>
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<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindergen®</td>
<td>Standard dilution</td>
<td>421 kJ</td>
<td>1.5 g</td>
<td>11.8 g</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na+ 2 mmol K+ 0.6 mmol Ca2+ 2.8 mmol P+ 3 mmol Low Vitamin A</td>
<td>Enteral feed or nutritional supplement for children</td>
<td>Kindergen powder: 400 gram = £31.50</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>(20%) of powder per 100 mL</td>
<td>(101 kcal)</td>
<td>whey protein</td>
<td>(sugars 1.2 g)</td>
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<tr>
<td>Powder provides: protein 7.5 g, carbohydrate 59 g, fat 26.3 g, energy 2104 kJ (504 kcal)/100 g.</td>
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<tr>
<td>Product</td>
<td>Manufacturer</td>
<td>Standard dilution (20%) of powder</td>
<td>Calorie content</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Protein</td>
<td>Electrolytes</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
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<tr>
<td>Modulen IBD®&lt;sup&gt;®&lt;/sup&gt; (Nestle Health Science)</td>
<td></td>
<td>420 kJ (100 kcal)</td>
<td>3.6 g casen</td>
<td>11 g (sugars 3.98 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Gluten-free Residual lactose</td>
<td>Crohn's disease active phase, and in remission if malnourished</td>
</tr>
<tr>
<td>ProSure®&lt;sup&gt;®&lt;/sup&gt; (Abbott Laboratories Ltd)</td>
<td></td>
<td>536 kJ (127 kcal)</td>
<td>6.65 g cows' milk</td>
<td>18.3 g (sugars 2.95 g)</td>
<td>2.56 g</td>
<td>2.07 g</td>
<td>Gluten-free</td>
<td>Residual lactose Contains fish oil</td>
<td>Nutritional supplement for patients with pancreatic cancer. Not suitable for child under 1 year; use with caution in child 1-4 years.</td>
</tr>
<tr>
<td>Renamil®&lt;sup&gt;®&lt;/sup&gt; (Stanningley Pharma)</td>
<td></td>
<td>2003 kJ (477 kcal)</td>
<td>4.6 g cows' milk</td>
<td>70.8 g</td>
<td>19.3 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free Electrolytes/100 g: Na&lt;sup&gt;+&lt;/sup&gt; 1.04 mmol K&lt;sup&gt;+&lt;/sup&gt; 0.13 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 10.22 mmol P&lt;sup&gt;-&lt;/sup&gt; 1.06 mmol Contains no vitamin A or vitamin D</td>
<td>Enteral feed or nutritional supplement for adults and children over 1 year with chronic renal failure.</td>
<td>Renamil powder: 1000 gram = £25.40</td>
</tr>
<tr>
<td>Renadren®&lt;sup&gt;®&lt;/sup&gt; (Stanningley Pharma Ltd)</td>
<td>Powder per 100 g</td>
<td>1558 kJ (372 kcal)</td>
<td>90 g whey protein</td>
<td>3.4 g</td>
<td>1 g</td>
<td>Nil</td>
<td>Gluten-free Do not use in cow’s milk allergy, or where absorption and digestive problems are present Electrolytes/100 g: Na&lt;sup&gt;+&lt;/sup&gt; 15.65 mmol K&lt;sup&gt;+&lt;/sup&gt; 4.60 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 4.74 mmol Mg 0.82 mmol P&lt;sup&gt;-&lt;/sup&gt; 3.55 mmol</td>
<td>Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis. Not suitable for child under 1 year.</td>
<td>Renadren powder 20 g sachets: 30 sachet = £69.60</td>
</tr>
<tr>
<td>Renastart®&lt;sup&gt;®&lt;/sup&gt; (Vitalfo International Ltd)</td>
<td>Powder per 100 g</td>
<td>414 kJ (99 kcal)</td>
<td>1.5 g cows' milk soya</td>
<td>12.5 g (sugars 1.3 g)</td>
<td>4.8 g</td>
<td>Nil</td>
<td>Contains lactose Electrolytes/100 mL: Na&lt;sup&gt;+&lt;/sup&gt; 2.1 mmol K&lt;sup&gt;+&lt;/sup&gt; 0.6 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 0.6 mmol P&lt;sup&gt;-&lt;/sup&gt; 0.6 mmol</td>
<td>Dietary management of renal failure in child from birth to 10 years.</td>
<td>Renastart powder: 400 gram = £28.96</td>
</tr>
<tr>
<td>Respifor®&lt;sup&gt;®&lt;/sup&gt; (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>633 kJ (150 kcal)</td>
<td>7.5 g cows' milk</td>
<td>22.5 g (sugars 6.4 g)</td>
<td>3.3 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Nutritional supplement for dietary management of disease-related malnutrition in patients with chronic obstructive pulmonary disease and body-mass index less than 20.</td>
<td>Respifor milkshake style liquid: chocolate, strawberry, vanilla 500 ml = £9.30</td>
</tr>
<tr>
<td>Supportan®&lt;sup&gt;®&lt;/sup&gt; (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows' milk</td>
<td>12.4 g (sugars 7.5 g)</td>
<td>6.7 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement in patients with pancreatic cancer or with lung cancer undergoing chemotherapy Not suitable for child under 1 year; use with caution in child 1-4 years</td>
<td>Supportan drink: cappuccino 800 ml = £11.12; tropical fruits 200 ml = £2.82; 800 ml = £11.28</td>
</tr>
</tbody>
</table>
### Table 4 Feed supplements

#### High-energy supplements: carbohydrate

Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxijul Sup® Soluble (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1615 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g Glucose polymer (sugars 8.6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Maxijul Sup Soluble: powder 132g sachets 4 sachet = £7.03; powder 200 gram = £2.82; 25000 gram = £168.65</td>
</tr>
<tr>
<td>Polycal® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1630 kJ (384 kcal)</td>
<td>Nil</td>
<td>96 g Maltodextrin (sugars 6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Polycal powder: 400 gram = £4.70</td>
</tr>
<tr>
<td></td>
<td>Liquid per 100 mL</td>
<td>1050 kJ (247 kcal)</td>
<td>Nil</td>
<td>61.9 g Maltodextrin (sugars 12.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement. Liquid not suitable for child under 3 years.</td>
<td>Polycal liquid: neutral, orange, 200 ml = £1.87</td>
</tr>
<tr>
<td>S.O.S.® (Vitalfo International Ltd)</td>
<td>Powder per 100 g</td>
<td>1590 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g (sugars 9 g)</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>S.O.S. products are age-range specific-consult product literature.</td>
<td>S.O.S.: 20 oral powder 42g sachets 30 sachet = £16.06; 10 oral powder 21g sachets 30 sachet = £8.03; 15 oral powder 31g sachets 30 sachet = £11.85; 25 oral powder 52g sachets 30 sachet = £19.86</td>
</tr>
<tr>
<td></td>
<td>Powder per 100 g</td>
<td>1590 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g Dried glucose syrup (sugars 9 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement. Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.</td>
<td>Vitajoule powder: 500 gram = £4.80</td>
</tr>
</tbody>
</table>

Contents of each sachet should be reconstituted with water to a total volume of 200 mL.
<table>
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<tr>
<th>Product</th>
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<th>ACBS Indications</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Calogen® (Nutricia Ltd)</td>
<td>Liquid (emulsion)</td>
<td>1850 kJ</td>
<td>Nil</td>
<td>0.1 g</td>
<td>50 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Calogen emulsion: neutral 200 ml = £4.78; 500 ml = £11.76; strawberry 200 ml = £4.78; 500 ml = £11.76</td>
<td>Calogen emulsion: neutral 200 ml = £4.78; 500 ml = £11.76</td>
</tr>
<tr>
<td>Fresubin® 5 kcal Shot (Fresenius Kabi Ltd)</td>
<td>Liquid (emulsion) per 100 mL</td>
<td>2100 kJ</td>
<td>Nil</td>
<td>4.0 g (sucrose)</td>
<td>53.8 g</td>
<td>0.4 g</td>
<td>Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement. Not suitable for child under 3 years.</td>
<td>Fresubin 5kcal shot drink: lemon, neutral 480 ml = £11.96</td>
<td>Fresubin 5kcal shot drink: lemon, neutral 480 ml = £11.96</td>
</tr>
<tr>
<td>Liquigen® (Nutricia Ltd)</td>
<td>Liquid (emulsion) per 100 mL</td>
<td>1850 kJ</td>
<td>Nil</td>
<td>Nil</td>
<td>50 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease, liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in epilepsy, and in type 1 lipoproteinemia Not suitable for child under 1 year</td>
<td>Liquigen emulsion: 250 ml = £10.04</td>
<td>Liquigen emulsion: 250 ml = £10.04</td>
</tr>
<tr>
<td>Medium-chain Triglyceride (MCT) Oil (Nutricia Ltd)</td>
<td>Liquid per 100 mL</td>
<td>3515 kJ</td>
<td>Nil</td>
<td>Nil</td>
<td>MCT</td>
<td>Nil</td>
<td>MCT 100%</td>
<td>Nutritional supplement for steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease and liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in management of epilepsy, type 1 hyperlipoproteinemia</td>
<td>MCT oil: 500 ml = £15.92</td>
<td>Medium-chain Triglyceride (MCT) Oil per 100 mL</td>
</tr>
</tbody>
</table>

**FAT AND CARBOHYDRATE**

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<thead>
<tr>
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<th>Energy</th>
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<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duocal® Super Soluble (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2061 kJ</td>
<td>Nil</td>
<td>72.7 g (sugars 6.5 g)</td>
<td>22.3 g (MCT 35 %)</td>
<td>Nil</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Duocal Super Soluble powder: 400 gram = £19.60</td>
</tr>
<tr>
<td>Energivit® (Nutricia Ltd)</td>
<td>Standard dilution (15%) of powder per 100 mL</td>
<td>309 kJ</td>
<td>Nil</td>
<td>10 g (sugars 0.99 g)</td>
<td>3.75 g</td>
<td>Nil</td>
<td>Lactose-free</td>
<td>For children requiring additional energy, vitamins, minerals, and trace elements following a protein-restricted diet</td>
<td>Energivit powder: 400 gram = £23.84</td>
</tr>
</tbody>
</table>

Powder provides: carbohydrate 66.7 g, fat 25 g, energy 2059 kJ (492 kcal)/100 g.
### High-energy supplements: protein

<table>
<thead>
<tr>
<th>Product</th>
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<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSource® Jelly</td>
<td>Semi-solid per 100 mL</td>
<td>315 kJ (75 kcal)</td>
<td>16.9 g collagen protein hydrolysate whey protein isolate</td>
<td>Less than 1 g</td>
<td>Nil</td>
<td>Less than 1 g</td>
<td>Gluten-free Lactose-free Contains porcine derivatives</td>
<td>Hypoproteinaemia Not recommended for child under 3 years</td>
<td>ProSource jelly: fruit punch, orange 118 ml = £1.94</td>
</tr>
<tr>
<td>Protifar®</td>
<td>Powder per 100 g</td>
<td>1580 kJ (373 kcal)</td>
<td>88.5 g cows' milk</td>
<td>less than 1.5 g</td>
<td>1.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Electrolytes/100 mL: Na⁺ 1.3 mmol K⁺ 1.28 mmol Ca²⁺ 33.75 mmol P⁺ 22.58 mmol</td>
<td>Nutritional supplement for use in biochemically proven hypoproteinaemia.</td>
<td>Protifar powder: 225 gram = £9.55</td>
</tr>
</tbody>
</table>

### PROTEIN AND CARBOHYDRATE

Not recommended for child under 3 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
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<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
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<th>Special Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dialamine®</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>264 kJ (62 kcal)</td>
<td>4.3 g protein equivalent (essential and non-essential amino acids)</td>
<td>11.2 g (sugars 10.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Contains vitamin C</td>
<td>Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis. Not suitable for child under 6 months.</td>
<td>Dialamine powder: 400 gram = £79.64</td>
</tr>
</tbody>
</table>

Powder provides: protein equivalent 25 g, carbohydrate 65 g, vitamin C 125 mg, energy 1530 kJ (360 kcal)/100 g.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
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<th>Protein</th>
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<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSource® Liquid</td>
<td>Liquid per 30 mL</td>
<td>420 kJ (100 kcal)</td>
<td>10 g collagen protein whey protein isolate</td>
<td>15 g (sugars 8 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free May contain porcine derivatives</td>
<td>Biochemically proven hypoproteinaemia Not recommended for child under 3 years.</td>
<td>ProSource liquid 30ml sachets: citrus berry, lemon, neutral, orange creme 100 sachet = £104.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
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<th>Protein</th>
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<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSource® Plus</td>
<td>Liquid per 30 mL</td>
<td>420 kJ (100 kcal)</td>
<td>15 g collagen protein whey protein isolate</td>
<td>11 g (sugars 10 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains porcine derivatives</td>
<td>Hypoproteinaemia</td>
<td>ProSource Plus liquid 30ml sachets: citrus berry, neutral, orange creme 100 sachet = £149.08</td>
</tr>
</tbody>
</table>
## PROTEIN, FAT, AND CARBOHYDRATE

Not suitable for child under 3 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
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<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calogen Extra</td>
<td>Liquid per 100 mL</td>
<td>1650 kJ (400 kcal)</td>
<td>5 g cows' milk</td>
<td>4.5 g (sugars 3.5 g)</td>
<td>40.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years.</td>
<td>Calogen Extra emulsion: neutral, strawberry 200 ml = €4.98</td>
</tr>
<tr>
<td>Calogen Extra Shots</td>
<td>Liquid per 100 mL</td>
<td>1650 kJ (400 kcal)</td>
<td>5 g cows' milk</td>
<td>4.5 g (sugars 3.5 g)</td>
<td>40.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose With vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years.</td>
<td>Calogen Extra Shots emulsion: neutral, strawberry 240 ml = €5.75</td>
</tr>
<tr>
<td>Calshake</td>
<td>Powder per 87 g</td>
<td>2504 kJ (598.5 kcal)</td>
<td>12 g cows' milk</td>
<td>70.2 g (sugars 22.4 g)</td>
<td>29.9 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement.</td>
<td>Calshake powder 87g sachets: banana, neutral, strawberry, vanilla 7 sachet = €18.41; Calshake powder 90g sachets chocolate: 7 sachet = €18.41</td>
</tr>
<tr>
<td>Enshake</td>
<td>Powder per 100 g</td>
<td>1893 kJ (450 kcal)</td>
<td>8.4 g cows' milk, soy protein isolate</td>
<td>69 g (sugars 14.5 g)</td>
<td>15.6 g</td>
<td>Nil</td>
<td>Residual lactose Contains vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-6 years.</td>
<td>Enshake oral powder 96.5g sachets: banana, chocolate, strawberry, vanilla 6 sachet = €15.22</td>
</tr>
<tr>
<td>MCT Procal</td>
<td>Powder per 100 g</td>
<td>2742 kJ (657 kcal)</td>
<td>12.5 g cows' milk</td>
<td>20.6 g (sugars 3.1 g)</td>
<td>63.1 g (MCT 99%)</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Dietary management of disorders of long-chain fatty acid oxidation, fat malabsorption, and other disorders requiring a low LCT, high MCT supplement. Not suitable for child under 1 year.</td>
<td>MCT Procal oral powder 16g sachets: 30 sachet = €26.09</td>
</tr>
</tbody>
</table>

Powder 16g provides: protein 2g, carbohydrate 3.3g, fat 10.1g, energy 439 kJ (105 kcal).
### PROTEIN, FAT, AND CARBOHYDRATE (product list continued)

Not suitable for child under 3 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
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<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-Cal® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2787 kJ</td>
<td>13.6 g</td>
<td>28.2 g</td>
<td>55.5 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
<td>Pro-Cal powder: 510 gram = £16.11; 1500 gram = £32.82; 12500 gram = £233.28</td>
</tr>
<tr>
<td>Pro-Cal® Shot (Vitaflo International Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1385 kJ</td>
<td>6.7 g</td>
<td>13.4 g</td>
<td>28.2 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Pro-Cal: shot starter pack 360 ml = £7.64; shot banana, neutral, strawberry 720 ml = £15.26</td>
</tr>
<tr>
<td>Scandishake Mix® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2099 kJ</td>
<td>4.7 g</td>
<td>65 g</td>
<td>24.7 g</td>
<td>Nil</td>
<td>Gluten-free Contains soya</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Scandishake Mix oral powder 85g sachets: banana, caramel, chocolate, strawberry, unflavoured, vanilla 6 sachet = £15.54</td>
</tr>
<tr>
<td>Vitasavoury® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2562 kJ</td>
<td>12 g</td>
<td>22.5 g</td>
<td>52 g</td>
<td>6.4 g</td>
<td>Contains soya (chicken flavour) Contains gluten (wheat) Contains celery (golden vegetable flavour)</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Vitasavoury powder 50g sachets: chicken, golden vegetable 10 sachet = £20.83</td>
</tr>
</tbody>
</table>

### Vitamin and Mineral supplements

Flavour not suitable for child under 6 months; To flavour unflavoured products, see Modju® Flavour System p. 1576.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FruitVits® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>133 kJ</td>
<td>Nil</td>
<td>8.3 g</td>
<td>0.1 g</td>
<td>3.3 g</td>
<td></td>
<td>Vitamin, mineral, and trace element supplement in children 3-10 years with restrictive therapeutic diets</td>
<td>FruitVits oral powder 6g sachets: 30 sachet = £70.55</td>
</tr>
<tr>
<td>Paediatric Seravit® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1275 kJ</td>
<td>Nil</td>
<td>75 g</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Vitamin, mineral, and trace element supplement in infants and children with restrictive therapeutic diets.</td>
<td>Seravit Paediatric powder: pineapple 200 gram = £20.69; unflavoured 200 gram = £19.41</td>
</tr>
<tr>
<td>Renavit® (Stanningley Pharma Ltd)</td>
<td>Tablet per 450 mg</td>
<td>3.15 kJ</td>
<td>Nil</td>
<td>0.17 g</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Dietary management of water-soluble vitamin deficiency in adults with renal failure on dialysis</td>
<td>Renavit tablets: 100 tablet = £12.50</td>
</tr>
</tbody>
</table>

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Feed supplements

PROTEIN, FAT, AND CARBOHYDRATE (product list continued)

Not suitable for child under 3 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-Cal® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2787 kJ</td>
<td>13.6 g</td>
<td>28.2 g</td>
<td>55.5 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
<td>Pro-Cal powder: 510 gram = £16.11; 1500 gram = £32.82; 12500 gram = £233.28</td>
</tr>
<tr>
<td>Pro-Cal® Shot (Vitaflo International Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1385 kJ</td>
<td>6.7 g</td>
<td>13.4 g</td>
<td>28.2 g</td>
<td>Nil</td>
<td>Contains lactose Gluten-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Pro-Cal: shot starter pack 360 ml = £7.64; shot banana, neutral, strawberry 720 ml = £15.26</td>
</tr>
<tr>
<td>Scandishake Mix® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2099 kJ</td>
<td>4.7 g</td>
<td>65 g</td>
<td>24.7 g</td>
<td>Nil</td>
<td>Gluten-free Contains soya</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Scandishake Mix oral powder 85g sachets: banana, caramel, chocolate, strawberry, unflavoured, vanilla 6 sachet = £15.54</td>
</tr>
<tr>
<td>Vitasavoury® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2562 kJ</td>
<td>12 g</td>
<td>22.5 g</td>
<td>52 g</td>
<td>6.4 g</td>
<td>Contains soya (chicken flavour) Contains gluten (wheat) Contains celery (golden vegetable flavour)</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Vitasavoury powder 50g sachets: chicken, golden vegetable 10 sachet = £20.83</td>
</tr>
</tbody>
</table>

### Vitamin and Mineral supplements

Flavour not suitable for child under 6 months; To flavour unflavoured products, see Modju® Flavour System p. 1576.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>FruitVits® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>133 kJ</td>
<td>Nil</td>
<td>8.3 g</td>
<td>0.1 g</td>
<td>3.3 g</td>
<td></td>
<td>Vitamin, mineral, and trace element supplement in children 3-10 years with restrictive therapeutic diets</td>
<td>FruitVits oral powder 6g sachets: 30 sachet = £70.55</td>
</tr>
<tr>
<td>Paediatric Seravit® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1275 kJ</td>
<td>Nil</td>
<td>75 g</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Vitamin, mineral, and trace element supplement in infants and children with restrictive therapeutic diets.</td>
<td>Seravit Paediatric powder: pineapple 200 gram = £20.69; unflavoured 200 gram = £19.41</td>
</tr>
<tr>
<td>Renavit® (Stanningley Pharma Ltd)</td>
<td>Tablet per 450 mg</td>
<td>3.15 kJ</td>
<td>Nil</td>
<td>0.17 g</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td>Dietary management of water-soluble vitamin deficiency in adults with renal failure on dialysis</td>
<td>Renavit tablets: 100 tablet = £12.50</td>
</tr>
</tbody>
</table>
Feed additives
Special additives for conditions of intolerance

Colief ®
- Transient Lactase Deficiency. For dosage and administration details, consult product literature.
- Lactase 50,000 units/g

Colief 50,000 units/g infant drops (Forum Health Products Ltd)
- 7 ml (ACBS) - NHS indicative price = £8.40

Fructose
- (Laevulose) For proven glucose/galactose intolerance

Dietade dietary foods fruit sugar (Margetts)
- 250 gram - No NHS indicative price available

Glucose
- (Dextrose monohydrate) For use as an energy supplement in sucrose-isomaltase deficiency
- (Laevulose) For proven glucose/galactose intolerance

Feed thickeners and pre-thickened drinks

Carobel, Instant ®
- For thickening feeds in the treatment of vomiting.
- POWDER, carob seed flour.

Instant Carobel powder (Cow & Gate Ltd)
- 135 gram (ACBS) - NHS indicative price = £2.91

Multi-thick ®
- For thickening of liquids and foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

Multi-thick powder (Abbott Laboratories Ltd)
- 250 gram (ACBS) - NHS indicative price = £4.83

Nutilis ® Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years.
- POWDER, dried glucose syrup, xanthan gum, guar gum, gluten- and lactose-free.

Nutilis Clear powder (Nutricia Ltd)
- 175 gram (ACBS) - NHS indicative price = £8.46

Nutilis ® Powder
- For thickening of food and fluid in dysphagia. Not suitable for child under 5 years.
- POWDER, carbohydrate 87.5 g, energy 1545 kJ (363 kcal)/100 g, contains modified starch. Gluten-free and lactose-free.

Nutilis powder (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £5.50

Resource ® Thickened Drink
- For dysphagia. Not suitable for children under 3 years.
- POWDER, carbohydrate content varies with flavour and chosen consistency (3 consistencies available), see product literature.

Resource Thickened Drink custard apple (Nestle Health Science)
- 114 ml (ACBS) - NHS indicative price = £0.78

Resource Thickened Drink custard orange (Nestle Health Science)
- 114 ml (ACBS) - NHS indicative price = £0.78

Resource Thickened Drink syrup apple (Nestle Health Science)
- 114 ml (ACBS) - NHS indicative price = £0.78

Resource Thickened Drink syrup orange (Nestle Health Science)
- 114 ml (ACBS) - NHS indicative price = £0.78

Resource ® ThickenUp Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 5 years.
- POWDER, maltodextrin, xanthum gum, gluten- and lactose-free.

Resource ThickenUp Clear powder (Nestle Health Science)
- 28.8 gram (ACBS) - NHS indicative price = £5.28 | 127 gram (ACBS) - NHS indicative price = £8.46

Resource ® ThickenUp
- For thickening of foods in dysphagia. Suitable for children above 3 years of age.
- POWDER, modified maize starch. Gluten-free.

Resource ThickenUp powder (Nestle Health Science)
- 227 gram (ACBS) - NHS indicative price = £4.66

SLO Drinks ®
- Nutritional supplement for patient hydration in the dietary management of dysphagia. Not suitable for children under 3 years.
- POWDER, carbohydrate content varies with flavour and chosen consistency (3 consistencies available), see product literature.

SLO Drink Stage 1: IDDSI 2 Mildly Thick oral powder blackcurrant (SLO Drinks Ltd)
- 25 cup (ACBS) - NHS indicative price = £7.50

SLO Drink Stage 1: IDDSI 2 Mildly Thick oral powder orange (SLO Drinks Ltd)
- 25 cup (ACBS) - NHS indicative price = £7.50

SLO Drink Stage 2: IDDSI 3 Moderately Thick oral powder blackcurrant (SLO Drinks Ltd)
- 25 cup (ACBS) - NHS indicative price = £7.50

SLO Drink Stage 2: IDDSI 3 Moderately Thick oral powder orange (SLO Drinks Ltd)
- 25 cup (ACBS) - NHS indicative price = £7.50

SLO Milkshakes ®
- Nutritional supplement in the dietary management of dysphagia. Not suitable for children under 3 years.
- POWDER, carbohydrate content varies with flavour and chosen consistency (2 consistencies available), see product literature.

SLO Milkshake+ Stage 1 oral powder chocolate (SLO Drinks Ltd)
- 7 x 50 gram (ACBS) - NHS indicative price = £5.88

SLO Milkshake+ Stage 1 oral powder strawberry (SLO Drinks Ltd)
- 7 x 50 gram (ACBS) - NHS indicative price = £5.88

SLO Milkshake+ Stage 2 oral powder chocolate (SLO Drinks Ltd)
- 7 x 50 gram (ACBS) - NHS indicative price = £5.88

SLO Milkshake+ Stage 2 oral powder strawberry (SLO Drinks Ltd)
- 7 x 50 gram (ACBS) - NHS indicative price = £5.88

Thick and Easy ®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

Thick and Easy powder (Fresenius Kabi Ltd)
- 225 gram (ACBS) - NHS indicative price = £5.41 | 4540 gram (ACBS) - NHS indicative price = £94.02

Thick & Easy powder 9g sachets (Fresenius Kabi Ltd)
- 100 sachet (ACBS) - NHS indicative price = £34.25

Thicken Aid ®
- For thickening of foods in dysphagia. Not suitable for children under 1 year.
- POWDER, modified maize starch, maltodextrin, gluten- and lactose-free.

Thicken Aid powder (M & A Pharmachem Ltd)
- 225 gram (ACBS) - NHS indicative price = £3.71

Thicken Aid powder 9g sachets (M & A Pharmachem Ltd)
- 100 sachet (ACBS) - NHS indicative price = £22.40

Thixo-D ®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

Thixo-D powder (Sutherland Health Ltd)
- 375 gram (ACBS) - NHS indicative price = £8.10

Thixo-D Cal-Free powder (Sutherland Health Ltd)
- 50 gram - NHS indicative price = £3.00

Flavouring preparations

FlavourPac ®
- For use with Vitaflor’s range of unflavoured protein substitutes for metabolic diseases; not suitable for child under 3 years.

FlavourPac oral powder 4g sachets blackcurrant (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £15.14

FlavourPac oral powder 4g sachets lemon (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £15.14
FlavourPac oral powder 4g sachets orange (Vitaflor International Ltd) 50 sachet (ACBS) - NHS indicative price = £15.14
FlavourPac oral powder 4g sachets raspberry (Vitaflor International Ltd) 50 sachet (ACBS) - NHS indicative price = £15.14
FlavourPac oral powder 4g sachets tropical (Vitaflor International Ltd) 50 sachet (ACBS) - NHS indicative price = £15.14
Modjul® Flavour System • For use with unflavoured amino acid and peptide-based Nutricia products used for the dietary management of various conditions including metabolic disorders and gastrointestinal disease.
POWDER
Nutricia Flavour Modjul powder blackcurrant (Nutricia Ltd) 100 gram (ACBS) - NHS indicative price = £13.20
Nutricia Flavour Modjul powder orange (Nutricia Ltd) 100 gram (ACBS) - NHS indicative price = £13.20
Nutricia Flavour Modjul powder pineapple (Nutricia Ltd) 100 gram (ACBS) - NHS indicative price = £13.20

Foods for special diets
Gluten-free foods
ACBS indications: established gluten-sensitive enteropathies including steatorrhoea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis.

Bread

LOAVES
Barkat® Loaf GLUTEN-FREE
Barkat gluten free brown rice bread (Gluten Free Foods Ltd) 500 gram (ACBS) - NHS indicative price = £5.84
Barkat gluten free par baked white bread sliced (Gluten Free Foods Ltd) 300 gram (ACBS) - NHS indicative price = £4.21
Barkat gluten free home fresh country loaf (Gluten Free Foods Ltd) 250 gram - NHS indicative price = £4.43
Barkat gluten free multigrain rice bread (Gluten Free Foods Ltd) 500 gram (ACBS) - NHS indicative price = £5.84
Barkat gluten free wholemeal bread sliced (Gluten Free Foods Ltd) 500 gram (ACBS) - NHS indicative price = £4.05
Barkat gluten free white rice bread (Gluten Free Foods Ltd) 500 gram (ACBS) - NHS indicative price = £5.84

Ener-G® Loaves GLUTEN-FREE
Ener-G gluten free brown rice bread (Gluten Free Foods Ltd) 474 gram (ACBS) - NHS indicative price = £5.47
Ener-G gluten free tapioca bread (Gluten Free Foods Ltd) 480 gram (ACBS) - NHS indicative price = £5.47
Ener-G gluten free rice loaf (Gluten Free Foods Ltd) 612 gram (ACBS) - NHS indicative price = £5.47
Ener-G gluten free Seattle brown loaf (Gluten Free Foods Ltd) 454 gram (ACBS) - NHS indicative price = £6.22
Ener-G gluten free white rice bread (Gluten Free Foods Ltd) 456 gram (ACBS) - NHS indicative price = £5.47

Genius Gluten Free® Loaf GLUTEN-FREE
Genius gluten free brown sandwich bread sliced (Genius Foods Ltd) 535 gram (ACBS) - NHS indicative price = £3.80
Genius gluten free white sandwich bread sliced (Genius Foods Ltd) 535 gram (ACBS) - NHS indicative price = £3.80
Glutafin® Loaves GLUTEN-FREE
Glutafin gluten free fibre loaf sliced (Dr Schar UK Ltd) 300 gram (ACBS) - NHS indicative price = £2.89
Glutafin gluten free white loaf sliced (Dr Schar UK Ltd) 300 gram (ACBS) - NHS indicative price = £2.89
Glutafin® Select Loaves GLUTEN-FREE
Glutafin gluten free Select fibre loaf sliced (Dr Schar UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.43
Glutafin gluten free Select fresh brown loaf sliced (Dr Schar UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.43
Glutafin gluten free Select fresh white loaf sliced (Dr Schar UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.43
Glutafin gluten free Select seeded loaf sliced (Dr Schar UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.72
Glutafin gluten free Select white loaf sliced (Dr Schar UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.43
Juvela® Loaf GLUTEN-FREE
Juvela gluten free fresh fibre loaf sliced (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.39
Juvela gluten free fresh white loaf sliced (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.69
Juvela gluten free fibre loaf sliced (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.54
Juvela gluten free part baked loaf (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.95
Juvela gluten free part baked fibre loaf (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.80
Juvela gluten free loaf unsliced (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.54
Juvela gluten free fibre loaf unsliced (Hero UK Ltd) 400 gram (ACBS) - NHS indicative price = £3.54
Lifestyle® Loaf GLUTEN-FREE
Lifestyle gluten free brown bread sliced (Ultrapharm Ltd) 400 gram (ACBS) - NHS indicative price = £2.82
Lifestyle gluten free high fibre bread sliced (Ultrapharm Ltd) 400 gram - NHS indicative price = £2.82
Lifestyle gluten free white bread sliced (Ultrapharm Ltd) 400 gram - NHS indicative price = £2.82
Warburtons® Loaf GLUTEN-FREE
Warburtons gluten free brown bread sliced (Warburtons Ltd) 400 gram (ACBS) - NHS indicative price = £3.06
Warburtons gluten free white bread sliced (Warburtons Ltd) 400 gram (ACBS) - NHS indicative price = £3.06
Wellfoods® Loaf GLUTEN-FREE
Wellfoods gluten free loaf sliced (Wellfoods Ltd) 600 gram - NHS indicative price = £5.05
Wellfoods gluten free loaf unsliced (Wellfoods Ltd) 600 gram - NHS indicative price = £4.95

BAGUETTES, BUNS AND ROLLS
Barkat® Baguettes and rolls GLUTEN-FREE
Barkat gluten free par baked rolls (Gluten Free Foods Ltd) 200 gram (ACBS) - NHS indicative price = £4.05
Barkat gluten free par baked baguettes (Gluten Free Foods Ltd) 200 gram (ACBS) - NHS indicative price = £4.05

Ener-G® Rolls GLUTEN-FREE
Ener-G gluten free dinner rolls (Gluten Free Foods Ltd) 280 gram (ACBS) - NHS indicative price = £3.71
Ener-G gluten free white round rolls (Gluten Free Foods Ltd) 220 gram - NHS indicative price = £2.98
Ener-G gluten free white long rolls (Gluten Free Foods Ltd) 220 gram - NHS indicative price = £2.98
Glutafin® Baguettes and rolls GLUTEN-FREE

www.getintopharma.com
Glutafin gluten free baguettes (Dr Schar UK Ltd)
350 gram (ACBS) - NHS indicative price = £3.51

Glutafin gluten free 4 white rolls (Dr Schar UK Ltd)
200 gram (ACBS) - NHS indicative price = £3.68

Glutafin gluten free part baked 4 fibre rolls (Dr Schar UK Ltd)
200 gram (ACBS) - NHS indicative price = £3.68

Glutafin gluten free Select Rolls
GLUTEN-FREE

Glutafin gluten free part baked 4 white rolls (Dr Schar UK Ltd)
150 gram (ACBS) - NHS indicative price = £2.81

Juvela gluten free part baked white bread rolls (Hero UK Ltd)
375 gram (ACBS) - NHS indicative price = £4.94

Juvela gluten free fresh fibre rolls (Hero UK Ltd)
425 gram (ACBS) - NHS indicative price = £4.42

Juvela gluten free fresh white rolls (Hero UK Ltd)
425 gram (ACBS) - NHS indicative price = £4.42

Juvela gluten free fibre bread rolls (Hero UK Ltd)
425 gram (ACBS) - NHS indicative price = £4.77

Juvela gluten free bread rolls (Hero UK Ltd)
425 gram (ACBS) - NHS indicative price = £4.77

Juvela gluten free part baked fibre bread rolls (Hero UK Ltd)
375 gram (ACBS) - NHS indicative price = £4.94

Lifestyle gluten free bread rolls (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £5.00

Lifestyle gluten free brown bread rolls (Ultrapharma Ltd)
400 gram (ACBS) - NHS indicative price = £2.82

Lifestyle gluten free high fibre bread rolls (Ultrapharma Ltd)
400 gram (ACBS) - NHS indicative price = £2.82

Glutafin Select flour mixes and xanthan gum

Barkat gluten free flour mix (Gluten Free Foods Ltd)
200 gram (ACBS) - NHS indicative price = £3.59

Glutafin gluten free crackers (Dr Schar UK Ltd)
200 gram - NHS indicative price = £3.46

Glutafin gluten free mini crackers (Dr Schar UK Ltd)
175 gram - NHS indicative price = £2.96

Glutafin gluten free crispbread (Dr Schar UK Ltd)
200 gram - NHS indicative price = £4.64

Glutafin Select flour mix
GLUTEN-FREE

Glutafin gluten free bread mix (Gluten Free Foods Ltd)
500 gram (ACBS) - NHS indicative price = £9.13

Glutafin gluten free all purpose flour mix (Gluten Free Foods Ltd)
500 gram (ACBS) - NHS indicative price = £4.74

Finax gluten free flour mix
GLUTEN-FREE

Finax gluten free coarse flour mix (Drossa Ltd)
900 gram (ACBS) - NHS indicative price = £8.85

Finax gluten free high fibre bread mix (Drossa Ltd)
1000 gram (ACBS) - NHS indicative price = £10.14

Glutafin gluten free Select bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66

Glutafin Select gluten free Select fibre bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66
Glutafin gluten free Select multipurpose fibre mix (Dr Schar UK Ltd) 500 gram (ACBS) - NHS indicative price = £6.66
Glutafin gluten free Select multipurpose white mix (Dr Schar UK Ltd) 500 gram (ACBS) - NHS indicative price = £6.66
Glutafin ® Flour mix GLUTEN-FREE
Glutafin gluten free multipurpose white mix (Dr Schar UK Ltd) 500 gram (ACBS) - NHS indicative price = £6.66
Juvela ® Flour mix GLUTEN-FREE
Juvela gluten free fibre mix (Hero UK Ltd) 500 gram (ACBS) - NHS indicative price = £7.35
Juvela gluten free harvest mix (Hero UK Ltd) 500 gram (ACBS) - NHS indicative price = £7.35
Juvela gluten free mix (Hero UK Ltd) 500 gram (ACBS) - NHS indicative price = £7.35
Mrs Crimble’s ® Flour mixes GLUTEN-FREE
Mrs Crimble’s gluten free bread mix (Stiletto Foods (UK) Ltd) 275 gram - NHS indicative price = £1.09
Mrs Crimble’s gluten free pastry mix (Stiletto Foods (UK) Ltd) 200 gram - NHS indicative price = £1.09
Orgran ® Flour mix GLUTEN-FREE
Orgran gluten free self-raising flour (Naturally Good Food Ltd) 500 gram - NHS indicative price = £3.10
Orgran gluten free all purpose plain flour (Naturally Good Food Ltd) 500 gram - NHS indicative price = £3.10
Proceli ® Flour mix GLUTEN-FREE
Proceli gluten free basic mix (Ambe Ltd) 1000 gram (ACBS) - NHS indicative price = £9.95
Pure ® Flour mix GLUTEN-FREE
Innovative Solutions Pure gluten free blended flour (Innovative Solutions (UK) Ltd) 1000 gram (ACBS) - NHS indicative price = £4.52
Innovative Solutions Pure gluten free brown rice flour (Innovative Solutions (UK) Ltd) 500 gram (ACBS) - NHS indicative price = £1.69
Innovative Solutions Pure gluten free white rice flour (Innovative Solutions (UK) Ltd) 500 gram (ACBS) - NHS indicative price = £1.79
Innovative Solutions Pure gluten free potato flour (Innovative Solutions (UK) Ltd) 500 gram (ACBS) - NHS indicative price = £1.79
Innovative Solutions Pure gluten free tapioca flour (Innovative Solutions (UK) Ltd) 500 gram (ACBS) - NHS indicative price = £2.42
Innovative Solutions Pure gluten free brown teff flour (Innovative Solutions (UK) Ltd) 1000 gram (ACBS) - NHS indicative price = £5.10
Innovative Solutions Pure gluten free white teff flour (Innovative Solutions (UK) Ltd) 1000 gram (ACBS) - NHS indicative price = £5.10
Tobia ® Flour mix GLUTEN-FREE
Tobia Teff gluten free brown bread mix (Tobia Teff UK Ltd) 1000 gram (ACBS) - NHS indicative price = £3.60
Tobia Teff gluten free white bread mix (Tobia Teff UK Ltd) 1000 gram (ACBS) - NHS indicative price = £3.60
Tritamyl ® Flour mix GLUTEN-FREE
Tritamyl gluten free brown bread mix (Gluten Free Foods Ltd) 1000 gram (ACBS) - NHS indicative price = £7.24
Tritamyl gluten free fibre mix (Gluten Free Foods Ltd) 2000 gram (ACBS) - NHS indicative price = £14.54
Tritamyl gluten free white bread mix (Gluten Free Foods Ltd) 2000 gram (ACBS) - NHS indicative price = £14.54
Wellfoods ® Flour mix GLUTEN-FREE
Wellfoods gluten free flour alternative (Wellfoods Ltd) 1000 gram - NHS indicative price = £7.80
XANTHAN GUM
Ener-G ® Xanthan gum GLUTEN-FREE
Ener-G xanthan gum (Gluten Free Foods Ltd) 170 gram (ACBS) - NHS indicative price = £6.63
Pure ® Xanthan gum GLUTEN-FREE
Innovative Solutions Pure xanthan gum (Innovative Solutions (UK) Ltd) 100 gram - NHS indicative price = £7.12
Pasta
Barkat ® Pasta GLUTEN-FREE
Barkat gluten free pasta animal shapes (Gluten Free Foods Ltd) 500 gram - NHS indicative price = £5.99
Barkat gluten free pasta macaroni (Gluten Free Foods Ltd) 500 gram - NHS indicative price = £5.99
Barkat gluten free pasta spaghetti (Gluten Free Foods Ltd) 500 gram - NHS indicative price = £5.99
Barkat gluten free pasta spirals (Gluten Free Foods Ltd) 500 gram - NHS indicative price = £5.99
Barkat gluten free pasta tagliatelle (Gluten Free Foods Ltd) 500 gram - NHS indicative price = £5.99
Barkat gluten free pasta buckwheat penne (Gluten Free Foods Ltd) 250 gram - NHS indicative price = £2.98
Barkat gluten free pasta buckwheat spirals (Gluten Free Foods Ltd) 250 gram - NHS indicative price = £2.98
BiAlimenta ® Pasta GLUTEN-FREE
BiAlimenta gluten free pasta acini di pepe (Drossa Ltd) 500 gram - NHS indicative price = £6.11 | 1000 gram - No NHS indicative price available
BiAlimenta gluten free pasta formati misti (Drossa Ltd) 3000 gram - NHS indicative price = £36.63
BiAlimenta gluten free pasta penne (Drossa Ltd) 500 gram - NHS indicative price = £6.11 | 1000 gram - No NHS indicative price available
BiAlimenta gluten free pasta sagnette (Drossa Ltd) 500 gram - NHS indicative price = £6.11
BiAlimenta gluten free pasta spirali (Drossa Ltd) 500 gram - NHS indicative price = £6.11
BiAlimenta gluten free pasta tubetti (Drossa Ltd) 500 gram - NHS indicative price = £6.03
BiAlimenta gluten free potato pasta gnocchi (Drossa Ltd) 500 gram - NHS indicative price = £5.71
BiAlimenta gluten free potato pasta perle di gnocchi (Drossa Ltd) 500 gram - NHS indicative price = £5.72
Glutafin ® Pasta GLUTEN-FREE
Glutafin gluten free pasta macaroni penne (Dr Schar UK Ltd) 500 gram - NHS indicative price = £6.73
Glutafin gluten free pasta spirals (Dr Schar UK Ltd) 500 gram - NHS indicative price = £6.73
Glutafin gluten free pasta long-cut spaghetti (Dr Schar UK Ltd) 500 gram - NHS indicative price = £6.73
Juvela ® Pasta GLUTEN-FREE
Juvela gluten free fibre penne (Hero UK Ltd) 500 gram - NHS indicative price = £6.61
Juvela gluten free pasta fusilli (Hero UK Ltd) 500 gram - NHS indicative price = £7.21
Juvela gluten free lasagne (Hero UK Ltd)
250 gram - NHS indicative price = £3.68
Juvela gluten free macaroni (Hero UK Ltd)
500 gram - NHS indicative price = £7.21
Juvela gluten free spaghetti (Hero UK Ltd)
500 gram - NHS indicative price = £7.21
Juvela gluten free tagliatelle (Hero UK Ltd)
250 gram - NHS indicative price = £3.47

Orgran ® Pasta
GLUTEN-FREE
Orgran gluten free pasta & corn lasagne (Naturally Good Foods Ltd)
200 gram - NHS indicative price = £3.13
Orgran gluten free pasta rice & corn macaroni (Naturally Good Foods Ltd)
250 gram - NHS indicative price = £2.42
Orgran gluten free pasta buckwheat spirals (Naturally Good Foods Ltd)
250 gram - NHS indicative price = £2.42

Rizopia ® Pasta
GLUTEN-FREE
Rizopia gluten free organic brown rice pasta fusilli (PGR Health Foods Ltd)
500 gram - NHS indicative price = £2.72
Rizopia gluten free organic brown rice pasta lasagne (PGR Health Foods Ltd)
375 gram - NHS indicative price = £2.72
Rizopia gluten free organic brown rice pasta penne (PGR Health Foods Ltd)
500 gram - NHS indicative price = £2.72
Rizopia gluten free organic brown rice pasta spaghetti (PGR Health Foods Ltd)
500 gram - NHS indicative price = £2.72

Pizza bases
Barkat ®, Pizza crust
GLUTEN-FREE
Barkat gluten free brown rice pizza crust (Gluten Free Foods Ltd)
150 gram - NHS indicative price = £5.10
Barkat gluten free white rice pizza crust (Gluten Free Foods Ltd)
150 gram - NHS indicative price = £5.10
Glutafin ® Pizza base
GLUTEN-FREE
Glutafin gluten free pizza base (Dr Schar UK Ltd)
500 gram - NHS indicative price = £6.56
Juvela ® Pizza base
GLUTEN-FREE
Juvela gluten free pizza base (Hero UK Ltd)
360 gram - NHS indicative price = £8.78

Proceli ® Pizza base
GLUTEN-FREE
Procel gluten free pizza base (Ambe Ltd)
250 gram - NHS indicative price = £3.30

Wellfoods ® Pizza base
GLUTEN-FREE
Wellfoods gluten free pizza base (Wellfoods Ltd)
600 gram - NHS indicative price = £9.13

Gluten- and wheat-free foods
ACBS indications: established gluten-sensitive enteropathies with coexisting established wheat sensitivity only.
Ener-G ® bread leaves, rolls and pizza bases
GLUTEN-FREE, WHEAT-FREE
Ener-G gluten free Seattle brown hamburger rolls (Gluten Free Foods Ltd)
320 gram - NHS indicative price = £4.08
Ener-G gluten free Seattle brown hot dog rolls (Gluten Free Foods Ltd)
320 gram - NHS indicative price = £4.08
Glutafin ® Flour mix, fibre and crispbread
GLUTEN-FREE, WHEAT-FREE
Glutafin gluten free crispbread (Dr Schar UK Ltd)
150 gram - NHS indicative price = £3.25
Glutafin gluten free bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66
Glutafin gluten free fibre bread mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66
Glutafin gluten free wheat free fibre mix (Dr Schar UK Ltd)
500 gram (ACBS) - NHS indicative price = £6.66

Low-protein foods
ACBS indications: inherited metabolic disorders, renal or liver failure, requiring a low-protein diet

Bread
Ener-G ® Rice bread
LOW PROTEIN
Ener-G low protein rice bread (Gluten Free Foods Ltd)
600 gram (ACBS) - NHS indicative price = £6.60
Juvela ® Loaf and rolls
LOW PROTEIN
Juvela gluten free loaf sliced (Hero UK Ltd)
400 gram (ACBS) - NHS indicative price = £3.54
Juvela low protein bread rolls (Hero UK Ltd)
330 gram (ACBS) - NHS indicative price = £4.52
Juvela low protein loaf sliced (Hero UK Ltd)
400 gram (ACBS) - NHS indicative price = £3.64
Loprofin ® Bread
LOW PROTEIN
Loprofin low protein part baked bread rolls (Nutricia Ltd)
260 gram (ACBS) - NHS indicative price = £4.48
Loprofin low protein part baked loaf sliced (Nutricia Ltd)
400 gram (ACBS) - NHS indicative price = £4.26

PK Foods ® Loaf
LOW PROTEIN
PK Foods low protein white bread sliced (Gluten Free Foods Ltd)
500 gram - NHS indicative price = £4.84

Cake, biscuits, and snacks
Juvela ® Cookies
LOW-PROTEIN
Juvela low protein cinnamon cookies (Hero UK Ltd)
125 gram (ACBS) - NHS indicative price = £7.62
Juvela low protein chocolate chip cookies (Hero UK Ltd)
110 gram (ACBS) - NHS indicative price = £7.62
Juvela low protein orange cookies (Hero UK Ltd)
125 gram (ACBS) - NHS indicative price = £7.62
Loprofin ® Wafers
LOW-PROTEIN
Loprofin low protein crackers (Nutricia Ltd)
150 gram (ACBS) - NHS indicative price = £3.91
Loprofin low protein herb crackers (Nutricia Ltd)
150 gram (ACBS) - NHS indicative price = £3.91

PK Foods ® Biscuits
LOW-PROTEIN
PK Foods Aminex low protein rusks (Gluten Free Foods Ltd)
200 gram (ACBS) - NHS indicative price = £5.14
PK Foods low protein crispbread (Gluten Free Foods Ltd)
75 gram (ACBS) - NHS indicative price = £2.46
Promin ® Cooked and flavoured pasta snax
LOW-PROTEIN
Promin low protein Snax salt & vinegar 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available | 12 sachet (ACBS) - NHS indicative price = £10.96

Promin low protein Snax ready salted 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available | 12 sachet (ACBS) - NHS indicative price = £10.96

Promin low protein Snax jalapeno 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available | 12 sachet (ACBS) - NHS indicative price = £10.96

Promin low protein Snax cheese & onion 25g sachets (Firstplay Dietary Foods Ltd)
3 sachet - No NHS indicative price available | 12 sachet (ACBS) - NHS indicative price = £10.96

Taranis ® Cake bars
LOW-PROTEIN

Taranis low protein apricot cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Taranis low protein lemon cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Taranis low protein pear cake (Lactalis Nutrition Sante)
240 gram (ACBS) - NHS indicative price = £6.08

Vita Bite ®

• Not recommended for any child under 1 year.

Bar, protein 30 mg (less than 2.5 mg phenylalanine), carbohydrate 15.35 g, fat 8.4 g, energy 572 kJ (137 kcal)/25 g.

VitaBite bar (Vitaflor International Ltd)
175 gram (ACBS) - NHS indicative price = £9.45

Vitaflor Choices ® Mini crackers
LOW-PROTEIN

Vitaflor Choices mini crackers (Vitaflor International Ltd)
40 gram (ACBS) - NHS indicative price = £0.93

Cereals
Loprofin ® breakfast cereal
LOW-PROTEIN

Loprofin low protein breakfast cereal flakes (Flavour Not Specified)
375 gram (ACBS) - No NHS indicative price available

Loprofin low protein breakfast cereal flakes chocolate (Nutricia Ltd)
375 gram (ACBS) - NHS indicative price = £8.65

Loprofin low protein breakfast cereal flakes strawberry (Nutricia Ltd)
375 gram (ACBS) - NHS indicative price = £8.65

Loprofin low protein breakfast cereal loops (Nutricia Ltd)
375 gram (ACBS) - NHS indicative price = £8.97

Promin ® Hot breakfast
LOW-PROTEIN

Promin low protein hot breakfast powder 56g sachets original (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £8.33

Promin low protein hot breakfast powder 57g sachets apple & cinnamon (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £8.33

Promin low protein hot breakfast powder 57g sachets banana (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £8.33

Promin low protein hot breakfast powder 57g sachets chocolate (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £8.33

Desserts
PK Foods ® Jelly
LOW-PROTEIN

PK Foods low protein jelly mix dessert cherry (Gluten Free Foods Ltd)
320 gram (ACBS) - NHS indicative price = £8.19

PK Foods low protein jelly mix dessert orange (Gluten Free Foods Ltd)
320 gram (ACBS) - NHS indicative price = £8.19

Promin ® Desserts
LOW-PROTEIN

Promin low protein dessert 36.5g sachets caramel (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £6.55

Promin low protein dessert 36.5g sachets chocolate & banana (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £6.55

Promin low protein dessert 36.5g sachets custard (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £6.55

Promin low protein dessert 36.5g sachets strawberry & vanilla (Firstplay Dietary Foods Ltd)
6 sachet (ACBS) - NHS indicative price = £6.55

Flour mixes and egg substitutes
Ener-G ® Egg replacer
LOW-PROTEIN

Ener-G low protein egg replacer (Gluten Free Foods Ltd)
454 gram (ACBS) - NHS indicative price = £5.17

Fate ® Flour mix
LOW PROTEIN

Fate low protein all purpose mix (Fate Special Foods)
500 gram (ACBS) - NHS indicative price = £6.97

Fate low protein chocolate cake mix (Fate Special Foods)
500 gram (ACBS) - NHS indicative price = £6.97

Fate low protein plain cake mix (Fate Special Foods)
500 gram (ACBS) - NHS indicative price = £6.97

Juvela ® Mix
LOW-PROTEIN

Juvela low protein mix (Hero UK Ltd)
500 gram (ACBS) - NHS indicative price = £7.79

Loprofin ® Flour mixes and egg substitutes
LOW-PROTEIN

Loprofin low protein egg replacer (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £16.81

Loprofin low protein egg white replacer (Nutricia Ltd)
100 gram (ACBS) - NHS indicative price = £10.81

Loprofin low protein cake mix chocolate (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £9.68

Loprofin low protein mix (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £9.01

PK Foods ® Flour mix and egg substitute
LOW-PROTEIN

PK Foods low protein egg replacer (Gluten Free Foods Ltd)
200 gram (ACBS) - NHS indicative price = £4.16

PK Foods low protein flour mix (Gluten Free Foods Ltd)
750 gram (ACBS) - NHS indicative price = £10.92

Pasta
Loprofin ® Pasta
LOW-PROTEIN

Loprofin low protein pasta animal shapes (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £9.20

Loprofin low protein pasta lasagne (Nutricia Ltd)
250 gram (ACBS) - NHS indicative price = £4.65

Loprofin low protein pasta penne (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £9.55

Loprofin low protein pasta tagliatelle (Nutricia Ltd)
250 gram (ACBS) - NHS indicative price = £4.60

Loprofin low protein pasta macaroni elbows (Nutricia Ltd)
250 gram (ACBS) - NHS indicative price = £4.60

Loprofin low protein pasta long cut spaghetti (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £9.55

www.getintopharma.com
**Promin® Pasta**  
LOW-PROTEIN  
**Promin low protein pasta alphabets** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin Plus low protein pasta macaroni** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin Plus low protein pasta flat noodles** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta shells** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta short cut spaghetti** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein tricolour pasta shells** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein X-Pot beef & tomato**  
240 gram (ACBS)  
**Promin low protein X-Pot rogan style curry**  
240 gram (ACBS)  
**Promin low protein X-Pot imitation rice**  
250 gram (ACBS)  
**Promin low protein potato pot with croutons cabbage & bacon**  
200 gram (ACBS)  
**Promin low protein potato pot with croutons onion**  
200 gram (ACBS)  
**Promin low protein potato pot with croutons sausage**  
200 gram (ACBS)  
**Promin low protein pasta spirals** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein tricolour pasta spirals** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta short cut spaghetti** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein potato pot with croutons onion**  
500 gram (ACBS)  
**Promin low protein pasta shells** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta short cut spaghetti** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein tricolour pasta shells** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta macaroni** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin Plus low protein pasta flat noodles** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20

**Pizza bases**  
**Juvela® Pizza base**  
LOW-PROTEIN  
**Juvela low protein pizza base** (Hero UK Ltd)  
560 gram  
**Juvela low protein pizza base** (Vitaflo International Ltd)  
30 sachet  
**Juvela low protein pizza base** (Nutricia Ltd)  
400 gram (ACBS) - NHS indicative price = £42.17

**Savoury meals and mixes**  
**Promin® Savoury meals and mixes**  
LOW-PROTEIN  
**Promin low protein cous cous** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.25  
**Promin low protein pasta elbows** (Firstplay Dietary Foods Ltd)  
500 gram - NHS indicative price = £7.20  
**Promin low protein pastameal** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein pasta macaroni** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin Plus low protein pasta spirals** (Firstplay Dietary Foods Ltd)  
500 gram (ACBS) - NHS indicative price = £7.20  
**Promin low protein potato pot with croutons onion** (Firstplay Dietary Foods Ltd)  
200 gram (ACBS) - NHS indicative price = £17.00  
**Promin low protein potato pot with croutons cabbage & bacon** (Firstplay Dietary Foods Ltd)  
200 gram (ACBS) - NHS indicative price = £17.00  
**Promin low protein potato pot with croutons sausage** (Firstplay Dietary Foods Ltd)  
200 gram (ACBS) - NHS indicative price = £17.00  
**Promin low protein X-Pot all day scramble** (Firstplay Dietary Foods Ltd)  
240 gram (ACBS) - NHS indicative price = £21.65

**Spreads**  
**Taranis® Spread**  
LOW-PROTEIN  
**Taranis low protein hazelnut spread** (Lactalis Nutrition Sante)  
230 gram (ACBS) - NHS indicative price = £7.95

**Nutritional supplements for metabolic diseases**  
**Glutaric aciduria (type I)**  
**GA Gel®**  
Nutritional supplement for dietary management of type 1 glutaric aciduria in children 6 months–10 years.  
GEL, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 10 g, carbohydrate 10.5 g, fat trace, energy 539 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.  
**GA gel oral powder 24g sachets** (Vitaflo International Ltd)  
30 sachet (ACBS) - NHS indicative price = £233.35

**GAI Anamix® Infant**  
Nutritional supplement for the dietary management of proven glutaric aciduria (type 1) in children from birth to 3 years.  
POWDER, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 15.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.5 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.  
**GAI Anamix Infant powder** (Nutricia Ltd)  
400 gram (ACBS) - NHS indicative price = £42.17

**XLYS, TRY Glutaridon®**  
Nutritional supplement for the dietary management of type 1 glutaric aciduria in children and adults; requires additional source of vitamins, minerals, and trace elements.  
POWDER, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 79 g, carbohydrate 4 g, energy 1411 kJ (332 kcal)/100 g. To flavour unflavoured products, see Modjul Flavour System p. 1576.  
**XLYS TRY Glutaridon powder** (Nutricia Ltd)  
500 gram (ACBS) - NHS indicative price = £201.74

**Glycogen storage disease**  
**Corn flour and corn starch**  
For glycogen storage disease  
**Glycosade®**  
A nutritional supplement for use in the dietary management of glycogen storage disease and other metabolic conditions where a constant supply of glucose is essential. Not suitable for use in children under 2 years.  
POWDER, protein 200 mg, carbohydrate (maize starch) 47.6 g, fat 100 mg, fibre less than 600 mg, energy 803 kJ (192 kcal)/60 g.  
**Glycosade oral powder 60g sachets** (Vitaflo International Ltd)  
50 sachet (ACBS) - NHS indicative price = £122.64

**Homocystinuria or hypermethioninaemia**  
**HCU Anamix® Infant**  
Nutritional supplement for the dietary management of proven vitamin B6 non-responsive homocystinuria or hypermethioninaemia in children from birth to 3 years.  
POWDER, protein equivalent (essential and non-essential amino acids except methionine) 13.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.  
**HCU Anamix Infant powder** (Nutricia Ltd)  
400 gram (ACBS) - NHS indicative price = £42.17
**Nutritional supplements for metabolic diseases**

- **HCU cooler** 15
  - A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 5.8 g, fat 30 mg, energy 315 kJ (75.3 kcal)/25 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

- **HCU Express** 15
  - A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 7 g, fat 500 mg, energy 395 kJ (92 kcal)/150 mL, with vitamins, minerals, and trace elements. HCU orange cooler 15 liquid (Vitafoam International Ltd) 130 ml (ACBS) - NHS indicative price = £12.31

- **HCU Express** 20
  - A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 4.7 g, fat 70 mg, energy 416 kJ (99 kcal)/34 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

- **HCU Express 20 oral powder 25g sachets** (Vitafoam International Ltd) 30 sachet (ACBS) - NHS indicative price = £66.17

- **HCU gel**
  - A methionine-free protein substitute for use as a nutritional supplement for the dietary management of children 1–10 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 10 g, carbohydrate 10.3 g, fat 20 mg, energy 339 kJ (81 kcal)/24 g with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

- **HCU gel oral powder 24g sachets** (Vitafoam International Ltd) 30 sachet (ACBS) - NHS indicative price = £233.29

- **HCU Lophlex** LQ 20
  - A nutritional supplement for the dietary management of homocystinuria in children over 3 years. LIQUID, protein equivalent (essential and non-essential amino acids except methionine) 20 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8 g sachet, with vitamins, minerals, and trace elements. HCU Lophlex LQ 20 liquid (Nutricia Ltd) 125 ml (ACBS) - NHS indicative price = £17.39

- **HCU LV**
  - Nutritional supplement for the dietary management of hypermethioninaemia or vitamin B6 non-responsive homocystinuria in children over 8 years. POWDER, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8 g sachet, with vitamins, minerals, and trace elements. To flavour unflavoured products, see Modul Flavour System p. 1576.

- **HCU-LV oral powder 27.8g sachets tropical** (Nutricia Ltd) 30 sachet (ACBS) - NHS indicative price = £53.40

- **HCU-LV oral powder 27.8g sachets unflavoured** (Nutricia Ltd) 30 sachet (ACBS) - NHS indicative price = £53.40

- **XMET Homidon**
  - Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children and adults. POWDER, protein equivalent (essential and non-essential amino acids, except methionine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. To flavour unflavoured products, see Modul Flavour System p. 1576.

- **XMET Homidon powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £201.74

- **HCU Maxamum**
  - Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria. POWDER, protein equivalent (essential and non-essential amino acids except methionine) 39 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see Modul Flavour System p. 1576. Maxamum products are generally intended for use in children over 8 years.

- **HCU Maxamum powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £170.70

**Hyperlysinæmia**

- Nutritional supplement for the dietary management of hyperlysinæmia in children from birth to 3 years.

- **HYPER LYS Anamix® Infant**
  - Nutritional supplement for the dietary management of proven hyperlysinæmia in children from birth to 3 years. POWDER, protein equivalent (essential and non-essential amino acids except lysine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.2 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

- **HYPER LYS Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £42.17

**Isovaleric acidaemia**

- Nutritional supplement for the dietary management of proven isovaleric acidaemia or other proven disorders of leucine metabolism in children from birth to 3 years.

- **IVA Anamix® Infant**
  - Nutritional supplement for the dietary management of proven isovaleric acidaemia or other proven disorders of leucine metabolism in children from birth to 3 years. POWDER, protein equivalent (essential and non-essential amino acids except leucine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.2 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

- **IVA Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £42.17

**Maple syrup urine disease**

- **MSUD Aid III®**
  - Nutritional supplement for the dietary management of maple syrup urine disease and related conditions in children and adults where it is necessary to limit the intake of branched chain amino acids. POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. To flavour unflavoured products, see Modul Flavour System p. 1576.

- **MSUD Aid III powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £201.74

- **MSUD Anamix® Infant**
  - Nutritional supplement for the dietary management of proven maple syrup urine disease in children from birth to 3 years. POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.2 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

- **MSUD Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £42.17
Nutritional supplements for metabolic diseases

MSUD Anamix® Junior LQ
- Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years.
  - LIQUID, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 510 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.

MSUD Anamix Junior LQ liquid (Nutricia Ltd)
- 125 mL (ACBS) - NHS indicative price = £9.78

MSUD cooler® 15
- Nutritional supplement for the dietary management of maple syrup urine disease in children 5 years and adults.
  - LIQUID, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 7 g, fat 500 mg, energy 393 kJ (92 kcal)/150–ML pouch, with vitamins, minerals, and trace elements.

MSUD orange cooler 15 liquid (Vitalfo International Ltd)
- 150 mL (ACBS) - NHS indicative price = £12.31

MSUD red cooler 15 liquid (Vitalfo International Ltd)
- 150 mL (ACBS) - NHS indicative price = £12.31

MSUD express® 15
- Nutritional supplement for the dietary management of maple syrup urine disease in children 8 years and adults.
  - POWDER, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 3.8 g, fat less than 100 mg, energy 515 kJ (75 kcal)/25 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

MSUD express 15 oral powder 25g sachets (Vitalfo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £362.37

MSUD express® 20
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults.
  - POWDER, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

MSUD express 20 oral powder 34g sachets (Vitalfo International Ltd)
- 50 sachet (ACBS) - NHS indicative price = £684.17

MSUD Gel
- Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years.
  - POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 10.5 g, fat less than 100 mg, energy 539 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

MSUD gel 24g sachets (Vitalfo International Ltd)
- 50 sachet (ACBS) - NHS indicative price = £236.03

MSUD Lophlex® LQ 20
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years.
  - LIQUID, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.

MSUD Lophlex LQ 20 liquid (Nutricia Ltd)
- 125 mL (ACBS) - NHS indicative price = £17.39

MSUD Maxamum®
- Nutritional supplement for the dietary management of maple syrup urine disease.
  - POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see Modul flavoured system p. 1576. Maxamum products are generally intended for use in children over 8 years.

MSUD Maxamum powder orange (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £170.70

MSUD Maxamum powder unflavoured (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £170.70

Methylmalonic or propionic acidaemia

MMA/PA Anamix® Infant
- Nutritional supplement for the dietary management of proven methylmalonic acidaemia or propionic acidaemia in children from birth.
  - POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

MSUD / PA Anamix infant powder (Nutricia Ltd)
- 400 gram (ACBS) - NHS indicative price = £42.17

XMTVI Asadon®
- Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia in children and adults.
  - POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1586 kJ (362 kcal)/100 g. To flavour unflavoured products, see Modul flavoured system p. 1576.

XMTVI Asadon powder (Nutricia Ltd)
- 200 gram (ACBS) - NHS indicative price = £80.69

MMA/PA Maxamum®
- Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia. POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 59 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see Modul Flavour system p. 1576. Maxamum products are generally intended for use in children over 8 years.

MMA/PA Maxamum powder (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £170.70

Other inborn errors of metabolism

Cystine500®
- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from 3 years.
  - POWDER, cystine 500 mg, carbohydrate 3.3 g, fat nil, energy 64 kJ (15 kcal)/4 g

Cystine500 oral powder sachets (Vitalfo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £59.28

DocOmega®
- Nutritional supplement for the dietary management of inborn errors of metabolism for adults and children from birth.
  - POWDER, protein (cows’ milk, soya) 100 mg, carbohydrate 5.2 g, fat 500 mg (of which docosahexaenoic acid 200 mg), fibre nil, energy 74 kJ (18 kcal)/4 g, with minerals

DocOmega oral powder 4g sachets (Vitalfo International Ltd)
- 50 sachet (ACBS) - NHS indicative price = £42.90

EAA® Supplement
- Nutritional supplement for the dietary management of disorders of protein metabolism including urea cycle disorders in children over 3 years.
  - POWDER, protein equivalent (essential amino acids) 5 g, carbohydrate 4 g, fat nil, energy 151 kJ (36 kcal)/12.5 g, with vitamins, minerals, and trace elements.

EAA Supplement oral powder 12.5g sachets (Vitalfo International Ltd)
- 50 sachet (ACBS) - NHS indicative price = £223.68
Nutritional supplements for metabolic diseases

**Isoleucine50**
- Nutritional supplement for use in the dietary management of inborn errors of amino acid metabolism in adults and children from birth.

**POWDER**, isoleucine 50 mg, carbohydrate 5.8 g, fat nil, energy 63 kJ (15 kcal)/4 g

**Isoleucine50 oral powder 4g sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £59.28

**KeyOmega**
- Nutritional supplement for the dietary management of inborn errors of metabolism.

**POWDER**, protein (cows' milk, soya) 170 mg, carbohydrate 2.8 g, fat 800 mg (of which arachidonic acid 200 mg, docosahexaenoic acid 100 mg), energy 80 kJ (19 kcal)/4 g

**KeyOmega oral powder 4g sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £43.87

**Leucine100**
- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.

**POWDER**, leucine 100 mg, carbohydrate 3.7 g, fat nil, energy 63 kJ (15 kcal)/4 g

**Leucine100 oral powder sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £59.28

**Low protein drink**
- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children over 1 year.

**POWDER**, protein (cows' milk) 4.5 g (phenylalanine 100 mg), carbohydrate 59.5 g, fat 29.9 g, fibre nil, energy 2194 kJ (528 kcal)/100 g, with vitamins, minerals, and trace elements.

Contains lactose.

Termed Milupa® L-p-drink by manufacturer.

**Milupa LP drink** (Nutricia Ltd)
400 gram (ACBS) - NHS indicative price = £10.00

**Phenylalanine50**
- Nutritional supplement for use in the dietary management of inborn errors of metabolism in adults and children over 6 months and adults.

**LIQUID**, carbohydrate 8.1 g (of which sugars 3.5 g), fat 3.8 g, energy 278 kJ (66 kcal)/100 mL. Contains lactose.

**Phenylalanine50 oral powder sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £57.56

**ProZero**
- A protein-free nutritional supplement for the dietary management of inborn errors of metabolism in children over 6 months and adults.

**LIQUID**, carbohydrate 8.1 g (of which sugars 3.5 g), fat 3.8 g, energy 278 kJ (66 kcal)/100 mL. Contains lactose.

**ProZero liquid** (Vitaflor International Ltd)
250 mL (ACBS) - NHS indicative price = £1.58 | 1000 mL (ACBS) - NHS indicative price = £6.31

**Tryptophan1000**
- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.

**POWDER**, tryptophan 1 g, carbohydrate 2.9 g, fat nil, energy 65 kJ (15 kcal)/4 g sachet.

**Tryptophan1000 oral powder 4g sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £5.42

**Valine50**
- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.

**POWDER**, valine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g

**Valine50 oral powder 4g sachets** (Vitaflor International Ltd)
30 sachet (ACBS) - NHS indicative price = £59.28

**Phenylketonuria**

**Easiphen**
- Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years.

**LIQUID**, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 6.7 g, carbohydrate 5.1 g, fat 2 g, energy 275 kJ (65 kcal)/100 mL with vitamins, minerals, and trace elements.

**Easiphen liquid** (Nutricia Ltd)
250 ml (ACBS) - NHS indicative price = £10.46

**L-Tyrosine**
- Nutritional supplement for the dietary management of phenylketonuria in pregnant women with low plasma tyrosine concentrations.

**POWDER**, L-tyrosine 20 g, carbohydrate 76.8 g, fat nil, energy 1612 kJ (379 kcal)/100 g.

**L-Tyrosine powder** (Nutricia Ltd)
100 gram (ACBS) - NHS indicative price = £23.76

**Lophlex**
- Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years and adults including pregnant women.

**POWDER**, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 2.5 g, fat 60 mg, fibre 220 mg, energy 355 kJ (91 kcal)/27.8 g sachet, with vitamins, minerals, and trace elements.

**Lophlex powder 27.8g sachets berry** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £31.40

**Lophlex powder 27.8g sachets orange** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £31.40

**Lophlex powder 27.8g sachets unflavoured** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £31.40

**Loprofin**
- Nutritional supplement for the dietary management of phenylketonuria in children over 1 year and adults.

LIQUID, protein (cows' milk) 400 mg (phenylalanine 10 mg), lactose 9.4 g, fat 2 g, energy 163 kJ (40 kcal)/100 mL.

**Loprofin PKU drink** (Nutricia Ltd)
200 mL (ACBS) - NHS indicative price = £0.81

**Loprofin Sno-Pro**
- Nutritional supplement for the dietary management of phenylketonuria, chronic renal failure and other inborn errors of amino acid metabolism.

**LIQUID**, protein (cows' milk) 220 mg (phenylalanine 12.5 mg), carbohydrate 8 g, fat 3.8 g, energy 275 kJ (65 kcal)/100 mL. Contains lactose.

**Loprofin SNO-PRO drink** (Nutricia Ltd)
200 mL (ACBS) - NHS indicative price = £1.35

**Phlexy-10**
- Nutritional supplement for the dietary management of phenylketonuria.

**CAPSULES**, protein equivalent (essential and non-essential amino acids except phenylalanine) 416.5 mg/capsule.

**Phlexy-10 500mg capsules** (Nutricia Ltd)
200 capsule (ACBS) - NHS indicative price = £4.03

**TABLETS**, protein equivalent (essential and non-essential amino acids except phenylalanine) 833 mg tablet.

**Phlexy-10 tablets** (Nutricia Ltd)
75 tablet (ACBS) - NHS indicative price = £30.24

**DRINK MIX**, powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.35 g, carbohydrate 8.8 g/20-g sachet.

**Phlexy-10 drink mix 20g sachets apple & blackcurrant** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £139.28

**Phlexy-10 drink mix 20g sachets citrus burst** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £139.28

**Phlexy-10 drink mix 20g sachets tropical surprise** (Nutricia Ltd)
30 sachet (ACBS) - NHS indicative price = £139.28
**Phlexy-Vits**

- For use as a vitamin and mineral component of restricted therapeutic diets in children over 11 years and adults with phenylketonuria and similar amino acid abnormalities.

**POWDER, vitamins, minerals, and trace elements**

**Phlexy-Vits powder 7g sachets** (Nutricia Ltd)
- 50 sachet (ACBS) - NHS indicative price = £77.23

**TABLETS, vitamins, minerals, and trace elements**

**Phlexy-Vits tablets** (Nutricia Ltd)
- 180 tablet (ACBS) - NHS indicative price = £88.51

**PK Aid 4**

- Nutritional supplement for the dietary management of phenylketonuria in children and adults.

**POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 79 g, carbohydrate 4.5 g, fat 25 g, fibre 5.3 g, energy 1420 kJ (343 kcal)/100 g. To flavour unflavoured products, see Modjul Flavour System p. 1576.

**PK Aid 4 powder** (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £155.07

**PKU Anamix Infant**

- Nutritional supplement for the dietary management of proven phenylketonuria in children from birth to 3 years.

**POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 4.9 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**PKU Anamix Infant powder** (Nutricia Ltd)
- 400 gram (ACBS) - NHS indicative price = £37.08

**PKU Anamix Junior**

- Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years.

**POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 11.5 g, fat 4.5 g, energy 566 kJ (135 mL)/36 g sachet, with vitamins, minerals, and trace elements.

**PKU Anamix Junior powder 36g sachets chocolate** (Nutricia Ltd)
- 30 sachet (ACBS) - NHS indicative price = £137.10

**PKU Anamix Junior powder 36g sachets neutral** (Nutricia Ltd)
- 30 sachet (ACBS) - NHS indicative price = £137.10

**PKU Anamix Junior powder 36g sachets berry** (Nutricia Ltd)
- 30 sachet (ACBS) - NHS indicative price = £137.10

**PKU Anamix Junior powder 36g sachets orange** (Nutricia Ltd)
- 30 sachet (ACBS) - NHS indicative price = £137.10

**PKU Anamix Junior LQ**

- Nutritional supplement for the dietary supplement of phenylketonuria in children 1–10 years.

**LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.

**PKU Anamix Junior LQ liquid berry** (Nutricia Ltd)
- 125 mL (ACBS) - NHS indicative price = £6.08

**PKU Anamix Junior LQ liquid orange** (Nutricia Ltd)
- 125 mL (ACBS) - NHS indicative price = £6.08

**PKU cooler10**

- Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.

**LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 4.7 g, energy 258 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements.

**PKU orange cooler 10 liquid** (Vitaflo International Ltd)
- 87 ml (ACBS) - NHS indicative price = £5.01

**PKU purple cooler 10 liquid** (Vitaflo International Ltd)
- 87 ml (ACBS) - NHS indicative price = £5.01

**PKU red cooler 10 liquid** (Vitaflo International Ltd)
- 87 ml (ACBS) - NHS indicative price = £5.01

**PKU white cooler 10 liquid** (Vitaflo International Ltd)
- 87 ml (ACBS) - NHS indicative price = £5.01

**PKU cooler15**

- Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.

**LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 7 g, energy 386 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements.

**PKU orange cooler 15 liquid** (Vitaflo International Ltd)
- 130 ml (ACBS) - NHS indicative price = £7.46

**PKU purple cooler 15 liquid** (Vitaflo International Ltd)
- 130 ml (ACBS) - NHS indicative price = £7.46

**PKU red cooler 15 liquid** (Vitaflo International Ltd)
- 130 ml (ACBS) - NHS indicative price = £7.46

**PKU white cooler 15 liquid** (Vitaflo International Ltd)
- 130 ml (ACBS) - NHS indicative price = £7.46

**PKU yellow cooler 15 liquid** (Vitaflo International Ltd)
- 130 ml (ACBS) - NHS indicative price = £7.46

**PKU cooler20**

- Nutritional supplement for the dietary management of phenylketonuria in children over 3 years.

**LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 9.4 g, energy 517 kJ (124 kcal)/174-mL pouch, with vitamins, minerals, and trace elements.

**PKU orange cooler 20 liquid** (Vitaflo International Ltd)
- 174 ml (ACBS) - NHS indicative price = £10.02

**PKU purple cooler 20 liquid** (Vitaflo International Ltd)
- 174 ml (ACBS) - NHS indicative price = £10.02

**PKU red cooler 20 liquid** (Vitaflo International Ltd)
- 174 ml (ACBS) - NHS indicative price = £10.02

**PKU white cooler 20 liquid** (Vitaflo International Ltd)
- 174 ml (ACBS) - NHS indicative price = £10.02

**PKU yellow cooler 20 liquid** (Vitaflo International Ltd)
- 174 ml (ACBS) - NHS indicative price = £10.02

**PKU express15**

- Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 3 years.

**POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 3.4 g, energy 310 kJ (74 kcal)/25 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

**PKU express 15 powder 25g sachets lemon** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £219.69

**PKU express 15 powder 25g sachets orange** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £219.69

**PKU express 15 powder 25g sachets tropical** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £219.69

**PKU express 15 powder 25g sachets unflavoured** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £219.69

**PKU express20**

- Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 3 years.

**POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 4.7 g, energy 422 kJ (101 kcal)/54 g, with vitamins, minerals, and trace elements. To flavour unflavoured products, see FlavourPac p. 1575.

**PKU express 20 powder 34g sachets lemon** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £283.83

**PKU express 20 powder 34g sachets orange** (Vitaflo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £283.83

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**Nutritional supplements for metabolic diseases**

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Nutritional supplement for the dietary management of proven phenylketonuria in children 6 months – 10 years (unflavoured), 1–10 years (flavoured).

**PKU Lophlex LQ 20**
- Nutritional supplement for the dietary management of phenylketonuria in children 6 months – 10 years (unflavoured), 1–10 years (flavoured).
- POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 4.4 g, fibre 250 mg, energy 245 kJ (58 kcal)/62.5 mL, with vitamins, minerals, and trace elements. PKU Orange contains soya. To flavour unflavoured products, see FlavourPac p. 1575.

**PKU Lophlex LQ 10**
- Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
- LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 4.4 g, fibre 250 mg, energy 245 kJ (58 kcal)/62.5 mL, with vitamins, minerals, and trace elements.

**PKU Lophlex LQ 10 liquid berry**
- Standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**PKU Lophlex LQ 10 liquid citrus**
- Standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**PKU Lophlex LQ 10 liquid orange**
- Standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**PKU Lophlex LQ 10 liquid orange tyrosinaemia**
- Nutritional supplement for the dietary management of tyrosinaemia type 1 (when nitisinone (NTBC) is used, see nitisinone p. 1067), type II, and type III, in children over 1 year.
- LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**PKU gel®**
- For use as part of the low-protein dietary management of phenylketonuria in children 6 months – 10 years (unflavoured), 1–10 years (flavoured).
- POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 10.3 g (unflavoured)/8.9 g (flavoured), fat less than 100 mg, energy 346 kJ (82 kcal)/322 kJ (76 kcal) (flavoured)/24 g, with vitamins, minerals, and trace elements. PKU Orange contains soya. To flavour unflavoured products, see FlavourPac p. 1575.

**PKU gel powder 24 sachets unflavoured**
- Nutritional supplement for the dietary management of proven phenylketonuria in children 6 months – 10 years (unflavoured), 1–10 years (flavoured).
- POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 10.3 g (unflavoured)/8.9 g (flavoured), fat less than 100 mg, energy 346 kJ (82 kcal)/322 kJ (76 kcal) (flavoured)/24 g, with vitamins, minerals, and trace elements. PKU Orange contains soya. To flavour unflavoured products, see FlavourPac p. 1575.
fat 500 mg, energy 393 kJ (92 kcal)/130 mL, with vitamins,
minerals, and trace elements.

**TYR orange cooler 15 liquid** (Vitaflo International Ltd)
130 ml (ACBS) - NHS indicative price = £12.31

**TYR red cooler 10 liquid** (Vitaflo International Ltd)
87 ml (ACBS) - NHS indicative price = £7.60

**TYR red cooler 15 liquid** (Vitaflo International Ltd)
130 ml (ACBS) - NHS indicative price = £12.31

**TYR red cooler 20 liquid** (Vitaflo International Ltd)
174 ml (ACBS) - NHS indicative price = £15.89

**TYR express15®**
Nutritional supplement for the dietary management of
tyrosinaemia in children over 8 years and adults.
 POWDER, protein equivalent (essential and non-essential amino
acids except tyrosine and phenylalanine) 15 g, carbohydrate
3.4 g, fat less than 100 mg, energy 310 kJ (74 kcal)/25 g, with
vitamins, minerals, and trace elements. To flavour unflavoured
products, see FlavourPac p. 1575.

**TYR express 15 oral powder 25g sachets** (Vitaflo International Ltd)
30 sachet (ACBS) - NHS indicative price = £362.37

**TYR express20®**
Nutritional supplement for the dietary management of
tyrosinaemia in children over 8 years.
 POWDER, protein equivalent (essential and non-essential amino
acids except tyrosine and phenylalanine) 20 g, carbohydrate
4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with
vitamins, minerals, and trace elements. To flavour unflavoured
products, see FlavourPac p. 1575.

**TYR express 20 oral powder 34g sachets** (Vitaflo International Ltd)
30 sachet (ACBS) - NHS indicative price = £468.17

**TYR Gel®**
Nutritional supplement for the dietary management of
tyrosinaemia in children 1–10 years.
 GEL, protein equivalent (essential and non-essential amino
acids except tyrosine and phenylalanine) 10 g, carbohydrate
10.3 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with
vitamins, minerals, and trace elements. To flavour unflavoured
products, see FlavourPac p. 1575.

**TYR gel oral powder 24g sachets** (Vitaflo International Ltd)
30 sachet (ACBS) - NHS indicative price = £233.29

**TYR Lophlex® LQ 20**
Nutritional supplement for the dietary management of
tyrosinaemia in children over 4 years and adults, including
pregnant women (in conjunction with standard folic acid
supplementation).
 LIQUID, protein equivalent (essential and non-essential amino
acids except phenylalanine and tyrosine) 20 g, carbohydrate
8.8 g, fat less than 500 mg, fibre 500 mg, energy 509 kJ
(120 kcal)/125 mL, with vitamins, minerals, and trace elements.

**TYR Lophlex LQ 20 liquid** (Nutricia Ltd)
125 ml (ACBS) - NHS indicative price = £17.39

**XPHEN TYR Tyrosidon**
Nutritional supplement for the management of tyrosinaemia in
children and adults where plasma-methionine concentrations
are normal.
 POWDER, protein equivalent (essential and non-essential amino
acids except phenylalanine and tyrosine) 77 g, carbohydrate
4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. To flavour
unflavoured products, see Modjul Flavour System p. 1576.

**XPHEN TYR Tyrosidon Free AA Mix powder** (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £201.74

**XPTM Tyrosidon®**
Nutritional supplement for the dietary management of
 tyrosinaemia type I in children and adults where plasma-
methionine concentrations are above normal.
 POWDER, protein equivalent (essential and non-essential amino
acids except methionine, phenylalanine, and tyrosine) 77 g,
carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. To
flavour unflavoured products, see Modjul Flavour System
p. 1576.
Appendix 3
Cautionary and advisory labels for dispensed medicines

Guidance for cautionary and advisory labels
Medicinal forms within BNF publications include code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that pharmacists will counsel patients and carers when necessary. Counselling needs to be related to the age, experience, background, and understanding of the individual patient or carer. The pharmacist should ensure understanding of how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on co-ordination, performance of skilled tasks (e.g. driving or work), any foods or medicines to be avoided, and what to do if a dose is missed should also be explained. Other matters, such as the possibility of staining of the clothes or skin, or discoloration of urine or stool by a medicine should also be mentioned.

For some medicines there is a special need for counselling, such as an unusual method or time of administration or a potential interaction with a common food or domestic remedy, and this should be mentioned where necessary.

Original packs
Most preparations are dispensed in unbroken original packs that include the further advice for the patient in the form of patient information leaflets. Label 10 may be of value where appropriate. More general leaflets advising on the administration of preparations such as eye drops, eye ointments, inhalers, and suppositories are also available.

Scope of labels
In general no label recommendations have been made for injections on the assumption that they will be administered by a healthcare professional or a well-instructed patient. The labelling is not exhaustive and pharmacists are recommended to use their professional discretion in labelling new preparations and those for which no labels are shown.

Individual labelling advice is not given on the administration of the large variety of antacids. In the absence of instructions from the prescriber, and if on enquiry the patient has had no verbal instructions, the directions given under 'Dose' should be used on the label.

It is recognised that there may be occasions when pharmacists will use their knowledge and professional discretion and decide to omit one or more of the recommended labels for a particular patient. In this case counselling is of the utmost importance. There may also be an occasion when a prescriber does not wish additional cautionary labels to be used, in which case the prescription should be endorsed 'NCL' (no cautionary labels). The exact wording that is required instead should then be specified on the prescription.

Pharmacists label medicines with various wordings in addition to those directions specified on the prescription. Such labels include 'Shake the bottle', 'For external use only', and 'Store in a cool place', as well as 'Discard... days after opening' and 'Do not use after... ', which apply particularly to antibiotic mixtures, diluted liquid and topical preparations, and to eye-drops. Although not listed in the BNF these labels should continue to be used when appropriate; indeed, 'For external use only' is a legal requirement on external liquid preparations, while 'Keep out of the reach of children' is a legal requirement on all dispensed medicines. Care should be taken not to obscure other relevant information with adhesive labelling.

It is a useful precaution for patients to take standard tablets with water or other liquid and for this reason no separate label has been recommended.

The label wordings recommended by the BNF apply to medicines dispensed against a prescription. Patients should be aware that a dispensed medicine should never be taken by, or shared with, anyone other than for whom the prescriber intended it. Therefore, the BNF does not include warnings against the use of a dispensed medicine by persons other than for whom it was specifically prescribed. The label or labels for each preparation are recommended after careful consideration of the information available. However, it is recognised that in some cases this information may be either incomplete or open to a different interpretation. The BNF will therefore be grateful to receive any constructive comments on the labelling suggested for any preparation.

Recommended label wordings
For BNF 61 (March 2011), a revised set of cautionary and advisory labels were introduced. All of the existing labels were user-tested, and the revised wording selected reflects terminology that is better understood by patients.

Wordings which can be given as separate warnings are labels 1–19, 29–30, and 32. Wordings which can be incorporated in an appropriate position in the directions for dosage or administration are labels 21–28. A label has been omitted for number 20; labels 51 and 35 no longer apply to any medicines in the BNF and have therefore been deleted.

If separate labels are used it is recommended that the wordings be used without modification. If changes are made to suit computer requirements, care should be taken to retain the sense of the original.

Welsh labels
Comprehensive Welsh translations are available for each cautionary and advisory label.

Labels

1 Warning: This medicine may make you sleepy

Rhybudd: Gall y feddygyniaeth hon eich gwneud yn ysglyd

To be used on preparations for children containing antihistamines, or other preparations given to children where the warnings of label 2 on driving or alcohol would not be appropriate.

2 Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol

Rhybudd: Gall y feddygyniaeth hon eich gwneud yn ysglyd. Peidiwch â gyrru, defnyddio offer llaw neu beiriannau os yw hyn yn digwydd. Peidiwch ag yfed alcohol

To be used on preparations for adults that can cause drowsiness, thereby affecting coordination and the ability to drive and operate hazardous machinery; label 1 is more appropriate for children. It is an offence to drive while under the influence of drink or drugs.

Some of these preparations only cause drowsiness in the first few days of treatment and some only cause drowsiness in higher doses.

In such cases the patient should be told that the advice applies until the effects have worn off. However many of these preparations can produce a slowing of reaction time and a loss of mental concentration that can have the same effects as drowsiness.

Avoidance of alcoholic drink is recommended because the effects of CNS depressants are enhanced by alcohol. Strict prohibition however could lead to some patients not taking the medicine. Pharmacists should therefore explain the risk
and encourage compliance, particularly in patients who may think they already tolerate the effects of alcohol (see also label 3). Queries from patients with epilepsy regarding fitness to drive should be referred back to the patient’s doctor.

Side-effects unrelated to drowsiness that may affect a patient’s ability to drive or operate machinery safely include blurred vision, dizziness, or nausea. In general, no label has been recommended to cover these cases, but the patient should be suitably counselled.

3 Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines.

Rhybudd: Gall y feddyginiaeth hon eich gwneud yn gysglyd. Peidiwch â gyrru, defnyddio offer llaw neu beiriannau os yw hyn yn digwydd

To be used on preparations containing monoamine-oxidase inhibitors; the warning to avoid alcohol and dealkoholised (low alcohol) drink is covered by the patient information leaflet.

Also to be used as for label 2 but where alcohol is not an issue.

4 Warning: Do not drink alcohol.

Rhybudd: Peidiwch ag yr yfed alcohol

To be used on preparations where a reaction such as flushing may occur if alcohol is taken (e.g. metronidazole). Alcohol may also enhance the hypoglycaemia produced by some oral antidiabetic drugs but routine application of a warning label is not considered necessary.

Patients should be advised not to drink alcohol for as long as they are receiving/using a course of medication, and in some cases for a period of time after the course is finished.

5 Do not take indigestion remedies 2 hours before or after you take this medicine.

Peidiwch â chymryd meddyginiaetha camdreuliad 2 awr cyn cynnwys haearn neu sinc, 2 awr cyn neu ar ôl y feddyginiaeth hon

To be used with label 25 on preparations coated to resist gastric acid (e.g. enteric-coated tablets). This is to avoid the possibility of premature dissolution of the coating in the presence of an alkaline pH.

Label 5 also applies to drugs such as gabapentin where the absorption is significantly affected by antacids. Pharmacists will be aware (from a knowledge of physiology) that the usual time during which indigestion remedies should be avoided is at least 2 hours before and after the majority of medicines have been taken; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

6 Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine.

Peidiwch â chymryd meddyginiaetha camdreuliad neu feddyginiaetha sy’n cynnwys haearn neu sinc, 2 awr cyn neu ar ôl y feddyginiaeth hon

To be used on preparations containing oloxacin and some other quinolones, doxycycline, tetracycline, minocycline, and penicillamine. These drugs chelate calcium, iron, and zinc and are less well absorbed when taken with calcium-containing antacids or preparations containing iron or zinc. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

7 Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine.

Peidiwch â chymryd llæth, meddyginiaetha camdreuliad, neu feddyginiaeth sy’n cynnwys haearn neu sinc, 2 awr cyn neu ar ôl y feddyginiaeth hon

To be used on preparations containing ciprofloxacin, norfloxacin, or tetracyclines that chelate calcium, iron, magnesium, and zinc, and are thus less available for absorption. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

8 Warning: Do not stop taking this medicine unless your doctor tells you to stop.

Rhybudd: Peidiwch â stopio cymryd y feddyginiaeth hon, oni bai fod eich meddyg yn dweud wrthych am stopio

To be used on preparations that contain a drug which is required to be taken over long periods without the patient necessarily perceiving any benefit (e.g. antituberculous drugs). Also to be used on preparations that contain a drug whose withdrawal is likely to be a particular hazard (e.g. clonidine for hypertension). Label 10 (see below) is more appropriate for corticosteroids.

9 Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop.

Gadewch i doddi mewn dŵr haul, hyd yn oed ar ddiwrnod ddwrg. Nid yw hyn yn arwydd o ddawel.

Patients should be advised not to drink alcohol for as long as they are receiving/using a course of medication, and in some cases for a period of time after the course is finished.

10 Warning: Read the additional information given with this medicine.

Rhybudd: Darllenwch y wybodaeth ychwanegol gyda’r feddyginiaeth hon

To be used particularly on preparations containing anticoagulants, lithium, and oral corticosteroids. The appropriate treatment card should be given to the patient and any necessary explanations given.

This label may also be used on other preparations to remind the patient of the instructions that have been given.

11 Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds.

Diogelwch eich croen rhag golau ddwrg. Nid oes beth sy’n wir iawn ar ddiwrnod ddwrg, oni bai eich bod yn cael cynhyrchion ddwrg.

To be used on preparations where a course of treatment should be completed to reduce the incidence of relapse or failure of treatment.

The preparations are antimicrobial drugs given by mouth. Very occasionally, some may have severe side-effects (e.g. diarrhoea in patients receiving clindamycin) and in such cases the patient may need to be advised of reasons for stopping treatment quickly and returning to the doctor.

12 Do not take anything containing aspirin while taking this medicine.

Peidiwch â chymryd unrhyw beth sy yw cynnwys aspirin gyda’r feddyginiaeth hon

To be used on preparations containing anticoagulants, lithium, and oral corticosteroids. The appropriate treatment card should be given to the patient and any necessary explanations given.

Label 12 should not be used for anticoagulants since label 10 is more appropriate.

13 Dissolve or mix with water before taking.

Gadewch i doddi mewn dwr ddwrg.

To be used on preparations that are intended to be dissolved in water (e.g. soluble tablets) or mixed with water (e.g. powders, granules) before use. In a few cases other liquids such as fruit juice or milk may be used.

14 This medicine may colour your urine. This is harmless.

Gall y feddyginiaeth hon lliwio eich dŵr. Nid yw hyn yn arwydd o ddawel.

To be used on preparations that may cause the patient’s urine to turn an unusual colour. These include triamterene (blue under some lights), levodopa (dark reddish), and rifampicin (red).
15 Caution: flammable. Keep your body away from fire or flames after you have put on the medicine.
Rhybudd: Ffilmadyw. Ar ôl rhoi’r fedyddginiaeth ymlaen, cadwch yn glir o dan neu fflamau
To be used on preparations containing sufficient flammable solvent to render them flammable if exposed to a naked flame.

16 Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening.
Rhewch y dabled i doddi dan eich tafod - peidiwch â caead wedi’i gau ym dynn. Gofynnwch am dabledi newydd 8 wythnos ar ôl ei hagor
To be used on glyceryl trinitrate tablets to remind the patient not to transfer the tablets to plastic or less suitable containers.

17 Do not take more than... in 24 hours
Peidwch â chmyrdd mwy na... mewn 24 awr
To be used on preparations for the treatment of acute migraine except those containing ergotamine, for which label 18 is used. The dose form should be specified, e.g. tablets or capsules.
It may also be used on preparations for which no dose has been specified by the prescriber.

18 Do not take more than... in 24 hours. Also, do not take more than... in any one week.
Peidwch â chmyrdd mwy na... mewn 24 awr. Hefyd, peidwch â chmyrdd mwy na... mewn wythnos
To be used on preparations containing ergotamine. The dose form should be specified, e.g. tablets or suppositories.

19 Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol.
Rhybudd: Bydd y fedyddginiaeth hon yn eich gweud neu ym gysglyd. Os ydych yn dal i deimlo y dyled wedi’i gwyrru, defnyddio offer laww neu bei niannau. Peidwch ag y fyd alcohol
To be used on preparations containing hypnotics (or some other drugs with sedative effects) prescribed to be taken at night. On the rare occasions when hypnotics are prescribed for daytime administration (e.g. nitrazepam in epilepsy), this label would clearly not be appropriate. Also to be used as an alternative to the label 2 wording (the choice being at the discretion of the pharmacist) for anxiotytics prescribed to be taken at night.
It is hoped that this wording will convey adequately the problem of residual morning sedation after taking ‘sleeping tablets’.

20 Take with or just after food, or a meal
Cymerwch gyda neu ar ôl bwyd
To be used on preparations that are liable to cause gastric irritation, or those that are better absorbed with food. Patients should be advised that a small amount of food is sufficient.

21 Take 30 to 60 minutes before food
Cymerwch 30 i 60 munud cyn bwyd
To be used on some preparations whose absorption is thereby improved. Most oral antibacterials require label 23 instead (see below).

22 Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
Cymerwch y fedyddginiaeth hon ar stumog wag. Mae hyn yn gofynnws awr cyn, neu 2 awr ar ôl bwyd
To be used on oral antibacterials whose absorption may be reduced by the presence of food and acid in the stomach.

23 Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
Cymerwch y fedyddginiaeth hon ar stumog wag. Mae hyn yn gofynnws awr cyn, neu 2 awr ar ôl bwyd
To be used on oral antibacterials whose absorption may be reduced by the presence of food and acid in the stomach.

24 Suck or chew this medicine
Bydd angen cni neu sugno’r fedyddginiaeth hon
To be used on preparations that should be sucked or chewed.
The pharmacist should use discretion as to which of these words is appropriate.
Appendix 4

Wound management products and elastics garments

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The correct dressing for wound management depends not only on the type of wound but also on the stage of the healing process. The principal stages of healing are: cleansing, removal of debris; granulation, vascularisation; epithelialisation. The ideal dressing for moist wound healing needs to ensure that the wound remains: moist with epithelialisation. The ideal dressing for moist wound healing is not appropriate (e.g. gangrenous toes associated with vascular disease). Advanced wound dressings are designed to control the environment for wound healing, for example to donate fluid (hydrogels), maintain hydration (hydrocolloids), or to absorb wound exudate (alginate, foams). Practices such as the use of irritant cleansers and desloughing agents may be harmful and are largely obsolete; removal of debris and dressing remnants should need minimal irrigation with lukewarm sterile sodium chloride 0.9% solution or water.

Hydrogel, hydrocolloid, and medical grade honey dressings can be used to deslough wounds by promoting autolytic debridement; there is insufficient evidence to support any particular method of debridement for difficult-to-heal surgical wounds. Sterile larvae (maggots) are also available for biosurgical removal of wound debris.

There have been few clinical trials able to establish a clear advantage for any particular product. The choice between different dressings depends not only on the type and stage of the wound, but also on patient preference or tolerance, site of the wound, and cost. For further information, see Buyers’ Guide: Advanced wound dressings (October 2008); NHS Purchasing and Supply Agency, Centre for Evidence-based Purchasing.

Prices quoted in Appendix 4 are basic NHS net prices; for further information see Prices in the BNF under How to use the BNF.

The table below gives suggestions for choices of primary dressing depending on the type of wound (a secondary dressing may be needed in some cases).

Basic wound contact dressings

Low adherence dressing

Low adherence dressings are used as interface layers under secondary absorbent dressings. Placed directly on the wound bed, non-absorbent, low adherence dressings are suitable for clean, granulating, lightly exuding wounds without necrosis, and protect the wound bed from direct contact with secondary dressings. Care must be taken to avoid granulation tissue growing into the weave of these dressings. Tulle dressings are manufactured from cotton or viscose fibres which are impregnated with white or yellow soft paraffin to prevent the fibres from sticking, but this is only partly successful and it may be necessary to change the

www.getintopharma.com
Basic wound contact dressings

### Wound contact material for different types of wounds

#### Wound PINK (epithelialising)

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence p. 1591</td>
<td>Soft polymer p. 1596</td>
<td>Foam with extra absorbency p. 1599</td>
</tr>
<tr>
<td>Vapour-permeable film p. 1595</td>
<td>Foam, low absorbent p. 1599</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
<tr>
<td>Soft polymer p. 1596</td>
<td>Alginate p. 1590</td>
<td>Alginate p. 1600</td>
</tr>
<tr>
<td>Hydrocolloid p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
</tbody>
</table>

#### Wound RED (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence p. 1591</td>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
<tr>
<td>Soft polymer p. 1596</td>
<td>Foam p. 1599</td>
<td>Foam with extra absorbency p. 1599</td>
</tr>
<tr>
<td>Hydrocolloid p. 1598</td>
<td>Alginate p. 1600</td>
<td>Alginate p. 1600</td>
</tr>
<tr>
<td>Foam, low absorbent p. 1599</td>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
</tbody>
</table>

#### Wound YELLOW (Sloughy) (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel p. 1594</td>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
<tr>
<td>Hydrocolloid p. 1598</td>
<td>Alginate p. 1600</td>
<td>Alginate p. 1600</td>
</tr>
<tr>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Foam p. 1599</td>
<td>Capillary-action p. 1601</td>
</tr>
</tbody>
</table>

#### Wound BLACK (Necrotic/Eschar)

Consider mechanical debridement alongside autolytic debridement

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel p. 1594</td>
<td>Hydrocolloid p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
</tr>
<tr>
<td>Hydrocolloid p. 1598</td>
<td>Hydrocolloid-fibrous p. 1598</td>
<td>Seek advice from wound care specialist</td>
</tr>
</tbody>
</table>

#### Wounds with signs of infection

Consider systemic antibacterials if appropriate; also consider odour-absorbent dressings. For malodorous wounds with slough or necrotic tissue, consider mechanical or autolytic debridement

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence with honey p. 1602</td>
<td>Hydrocolloid-fibrous with silver p. 1604</td>
<td>Hydrocolloid-fibrous with silver p. 1604</td>
</tr>
<tr>
<td>Low adherence with iodine p. 1602</td>
<td>Foam with silver p. 1603</td>
<td>Foam extra absorbent, with silver p. 1603</td>
</tr>
<tr>
<td>Low adherence with silver p. 1603</td>
<td>Alginate with silver p. 1603</td>
<td>Alginate with honey p. 1602</td>
</tr>
<tr>
<td>Hydrocolloid with silver p. 1604</td>
<td>Honey-topical p. 1602</td>
<td>Alginate with silver p. 1603</td>
</tr>
<tr>
<td></td>
<td>Cadoxomer-iodine p. 1602</td>
<td></td>
</tr>
</tbody>
</table>

Note: In each section of this table the dressings are listed in order of increasing absorbency.

Some wound contact (primary) dressings require a secondary dressing.

### Knitted polyester primary dressing

**Atraman**

Non-adherent knitted polyester primary dressing impregnated with neutral triglycerides.

**Atraman dressing** (Paul Hartmann Ltd) 10cm × 20cm= £0.80, 20cm × 30cm= £2.20, 5cm × 5cm= £0.34, 7.5cm × 10cm= £0.35

**Knitted viscose primary dressing**

**N-A Dressing**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A dressing** (Systagenix Wound Management Ltd) 19cm × 9.5cm= £0.67, 9.5cm × 9.5cm= £0.35

**N-A Ultra**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A Ultra dressing** (Systagenix Wound Management Ltd) 19cm × 9.5cm= £0.64, 9.5cm × 9.5cm= £0.34

**Profore**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Profore** (Smith & Nephew Healthcare Ltd) wound contact layer 14cm × 20cm= £0.33

**Tricotex**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Tricotex dressing** (Smith & Nephew Healthcare Ltd) 9.5cm × 9.5cm= £0.35

**Paraffin Gauze Dressing**

**Cuticell**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading.

**Cuticell** (BSN Medical Ltd) Classic dressing 10cm × 10cm= £0.30

**Jelonet**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading.

**Jelonet** (Smith & Nephew Healthcare Ltd) dressing 10cm × 10cm= £0.42

**Neotulle**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin; for light or normal loading.

**Neotulle** (Neomedic Ltd) dressing 10cm × 10cm= £0.29
Absorvent dressings
Perforated film absorvent dressings are suitable only for wounds with mild to moderate amounts of exudate; they are not appropriate for leg ulcers or for other lesions that produce large quantities of viscous exudate. Dressings with an absorbent cellulose or polymer wadding layer are suitable for use on moderately to heavily exuding wounds.

Absorbent cellulose dressing

CelluDress Absorbent Cellulose Dressing with Fluid Repellent Backing

CelluDress dressing (Medicareplus International Ltd) 10cm x 10cm= £0.19, 10cm x 15cm= £0.20, 10cm x 20cm= £0.22, 15cm x 20cm= £0.30, 20cm x 25cm= £0.40, 20cm x 30cm= £0.85

Eclipse Absorbent Cellulose Dressing with Fluid Repellent Backing

Eclipse (Advancis Medical) Boot dressing 60cm x 70cm= £13.88, dressing 15cm x 15cm= £0.98, 20cm x 30cm= £2.16, 60cm x 40cm= £8.21

Exu-Dry

Absorbent Cellulose Dressing with Fluid Repellent Backing

Exu-Dry dressing (Smith & Nephew Healthcare Ltd) 10cm x 15cm= £1.16, 15cm x 23cm= £2.36, 23cm x 38cm= £5.49

Mesorb

Cellulose wadding pad with gauze wound contact layer and non-woven repellent backing

Mesorb dressing (Molynex Health Care Ltd) 10cm x 10cm= £0.63, 10cm x 15cm= £0.62, 10cm x 20cm= £1.01, 15cm x 20cm= £1.44, 20cm x 25cm= £2.27, 20cm x 30cm= £2.57

Zetuvit E

Absorbent Cellulose Dressing with Fluid Repellent Backing; sterile or non-sterile

Zetuvit (Paul Hartmann Ltd) E non-sterile dressing 10cm x 10cm= £0.07, 10cm x 20cm= £0.09, 20cm x 20cm= £0.15, 20cm x 40cm= £0.28, sterile dressing 10cm x 10cm= £0.22, 10cm x 20cm= £0.25, 20cm x 20cm= £0.40, 20cm x 40cm= £1.12

Absorvent perforated dressing

Adpore

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Adpore dressing (Medicareplus International Ltd) 10cm x 10cm= £0.10, 10cm x 15cm= £0.16, 10cm x 20cm= £0.30, 10cm x 25cm= £0.34, 10cm x 30cm= £0.42, 10cm x 35cm= £0.50, 7cm x 8cm= £0.08

Cosmopore E

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Cosmopore E dressing (Paul Hartmann Ltd) 10cm x 20cm= £0.46, 10cm x 25cm= £0.57, 10cm x 30cm= £0.69, 7cm x 7cm= £0.08, 6cm x 10cm= £0.18, 8cm x 15cm= £0.28

Cutiplast Steril

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Cutiplast Steril dressing (Smith & Nephew Healthcare Ltd) 10cm x 20cm= £0.32, 10cm x 25cm= £0.33, 10cm x 30cm= £0.44, 8cm x 10cm= £0.11, 8cm x 15cm= £0.25

Leukomed

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Leukomed dressing (BSN medical ltd) 10cm x 20cm= £0.44, 10cm x 25cm= £0.50, 10cm x 30cm= £0.64, 10cm x 35cm= £0.74, 7cm x 7cm= £0.09, 8cm x 10cm= £0.19, 8cm x 15cm= £0.33

Medipore + Pad

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Medipore + Pads dressing (3M Health Care Ltd) 10cm x 10cm= £0.16, 10cm x 15cm= £0.25, 10cm x 20cm= £0.38, 10cm x 25cm= £0.46, 10cm x 35cm= £0.65, 5cm x 7.2cm= £0.08

Medisafe

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Medisafe dressing (Neomedic Ltd) 6cm x 8cm= £0.08, 8cm x 10cm= £0.13, 8cm x 15cm= £0.23, 9cm x 15cm= £0.29, 9cm x 20cm= £0.34, 9cm x 25cm= £0.36

Mepore

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Mepore dressing (Molynex Health Care Ltd) 10cm x 11cm= £0.22, 11cm x 15cm= £0.36, 7cm x 8cm= £0.11, 9cm x 20cm= £0.44, 9cm x 25cm= £0.61, 9cm x 30cm= £0.70, 9cm x 35cm= £0.76

PremierPore

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

PremierPore dressing (Sherwood) 10cm x 10cm= £0.12, 10cm x 15cm= £0.18, 10cm x 20cm= £0.32, 10cm x 25cm= £0.36, 10cm x 30cm= £0.45, 10cm x 35cm= £0.52, 5cm x 7cm= £0.05

Primapore

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Primapore dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm= £0.13, 10cm x 15cm= £0.20, 10cm x 20cm= £0.35, 10cm x 25cm= £0.40, 10cm x 30cm= £0.49, 10cm x 35cm= £0.58, 6cm x 7cm= £0.06

Softpore

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Softpore dressing (Richardson Healthcare Ltd) 10cm x 10cm= £0.45, 10cm x 25cm= £0.51, 10cm x 30cm= £0.64, 10cm x 35cm= £0.99, 6cm x 8.3cm= £0.18, 6cm x 10cm= £0.20, 8cm x 15cm= £0.34

Telfa Island

Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive barrier.

Telfa Island dressing (H & R Healthcare Ltd) 10cm x 12.5cm= £0.27, 10cm x 20cm= £0.35, 10cm x 25cm= £0.45, 10cm x 35cm= £0.62, 5cm x 10cm= £0.08

Absorvent perforated plastic film faced dressing

Absopad

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Absopad dressing (Medicareplus International Ltd) 10cm x 10cm= £0.13, 20cm x 10cm= £0.28

Askina Pad

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Askina (Braun Medical Ltd) Pad dressing 10cm x 10cm= £0.21

Melolin

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Melolin dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm= £0.28, 20cm x 10cm= £0.55, 5cm x 5cm= £0.17

Skintact

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Skintact dressing (Robinson Healthcare) 10cm x 10cm= £0.17, 20cm x 10cm= £0.34, 5cm x 5cm= £0.10

Solvaline N

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Solvaline N dressing (Lohmann & Rauscher) 10cm x 10cm= £0.18, 20cm x 10cm= £0.37, 5cm x 5cm= £0.10

Telfa

Low-adherence primary dressing consisting of 3 layers—perforated polyfilmy wound contact layer, absorbent cotton pad, and hydrophilic backing.

Telfa dressing (H & R Healthcare Ltd) 10cm x 7.5cm= £0.16, 15cm x 7.5cm= £0.18, 20cm x 7.5cm= £0.29, 7.5cm x 5cm= £0.12
Super absorbent cellulose and polymer primary dressing

**Curea P1**
Super absorbent cellulose and polymer primary dressing. 
*Curea P1 dressing* (Charles S. Bullen Stomacare Ltd) 10cm × 10cm square= £2.17, 10cm × 20cm rectangular= £3.67, 10cm × 30cm rectangular= £5.29, 12cm × 12cm square= £2.67, 20cm × 20cm square= £6.95, 20cm × 30cm rectangular= £10.11, 7.5cm × 7.5cm square= £1.73

**Curea P2**
Super absorbent cellulose and polymer primary dressing (non-adherent) 
*Curea P2 dressing* (Charles S. Bullen Stomacare Ltd) 10cm × 20cm rectangular= £4.53, 11cm × 11cm square= £2.49, 20cm × 20cm square= £7.88, 20cm × 30cm rectangular= £10.68

**Cutisorb Ultra**
Super absorbent cellulose and polymer primary dressing 
*Cutisorb Ultra dressing* (Bion Medical Ltd) 10cm × 10cm square= £2.13, 10cm × 20cm rectangular= £3.56, 20cm × 20cm square= £6.68, 20cm × 30cm rectangular= £10.06

**DryMax Extra**
Super absorbent cellulose and polymer primary dressing 
*DryMax Extra Soft dressing* (Essure Healthcare Ltd) 10cm × 10cm square= £0.87, 10cm × 20cm rectangular= £1.04, 20cm × 20cm square= £1.84, 20cm × 30cm rectangular= £2.33

**ELECT Superabsorber**
Super absorbent cellulose and polymer primary dressing

**Zetuvit Plus**
Super absorbent cellulose primary dressing 
*Zetuvit Plus dressing* (Paul Hartmann Ltd) 10cm × 10cm= £0.83, 10cm × 20cm= £1.15, 15cm × 20cm= £1.32, 20cm × 25cm= £1.80, 20cm × 40cm= £2.79

**Super absorbent hydroconductive dressing**

**Drawtex**
Super absorbent hydroconductive dressing with absorbent, cross-action structures of viscose, polyester and cotton

**Drawtex dressing** (Martindale Pharmaceuticals Ltd) 10cm × 1.3m= £16.00, 10cm × 10cm= £2.24, 10cm × 1m= £16.00, 15cm × 20cm= £6.00, 20cm × 1m= £25.00, 20cm × 20cm= £6.98, 5cm × 5cm= £0.95, 7.5cm × 1m= £13.50, 7.5cm × 7.5cm= £1.77

**Advanced wound dressings**
Advanced wound dressings can be used for both acute and chronic wounds. Categories for dressings in this section start with the least absorptive, moisture-donating hydrogel dressings, followed by increasingly more absorptive dressings. These dressings are classified according to their primary component; some dressings are comprised of several components.

**Hydrogel dressings**
Hydrogel dressings are most commonly supplied as an amorphous, cohesive topical application that can take up the shape of a wound. A secondary, non-absorbent dressing is needed. These dressings are generally used to donate liquid to dry sloughy wounds and facilitate autolytic debridement of necrotic tissue; some also have the ability to absorb very small amounts of exudate. Hydrogel products that do not contain propylene glycol should be used if the wound is to be treated with laser therapy. Hydrogel sheets have a fixed structure and limited fluid-handling capacity; hydrogel sheet dressings are best avoided in the presence of infection, and are unsuitable for heavily exuding wounds.

**Hydrogel application (amorphous)**

**ActiHeal Hydrogel**
Hydrogel containing guar gum and propylene glycol

**ActiHeal (Advanced Medical Solutions Ltd)** Hydrogel dressing= £1.41

**Aquaform**
Hydrogel containing modified starch copolymer

**Aquaform (Aspan Medical Europe Ltd)** Hydrogel dressing= £2.04

**Askina Gel**
Hydrogel containing modified starch and glycerol

**Askina (B.Braun Medical Ltd)** Gel dressing= £2.06

**Cutimed**
Hydrogel

**Cutimed (BSN medical Ltd)** Gel dressing= £3.10

**Flexigran**
Hydrogel containing modified starch and glycerol

**Flexigran (A1 Pharmaceuticals) Gel dressing= £1.90**

**granuGel**
Hydrogel containing carboxymethylcellulose, pectin and propylene glycol

**granuGel (Convatec Ltd) Hydrocolloid Gel dressing= £2.39**

**Intrasite Gel**
Hydrogel containing modified carmellose polymer and propylene glycol

**Intrasite (Smith & Nephew Healthcare Ltd) Gel dressing= £3.68**

**Nu-Gel**
Hydrogel containing alginate and propylene glycol

**Nu-Gel (Syagenex Wound Management Ltd) dressing= £2.11**

**Purilon Gel**
Hydrogel containing carboxymethylcellulose and calcium alginate

**Purilon (Coloplast Ltd) Gel dressing= £2.33**

**Hydrogel sheet dressings**

**ActiFormCool**
Hydrogel dressing

**ActiFormCool sheet (L&R Medical UK Ltd) 10cm × 10cm square= £2.71, 10cm × 15cm rectangular= £3.89, 20cm × 20cm square= £8.14, 5cm × 6.5cm rectangular= £1.84**

**Aquafo**
Hydrogel dressing

**Aquafo (Covidien (UK) Commercial ltd) sheet 7.5cm discs= £2.60**

**Coolie**
Hydrogel dressing (without adhesive border)

**Coolie (Zeroderma Ltd) sheet 7cm discs= £1.96**

**Gel FX**
Hydrogel dressing (without adhesive border)

**Gel FX sheet (Synergy Health (UK) Ltd) 10cm × 10cm square= £1.60, 15cm × 15cm square= £3.20**

**Geliperm**
Hydrogel sheets

**Geliperm (Geistlich 500 Ltd) sheet 10cm × 10cm square= £2.53**

**Hydrosorb**
Absorbent, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film

**Hydrosorb sheet (Paul Hartmann Ltd) 10cm × 10cm square= £2.29, 20cm × 20cm square= £6.87, 5cm × 7.5cm rectangular= £1.60**

**Hydrosorb Comfort**
Absorbent, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film (with adhesive border, waterproof)

**Hydrosorb Comfort sheet (Paul Hartmann Ltd) 12.5cm × 12.5cm square= £3.66, 4.5cm × 6.5cm rectangular= £1.90, 7.5cm × 10cm rectangular= £2.52**

**Intrasite Conformable**
Soft non-woven dressing impregnated with Intrasite® gel

**Intrasite Conformable dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square= £1.85, 10cm × 20cm rectangular= £2.50, 10cm × 40cm rectangular= £4.47**

**Novogel**
Glycerol-based hydrogel sheets (standard or thin)

**Novogel sheet (Ford Medical Associates Ltd) 10cm × 10cm square= £3.18, 15cm × 20cm rectangular= £6.07, 20cm × 40cm rectangular= £11.56, 30cm × 30cm (0.15cm thickness) square= £12.71, (0.30cm thickness) square= £13.47, 5cm × 7.5cm rectangular= £1.99, 7.5cm diameter circular= £2.92**

**SanoSkin NET**
Hydrogel sheet (without adhesive border)

**SanoSkin (Ideal Medical Solutions Ltd) NET sheet 8.5cm × 12cm rectangular= £2.28**

**VacuNet**
Non-adherent, hydrogel coated polyester net dressing
Vapour-permeable films and membranes

VacuNet dressing (Proteus Healthcare Ltd) 10cm × 10cm square = £1.93, 10cm × 15cm rectangular = £2.86

Sodium hyaluronate dressings

The hydrating properties of sodium hyaluronate promote wound healing, and dressings can be applied directly to the wound, or to a primary dressing (a secondary dressing should also be applied). The iodine and potassium iodide in these dressings prevent the bacterial decay of sodium hyaluronate in the wound. Hydrolane® should be used with caution in thyroid disorders.

Hydrolane
Sodium hyaluronate 1.5%, potassium iodide 0.15%, iodine 0.1%, in a viscous solution

Vapour-permeable films and membranes

Vapour-permeable films and membranes allow the passage of water vapour and oxygen but are impermeable to water and micro-organisms, and are suitable for lightly exuding wounds. They are highly conformable, provide protection, and a moist healing environment; transparent film dressings permit constant observation of the wound. Water vapour loss can occur at a slower rate than exudate is generated, so that fluid accumulates under the dressing, which can lead to tissue maceration and to wrinkling at the adhesive contact site (with risk of bacterial entry). Newer versions of these dressings have increased moisture vapour permeability. Despite these advances, vapour-permeable films and membranes are unsuitable for infected, large heavily exuding wounds, and chronic leg ulcers. Vapour-permeable films and membranes are suitable for partial-thickness wounds with minimal exudate, or wounds with eschar. Most commonly, they are used as a secondary dressing over alginites or hydrogels; film dressings can also be used to protect the fragile skin of patients at risk of developing minor skin damage caused by friction or pressure.

Non-woven fabric dressing with viscose-rayon pad.

Niko Fix
For intravenous and subcutaneous catheter sites

Niko (Unomedical Ltd) Fix dressing 7cm × 8.5cm = £0.20

Vapour-permeable Adhesive Film Dressing (Semi-permeable Adhesive Dressing)
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

Askina Derm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Askina Derm dressing (B.Braun Medical Ltd) 10cm × 12cm = £1.11, 10cm × 20cm = £2.12, 15cm × 20cm = £2.57, 20cm × 30cm = £4.59, 6cm × 7cm = £0.38

C-View
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

C-View dressing (Aspen Medical Europe Ltd) 10cm × 12cm = £1.03, 12cm × 12cm = £1.10, 15cm × 20cm = £2.38, 6cm × 7cm = £0.38

Dressfilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Dressfilm (St Georges Medical Ltd) dressing 15cm × 20cm = £1.90

Hydrofilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Hydrofilm dressing (Paul Hartmann Ltd) 10cm × 12.5cm = £0.43, 10cm × 15cm = £0.54, 10cm × 25cm = £0.83, 12cm × 25cm = £0.88, 15cm × 20cm = £0.99, 20cm × 30cm = £1.63, 6cm × 7cm = £0.23

Hypafix Transparent
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Leukomed T
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Leukomed T dressing (BSN medical Ltd) 10cm × 12.5cm = £1.05, 11cm × 14cm = £1.27, 15cm × 20cm = £2.44, 15cm × 25cm = £2.60, 7.2cm × 5cm = £0.39, 8cm × 10cm = £0.72

Mepitel Film
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Mepitel Film dressing (Mölnlycke Health Care Ltd) 10.5cm × 12cm = £1.32, 10.5cm × 25cm = £2.57, 15.5cm × 20cm = £3.26, 6.5cm × 7cm = £0.49

Mepore Film
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Mepore Film dressing (Smith & Nephew Healthcare Ltd) 10cm × 1m = £6.78, 5cm × 1m = £4.02

OpSite Flexigrid
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

OpSite Flexigrid dressing (Smith & Nephew Healthcare Ltd) 12cm × 12cm = £1.16, 15cm × 20cm = £2.93, 6cm × 7cm = £0.41

Polyskin II
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Kendall Film dressing (H & R Healthcare Ltd) 10cm × 12cm = £1.03, 10cm × 20cm = £2.04, 15cm × 20cm = £2.35, 20cm × 25cm = £4.11, 4cm × 4cm = £0.36, 6cm × 7cm = £0.40

ProtectFilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

ProtectFilm dressing (Wallace, Cameron & Company Ltd) 10cm × 12cm = £0.20, 15cm × 20cm = £0.40, 6cm × 7cm = £0.11

Suprasorb F
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Suprasorb F dressing (Lohmann & Rauscher) 10cm × 12cm = £0.83, 15cm × 20cm = £2.58, 5cm × 7cm = £0.34

Tegaderm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Tegaderm Film dressing (3M Health Care Ltd) 12cm × 12cm = £1.11, 15cm × 20cm = £2.41, 6cm × 7cm = £0.39

Tegaderm diamond
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Tegaderm Diamond dressing (3M Health Care Ltd) 10cm × 12cm = £1.21, 6cm × 7cm = £0.45
Vellafilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces
Vellafilm dressing (Advancis Medical) 12cm × 12cm = £1.11, 12cm × 35cm = £2.77, 15cm × 20cm = £2.12

Vapour-permeable Adhesive Film Dressing with absorbent pad
Adpore Ultra
Film dressing with absorbent pad
Adpore Ultra dressing (Medicareus International Ltd) 10cm × 10cm = £0.14, 10cm × 15cm = £0.22, 10cm × 20cm = £0.33, 10cm × 25cm = £0.35, 10cm × 30cm = £0.52, 7cm × 8cm = £0.12

Vapour-permeable Adhesive Film Dressing with absorbent pad
Alldress
Film dressing with absorbent pad
Alldress dressing (Molyncke Health Care Ltd) 10cm × 10cm = £0.97, 15cm × 15cm = £2.11, 15cm × 20cm = £2.61

C-View Post-Op
Film dressing with absorbent pad
C-View Post-Op dressing (Aspen Medical Europe Ltd) 10cm × 12cm = £1.11, 10cm × 25cm = £1.61, 10cm × 35cm = £2.62, 6cm × 7cm = £0.40

Clearpore
Film dressing with absorbent pad
Clearpore dressing (Richards Healthcare Ltd) 10cm × 10cm = £0.20, 10cm × 15cm = £0.24, 10cm × 20cm = £0.36, 10cm × 25cm = £0.40, 10cm × 30cm = £0.65, 6cm × 10cm = £0.15, 6cm × 7cm = £0.12

Hydrofilm Plus
Film dressing with absorbent pad
Hydrofilm Plus dressing (Paul Hartmann Ltd) 10cm × 20cm = £0.47, 10cm × 25cm = £0.61, 10cm × 30cm = £0.70, 7.2cm × 5cm = £0.18, 9cm × 10cm = £0.28, 9cm × 15cm = £0.31

Leukomed T Plus
Film dressing with absorbent pad
Leukomed T Plus dressing (BSN medical Ltd) 10cm × 20cm = £1.38, 10cm × 25cm = £1.55, 10cm × 30cm = £2.60, 10cm × 35cm = £3.16, 7.2cm × 5cm = £0.28, 8cm × 10cm = £0.55, 8cm × 15cm = £0.83

Mepore Film & Pad
Film dressing with absorbent pad
Mepore Film & Pad dressing (Molyncke Health Care Ltd) 4cm × 5cm = £0.24, 5cm × 7cm = £0.25, 9cm × 10cm = £0.63, 9cm × 15cm = £0.92, 9cm × 20cm = £1.37, 9cm × 25cm = £1.51, 9cm × 30cm = £2.03, 9cm × 35cm = £2.52

Mepore Ultra
Film dressing with absorbent pad
Mepore Ultra dressing (Molyncke Health Care Ltd) 10cm × 11cm = £0.81, 11cm × 15cm = £1.19, 7cm × 8cm = £0.41, 9cm × 20cm = £1.52, 9cm × 25cm = £1.68, 9cm × 30cm = £2.77

OpSite Plus
Film dressing with absorbent pad
OpSite Plus dressing (Smith & Nephew Healthcare Ltd) 10cm × 12cm = £1.23, 10cm × 20cm = £2.07, 10cm × 35cm = £3.43, 6.5cm × 5cm = £0.33, 8.5cm × 9.5cm = £0.91

OpSite Post-op
Film dressing with absorbent pad
OpSite Post-op dressing (Smith & Nephew Healthcare Ltd) 10cm × 12cm = £1.21, 10cm × 20cm = £2.03, 10cm × 25cm = £2.56, 10cm × 30cm = £3.03, 10cm × 35cm = £3.37, 8.5cm × 15.5cm = £1.23, 8.5cm × 9.5cm = £0.89

Pharmapore-PU
Film dressing with absorbent pad
Pharmapore-PU dressing (Wallace, Cameron & Company Ltd) 10cm × 25cm = £0.38, 10cm × 30cm = £0.58, 8.5cm × 15.5cm = £0.20

PremierPore VP
Film dressing with absorbent pad
PremierPore VP dressing (Shermond) 10cm × 10cm = £0.16, 10cm × 15cm = £0.24, 10cm × 20cm = £0.36, 10cm × 25cm = £0.38, 10cm × 30cm = £0.57, 10cm × 35cm = £0.70, 5cm × 7cm = £0.13

Tegaderm
Film dressing with absorbent pad
Tegaderm + Pad dressing (3M Health Care Ltd) 5cm × 7cm = £0.26, 9cm × 10cm = £0.65, 9cm × 15cm = £0.96, 9cm × 20cm = £1.41, 9cm × 25cm = £1.58, 9cm × 35cm = £2.62

Tegaderm Absorbent Clear
Film dressing with clear acrylic polymer oval-shaped pad or rectangular-shaped pad
Tegaderm Absorbent Clear Acrylic dressing (3M Health Care Ltd) 11.1cm × 12.7cm oval = £4.14, 14.2cm × 15.8cm oval = £5.83, 14.9cm × 15.2cm rectangular = £8.73, 16.8cm × 19cm sacral = £10.45, 20cm × 20.3cm rectangular = £14.02, 7.6cm × 9.5cm oval = £3.20

Vapour-permeable transparent film dressing with adhesive foam border.

Central Gard
For intravenous and subcutaneous catheter sites
Central Gard dressing (Unomedical Ltd) 16cm × 7cm = £0.98, 16cm × 8.8cm = £1.07

East-V
For intravenous and subcutaneous catheter sites
East-V (Convatec Ltd) dressing 7cm × 7.5cm = £0.38

Vapour-permeable transparent, adhesive film dressing.

Hydrofilm I.V. Control
For intravenous and subcutaneous catheter sites
Hydrofilm (Paul Hartmann Ltd) I.V. Control dressing 7cm × 9cm = £0.31

Vapour-permeable, transparent, adhesive film dressing.

IV3000
For intravenous and subcutaneous catheter sites
IV3000 dressing (Smith & Nephew Healthcare Ltd) 10cm × 12cm = £1.44, 5cm × 6cm = £0.43, 6cm × 7cm = £0.57, 7cm × 9cm = £0.75, 9cm × 12cm = £1.49

Mepore IV
For intravenous and subcutaneous catheter sites
Mepore IV dressing (Molyncke Health Care Ltd) 10cm × 11cm = £1.09, 5cm × 5.5cm = £0.31, 8cm × 9cm = £0.40

Pharmapore-PU IV
For intravenous and subcutaneous catheter sites
Pharmapore-PU IV dressing (Wallace, Cameron & Company Ltd) 6cm × 7cm = £0.08, 7cm × 8.5cm = £0.07, 7cm × 9cm = £0.17

Tegaderm IV
For intravenous and subcutaneous catheter sites
Tegaderm IV Advanced dressing with securing tapes (3M Health Care Ltd) 10cm × 15.5cm = £1.67, 7cm × 8.5cm = £0.59

Soft polymer dressings
Dressings with soft polymer, often a soft silicone polymer, in a non-adherent or gently adherent layer are suitable for use on lightly to moderately exuding wounds. For moderately to heavily exuding wounds, an absorbent secondary dressing can be added, or a soft polymer dressing with an absorbent pad can be used. Wound contact dressings coated with soft silicone have gentle adhesive properties and can be used on fragile skin areas or where it is beneficial to reduce the frequency of primary dressing changes. Soft polymer dressings should not be used on heavily bleeding wounds; blood clots can cause the dressing to adhere to the wound surface. For silicone keloid dressings see under Specialised dressings.

Cellulose dressings
Sorbion Sachet Border
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope, with adhesive border
Cutimed Sorbion Sachet Border dressing (BSN medical Ltd) 10cm × 10cm square = £3.03, 15cm × 15cm square = £4.61, 25cm × 15cm rectangular = £7.18

Sorbion Sachet EXTRA
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
Cutimed Sorbion Sachet Extra dressing (BSN medical Ltd) 10cm × 10cm= £2.31, 20cm × 20cm= £3.83, 20cm × 20cm= £7.19, 30cm × 20cm= £10.26, 5cm × 5cm= £1.49, 7.5cm × 7.5cm= £1.83

Sorbion Sachet Multi Star
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
Cutimed Sorbion Sachet Multi Star dressing (BSN medical Ltd) 14cm × 14cm= £5.02, 8cm × 8cm= £3.07

Sorbion Sachet S Drainage
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope (‘V’ shaped dressing)
Cutimed (BSN medical Ltd) Sorbion Sachet S drainage dressing 10cm × 10cm= £2.71

Suprasorb X
Biosynthetic cellulose fibre dressing
Suprasorb X dressing (Lohmann & Rauscher) 14cm × 20cm rectangular= £8.67, 2cm × 21cm rope= £6.74, 5cm × 5cm square= £2.10, 9cm × 9cm square= £4.38

With absorbent pad
Advazorb Border
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border dressing (Advacnis Medical) 10cm × 10cm= £2.12, 10cm × 20cm= £2.92, 20cm × 20cm= £4.28, 12.5cm × 12.5cm= £2.60, 15cm × 15cm= £3.17, 20cm × 20cm= £5.50, 7.5cm × 7.5cm= £1.20

Advazorb Border Lite
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border Lite dressing (Advacnis Medical) 10cm × 10cm= £1.90, 10cm × 20cm= £2.63, 10cm × 30cm= £3.86, 12.5cm × 12.5cm= £2.34, 15cm × 15cm= £2.86, 20cm × 20cm= £4.35, 7.5cm × 7.5cm= £1.08

Advazorb Siflix
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Siflix dressing (Advacnis Medical) 10cm × 10cm= £1.86, 10cm × 20cm= £3.20, 12.5cm × 12.5cm= £2.61, 15cm × 15cm= £5.38, 20cm × 20cm= £5.02, 7.5cm × 7.5cm= £1.00

Advazorb Siflix Lite
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Siflix Lite dressing (Advacnis Medical) 10cm × 10cm= £1.68, 10cm × 20cm= £2.88, 12.5cm × 12.5cm= £2.35, 15cm × 15cm= £3.04, 20cm × 20cm= £4.51, 7.5cm × 7.5cm= £0.90

Allevyn Gentle
Soft gel wound contact dressing with polyurethane foam film backing
Allevyn Gentle dressing (Smith & Nephew Healthcare Ltd) Heel dressing 23cm × 23.2cm= £9.90, dressing 10cm × 10cm= £2.25, 12.5cm × 12.5cm= £2.75, 17.5cm × 17.5cm= £5.43, 7.5cm × 7.5cm= £1.53

Allevyn Gentle Border
Silicone gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border dressing (Smith & Nephew Healthcare Ltd) Heel dressing 23cm × 23.2cm= £9.90, dressing 10cm × 10cm= £2.25, 12.5cm × 12.5cm= £2.75, 17.5cm × 17.5cm= £5.43, 7.5cm × 7.5cm= £1.53

Allevyn Gentle Border Lite
Silicone gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border Lite dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm= £2.22, 15cm × 15cm= £3.91, 5.5cm × 12cm= £1.90, 5cm × 5cm= £0.92, 8cm × 15cm= £3.52

Allevyn Life
Silicone wound contact dressing, with central mesh screen, polyurethane foam film backing and adhesive border
Allevyn Life dressing (Smith & Nephew Healthcare Ltd) 10.3cm × 10.3cm= £1.74, 12.9cm × 12.9cm= £2.55, 15.4cm × 15.4cm= £3.12, 21cm × 21cm= £6.14

Cutimed Siltec
Soft silicone wound contact dressing, with polyurethane foam film backing
Cutimed Siltec (BSN medical Ltd) Sacrum dressing 17.5cm × 17.5cm= £4.58, 23cm × 23cm= £6.25, dressing 10cm × 10cm= £2.28, 10cm × 20cm= £3.76, 15cm × 15cm= £4.25, 20cm × 20cm= £6.45, 5cm × 5cm= £1.22

Cutimed Siltec B
Soft silicone wound contact dressing, with polyurethane foam film backing, with adhesive border, for lightly to moderately exuding wounds
Cutimed Siltec B dressing (BSN medical Ltd) 12.5cm × 12.5cm= £2.32, 15cm × 15cm= £3.09, 17.5cm × 17.5cm= £4.99, 22.5cm × 22.5cm= £6.09, 7.5cm × 7.5cm= £1.36

Cutimed Siltec L
Soft silicone wound contact dressing, with polyurethane foam film backing, for lightly to moderately exuding wounds
Cutimed Siltec L dressing (BSN medical Ltd) 10cm × 10cm= £1.58, 15cm × 15cm= £3.48, 5cm × 5cm= £1.08

Eclipse Adherent
Soft silicone wound contact layer with absorbent pad and film backing
Eclipse Adherent dressing (Advacnis Medical) 10cm × 10cm= £3.01, 10cm × 20cm= £3.78, 15cm × 15cm= £5.03, 20cm × 30cm= £10.06, 17cm × 19cm sacral= £3.79, 22cm × 23cm sacral= £6.28

Flivasarb
Absorbent polymer dressing with non-adherent wound contact layer
Flivasarb Adhesive
Absorbent polymer dressing with non-adherent wound contact layer and adhesive border
Flivasarb Adhesive dressing (Lohmann & Rauscher) 12cm × 12cm square= £3.43, 15cm × 15cm square= £4.70

Mepilex
Absorbent soft silicone dressing with polyurethane foam film backing
Mepilex (Molnlycke Health Care Ltd) Heel dressing 13cm × 20cm= £5.50, 15cm × 22cm= £6.38, XT dressing 10cm × 11cm= £2.68, 11cm × 20cm= £4.43, 15cm × 16cm= £4.86, 20cm × 21cm= £7.34, dressing 5cm × 5cm= £1.22

Mepilex Border
Absorbent soft silicone dressing with polyurethane foam film backing and adhesive border
Mepilex Border (Molnlycke Health Care Ltd) Heel dressing 18.5cm × 24cm= £6.63, Sacrum dressing 18cm × 18cm= £4.85, 23cm × 23cm= £7.91, dressing 10cm × 12.5cm= £2.72, 10cm × 20cm= £3.72, 10cm × 30cm= £5.58, 15cm × 17.5cm= £4.18, 17cm × 20cm= £6.07

Mepilex Border Lite
Thin absorbent soft silicone dressing with polyurethane foam film backing and adhesive border
Mepilex Border Lite dressing (Molnlycke Health Care Ltd) 15cm × 15cm= £3.94, 4cm × 5cm= £0.92, 5cm × 12.5cm= £2.01, 7.5cm × 7.5cm= £1.35

Mepilex Lite
Thin absorbent soft silicone dressing with polyurethane foam film backing
Mepilex Lite dressing (Molnlycke Health Care Ltd) 10cm × 10cm= £2.17, 15cm × 15cm= £4.22, 20cm × 50cm= £6.66, 6cm × 8.5cm= £1.82

Mepilex Transfer
Soft silicone exudate transfer dressing
Mepilex Transfer dressing (Molnlycke Health Care Ltd) 10cm × 12cm= £3.54, 15cm × 20cm= £10.72, 20cm × 50cm= £21.39, 7.5cm × 8.5cm= £2.25

Sorbion Sana
Non-adherent polyethylene wound contact dressing with absorbent core
Cutimed Sorbion Sana Gentle dressing (BSN medical Ltd) 12cm × 12cm= £2.56, 12cm × 22cm= £4.61, 22cm × 22cm= £8.21, 8.5cm × 8.5cm= £2.04

Urgotul Duo
Non-adherent soft polymer wound contact dressing with absorbent pad
Urgotul Duo dressing (Urgo Ltd) 10cm × 12cm= £3.93, 15cm × 20cm= £9.13, 5cm × 10cm= £2.54
Without absorbent pad

Adaptic Touch
Non-adherent soft silicone wound contact dressing

Adaptic Touch dressing (Sysmec Wound Management Ltd) 12cm × 15cm = £4.65, 20cm × 32cm = £12.50, 5cm × 7.6cm = £1.13, 7.6cm × 11cm = £2.25

Askin SilNet
Soft silicone-coated wound contact dressing

Askin SilNet dressing (Braun Medical Ltd) 10cm × 18cm = £5.12, 20cm × 30cm = £12.53, 5cm × 7.5cm = £1.16, 7.5cm × 10cm = £2.35

Mepitel
Soft silicone, semi-transparent wound contact dressing

Mepitel dressing (Molnlycke Health Care Ltd) 12cm × 15cm = £5.65, 5cm × 7cm = £1.41, 8cm × 10cm = £2.82

Mepitel One
Soft silicone, thin, transparent wound contact dressing

Mepitel One dressing (Molnlycke Health Care Ltd) 13cm × 15cm = £4.98, 24cm × 27.5cm = £14.25, 6cm × 7cm = £1.22, 9cm × 10cm = £2.41

Physioteulle
Non-adherent soft polymer wound contact dressing

Physioteulle dressing (Coloplast Ltd) 10cm × 10cm = £2.32, 15cm × 20cm = £7.07

Silflex
Soft silicone-coated polyester wound contact dressing

Silflex dressing (Advancis Medical) 12cm × 15cm = £4.61, 20cm × 30cm = £11.88, 35cm × 60cm = £19.83, 5cm × 7cm = £1.12, 8cm × 10cm = £2.29

Silon-TSR
Soft silicone polymer wound contact dressing

Silon-TSR dressing (Bio Med Sciences) 13cm × 13cm = £3.52, 13cm × 25cm = £7.79, 28cm × 30cm = £7.37

Sorbion Contact
Non-adherent soft polymer wound contact dressing

Cutimed Sorbion Contact dressing (BSN medical Ltd) 10cm × 10cm = £2.04, 10cm × 20cm = £4.10, 20cm × 20cm = £7.18, 20cm × 30cm = £10.26, 7.5cm × 7.5cm = £1.53

Tegaderm Contact
Non-adherent soft polymer wound contact dressing

Tegaderm Contact dressing (3M Health Care Ltd) 20cm × 25cm = £10.94, 7.5cm × 10cm = £2.29

Urgotul
Non-adherent soft polymer wound contact dressing

Urgotul dressing (Urgo Ltd) 10cm × 10cm = £3.13, 10cm × 40cm = £10.53, 18cm × 15cm = £6.66, 15cm × 20cm = £8.86, 20cm × 30cm = £14.25, 5cm × 5cm = £1.57

Hydrocolloid dressings
Hydrocolloid dressings are usually presented as a hydrocolloid layer on a vapour-permeable film or foam pad. Semi-permeable to water vapour and oxygen, these dressings form a gel in the presence of exudate to facilitate rehydration in lightly to moderately exuding wounds and promote autolytic debridement of dry, sloughy, or necrotic wounds: they are also suitable for promoting granulation. Hydrocolloid-fibre dressings made from modified carmellose fibres resemble alginate dressings; hydrocolloid-fibre dressings are more absorptive and suitable for moderately to heavily exuding wounds.

Hydrocolloid-fibre dressings

Aquacel
Soft non-woven pad containing hydrocolloid-fibres

Aquacel (Convatec Ltd) Ribbons dressing 1cm × 45cm = £1.89, 2cm × 45cm = £2.52, dressing 10cm × 10cm square = £2.49, 15cm × 15cm square = £4.68, 4cm × 10cm rectangular = £1.34, 4cm × 20cm rectangular = £1.97, 4cm × 30cm rectangular = £2.97, 5cm × 5cm square = £1.05

Aquacel Foam
Soft non-woven pad containing hydrocolloid-fibres with foam layer; with or without adhesive border

Aquacel Foam dressing (adhesive) (Convatec Ltd) 10cm × 10cm = £2.20, 12.5cm × 12.5cm = £2.72, 17.5cm × 17.5cm = £5.45, 19.8cm × 14cm heel = £5.57, 20cm × 16.9cm sacral = £5.00, 21cm × 21cm = £7.97, 25cm × 30cm = £10.32, 3cm × 8cm = £1.44, (non-adhesive) 10cm × 10cm = £2.60, 15cm × 15cm = £4.37, 15cm × 20cm = £5.97, 20cm × 20cm = £7.12

UrgoClean Pad
Pad, hydrocolloid fibres coated with soft-adherent lipocolloid wound contact layer

UrgoClean Pad dressing (Urgo Ltd) 10cm × 10cm square = £2.16, 20cm × 15cm rectangular = £4.06, 6cm × 6cm square = £0.97

UrgoClean Rope
Rope, non-woven rope containing hydrocolloid fibres

UrgoClean rope dressing (Urgo Ltd) 2.5cm × 40cm = £2.43, 5cm × 40cm = £3.21

Polyurethane matrix dressing

Cutinova Hydro
Polyurethane matrix with absorbent particles and waterproof polyurethane film

Cutinova Hydro dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square = £2.61, 15cm × 20cm rectangular = £5.53, 5cm × 6cm rectangular = £1.30

With adhesive border

Biatain Super
Semi-permeable hydrocolloid dressing; without adhesive border

Biatain Super dressing (adhesive) (Coloplast Ltd) 10cm × 10cm square = £2.21, 12.5cm × 12.5cm square = £3.66, 12cm × 20cm rectangular = £3.67, 15cm × 15cm square = £4.41, 20cm × 20cm square = £6.87

Granuflex Border
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethane film

Granuflex Border Dressing (Convatec Ltd) 10cm × 10cm square = £3.42, 10cm × 13cm triangular = £4.04, 15cm × 15cm square = £6.53, 15cm × 18cm triangular = £6.29, 6cm × 6cm square = £1.81

Hydrocoll Border
Hydrocolloid dressing with adhesive border and absorbent wound contact pad

Hydrocoll Border (bevelled edge) dressing (Paul Hartmann Ltd) 10cm × 10cm square = £2.46, 12cm × 18cm sacral = £3.69, 15cm × 15cm square = £4.63, 5cm × 5cm square = £1.03, 7.5cm × 7.5cm square = £1.69, 8cm × 12cm concave = £2.17

Tegaderm Hydrocolloid
Hydrocolloid dressing with adhesive border; normal or thin

Tegaderm Hydrocolloid (3M Health Care Ltd) Thin dressing 10cm × 12cm oval = £1.56, 13cm × 15cm oval = £2.92, dressing 10cm × 12cm oval = £2.34, 13cm × 15cm oval = £4.37, 17.1cm × 16.1cm sacral = £4.89

Ulltec Pro
Semi-permeable hydrocolloid dressing with adhesive border

Ulltec Pro dressing (adhesive) (Convalon (UK) Commercial Ltd) 15cm × 18cm sacral = £3.30, 19.5cm × 23cm sacral = £4.98, 21cm × 21cm square = £4.67

Without adhesive border

ActiveVeal Hydrocolloid
Semi-permeable polyurethane film backing, hydrocolloid wound contact layer, with or without polyurethane foam later

ActiveVeal Hydrocolloid (Advanced Medical Solutions Ltd) dressing 10cm × 10cm square = £1.58, 15cm × 15cm square = £3.43, 15cm × 18cm sacral = £3.98, 5cm × 7.5cm rectangular = £0.78, foam backed dressing 10cm × 10cm square = £1.55, 15cm × 15cm square = £2.91, 15cm × 18cm sacral = £3.36, 5cm × 7.5cm rectangular = £0.97

Askin Biofilm Transparent
Semi-permeable, polyurethane film dressing with hydrocolloid adhesive

Askin Biofilm Transparent dressing (Braun Medical Ltd) 10cm × 10cm square = £1.10, 20cm × 20cm square = £3.25
Foam dressings

**Biatain Super**
Semi-permeable, hydrocolloid film dressing without adhesive border

**Biatain Super dressing (non-adhesive)** (Coloplast Ltd) 10cm x 10cm square = £2.21, 12.5cm x 12.5cm square = £3.66, 15cm x 20cm rectangular = £3.67, 15cm x 15cm square = £4.41, 20cm x 20cm square = £6.87

**Comfeel Plus Contour**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Contour dressing** (Coloplast Ltd) 6cm x 8cm = £2.27, 9cm x 11cm = £3.93

**Comfeel Plus Pressure Relieving**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Pressure Relief dressing** (Coloplast Ltd) 10cm diameter circular = £4.74, 15cm diameter circular = £7.14, 7cm diameter circular = £3.94

**Comfeel Plus Transparent**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Transparent dressing** (Coloplast Ltd) 10cm x 10cm square = £1.31, 15cm x 15cm square = £3.41, 15cm x 20cm rectangular = £3.46, 20cm x 20cm square = £3.48, 5cm x 15cm rectangular = £1.62, 5cm x 25cm rectangular = £2.63, 5cm x 7cm rectangular = £0.68, 9cm x 14cm rectangular = £2.49, 9cm x 25cm rectangular = £3.53

**Comfeel Plus Ulcer**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Dressing** (Coloplast Ltd) 10cm x 10cm square = £2.50, 20cm x 25cm square = £7.72, 4cm x 6cm rectangular = £0.98

**Duoderm Extra Thin**
Semi-permeable hydrocolloid dressing

**Duoderm Extra Thin dressing** (Convatec Ltd) 10cm x 10cm square = £1.36, 15cm x 15cm square = £2.93, 5cm x 10cm rectangular = £0.78, 7.5cm x 7.5cm square = £0.82, 9cm x 15cm rectangular = £1.81, 5cm x 25cm rectangular = £2.98, 9cm x 35cm rectangular = £4.05

**Duoderm Signal**
Semi-permeable hydrocolloid dressing with ‘Time to change’ indicator

**Duoderm Signal dressing** (Convatec Ltd) 10cm x 10cm square = £2.17, 11cm x 19cm oval = £3.33, 14cm x 14cm square = £3.81, 18.5cm x 19.5cm heel = £5.33, 20cm x 20cm square = £7.58, 22.5cm x 20cm sacral = £6.23

**Flexigran**
Semi-permeable hydrocolloid dressing without adhesive border; normal or thin

**Flexigran (A1 Pharmaceuticals)** Thin dressing 10cm x 10cm square = £1.08, dressing 10cm x 10cm square = £2.19

**Granuflex**
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethane film

**Granuflex (modified) dressing** (Convatec Ltd) 10cm x 10cm square = £2.87, 15cm x 15cm square = £5.45, 15cm x 20cm rectangular = £5.90, 20cm x 20cm square = £8.20

**Hydrocol Basic**
Hydrocolloid dressing with absorbent wound contact pad

**Hydrocoll (Paul Hartmann Ltd)** Basic dressing 10cm x 10cm square = £2.50

**Hydrocoll Thin Film**
Thin hydrocolloid dressing with absorbent wound contact pad

**Hydrocoll Thin Film dressing** (Paul Hartmann Ltd) 10cm x 10cm square = £1.18, 15cm x 15cm square = £2.65, 7.5cm x 7.5cm square = £0.71

**Nu-Derm**
Semi-permeable hydrocolloid dressing (normal and thin)

**Nu-Derm dressing** (Syagenics Wound Management Ltd) 10cm x 10cm square = £1.57, 15cm x 15cm square = £3.21, 15cm x 18cm square = £4.49, 20cm x 20cm square = £6.41, 5cm x 5cm square = £0.86, 8cm x 12cm heel/elbow = £3.21, thin 10cm x 10cm square = £1.07

**Tegaderm Hydrocolloid**
Hydrocolloid dressing without adhesive border; normal and thin

**Tegaderm Hydrocolloid** (3M Health Care Ltd) Thin dressing 10cm x 10cm square = £1.57, dressing 10cm x 10cm square = £2.39

**Ultec Pro**
Semi-permeable hydrocolloid dressing; without adhesive border

**Ultec Pro dressing** (Covidien (UK) Commercial Ltd) 10cm x 10cm square = £2.28, 15cm x 15cm square = £4.44, 20cm x 20cm square = £6.69

**Foam dressings**
Dressings containing hydrophilic polyurethane foam (adhesive or non-adhesive), with or without plastic film-backing, are suitable for all types of exuding wounds, but not for dry wounds; some foam dressings have a moisture-sensitive film backing with variable permeability dependent on the level of exudate. Foam dressings vary in their ability to absorb exudate; some are suitable only for lightly to moderately exuding wounds, others have greater fluid-handling capacity and are suitable for heavily exuding wounds. Saturated foam dressings can cause maceration of healthy skin if left in contact with the wound. Foam dressings can be used in combination with other primary wound contact dressings. If used under compression bandaging or compression garments, the fluid-handling capacity of the foam dressing may be reduced. Foam dressings can also be used to provide a protective cushion for fragile skin. A foam dressing containing ibuprofen is available and may be useful for treating painful exuding wounds.

**Cavi-Care**
Soft, conforming cavity wound dressing prepared by mixing thoroughly for 15 seconds immediately before use and allowing to expand its volume within the cavity

**Polyurethane Foam Dressing**

**Cutimed Cavity**

**Cutimed Cavity dressing** (BSN medical Ltd) 10cm x 10cm = £3.20, 15cm x 15cm = £4.81, 5cm x 6cm = £1.93

**Kendall**

**Kendall Foam dressing** (H & R Healthcare Ltd) 10cm x 10cm square = £1.06, 10cm x 20cm rectangular = £2.05, 12.5cm x 12.5cm square = £1.80, 15cm x 15cm square = £2.60, 20cm x 20cm square = £3.01, 5cm x 5cm square = £0.71, 7.5cm x 7.5cm square = £1.21, 8.5cm x 7.5cm rectangular (fenestrated) = £0.91

**Polyurethane Foam Film Dressing with Adhesive Border**

**ActivHeal Foam Adhesive**

**ActivHeal Foam Adhesive dressing** (Advanced Medical Solutions Ltd) 10cm x 10cm square = £1.63, 12.5cm x 12.5cm square = £1.68, 15cm x 15cm square = £2.15, 20cm x 20cm square = £4.50, 7.5cm x 7.5cm square = £1.18

**Allevyn Adhesive**

**Allevyn Adhesive dressing** (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £2.24, 12.5cm x 12.5cm square = £2.74, 12.5cm x 22.5cm rectangular = £4.27, 17.5cm x 17.5cm square = £5.41, 17cm x 17cm anatomically shaped sacral = £4.07, 22.5cm x 22.5cm square = £7.88, 22cm x 22cm anatomically shaped sacral = £5.86, 7.5cm x 7.5cm square = £1.53

**Biatain Adhesive**

**Biatain Adhesive dressing** (Coloplast Ltd) 10cm x 10cm square = £1.80, 12.5cm x 12.5cm square = £2.62, 17cm diameter contour = £5.09, 18cm x 18cm square = £5.29, 18cm x 28cm rectangular = £7.84, 19cm x 20cm heel = £5.29, 23cm x 23cm sacral = £4.53

**Biatain Silicone**

**Biatain Silicone dressing** (Coloplast Ltd) 10cm x 10cm = £2.18, 12.5cm x 12.5cm = £2.67, 15cm x 15cm = £3.96, 17.5cm x 17.5cm = £5.26, 7.5cm x 7.5cm = £1.48
### 1600 Advanced wound dressings

#### Kendall Island
**Kendall Foam Island dressing (H & R Healthcare Ltd)**
- 10cm x 10cm square = £1.54, 15cm x 15cm square = £2.90, 20cm x 20cm square = £5.46

**PermaFoam**
**PermaFoam dressing (adhesive)** (Paul Hartmann Ltd)
- 16.5cm x 18cm concave = £4.12, 18cm x 18cm sacral = £3.39, 22cm x 22cm sacral = £3.89

**PermaFoam Comfort**
**PermaFoam Comfort dressing (Paul Hartmann Ltd)**
- 10cm x 20cm rectangular = £3.43, 11cm x 11cm square = £2.17, 15cm x 15cm square = £3.55, 20cm x 20cm square = £5.15, 8cm x 8cm square = £1.14

**PolyMem**
**PolyMem dressing (Aspen Medical Europe Ltd) (adhesive)**
- 5cm x 5cm square = £0.52, 16.5cm x 20.5cm oval = £6.79, 18.4cm x 20cm sacral = £4.56, 5cm x 7.6cm oval = £1.16, 8.8cm x 12.7cm oval = £2.06

**Tegaderm Foam Adhesive**
**Tegaderm Foam dressing (adhesive)** (3M Health Care Ltd)
- 10cm x 11cm oval = £2.39, 13.9cm x 13.9cm circular (heel) = £4.25, 14.3cm x 14.3cm circular = £3.57, 14.3cm x 15.6cm oval = £4.28, 19cm x 22.2cm oval = £7.01, 6.9cm x 6.9cm soft cloth border = £1.72, 6.9cm x 7.6cm oval = £1.47

**Tielle**
**Tielle (Systagenix Wound Management Ltd) Lite dressing (11cm x 11cm square) = £2.30, dressing (15cm x 15cm square) = £3.92, 15cm x 20cm rectangular = £4.90, 18cm x 18cm square = £4.99, 7cm x 9cm rectangular = £1.29

**Tielle Lite**
**Tielle Lite dressing (Systagenix Wound Management Ltd)**
- 11cm x 11cm square = £2.30, dressing 15cm x 15cm square = £3.92, 15cm x 20cm rectangular = £4.90, 18cm x 18cm square = £4.99, 7cm x 9cm rectangular = £1.29

**Biatain -iBu Soft-Hold**
**Biatain-iBu Soft-Hold dressing (Coloplast Ltd)**
- 10cm x 12cm rectangular = £3.40, 10cm x 22.5cm rectangular = £5.34, 15cm x 15cm square = £5.34

**Biatain Non-Adhesive**
**Biatain Non-Adhesive dressing (Coloplast Ltd)**
- 10cm x 10cm square = £2.44, 10cm x 20cm rectangular = £4.03, 15cm x 15cm square = £4.50, 20cm x 20cm square = £6.68, 5cm x 7cm rectangular = £1.34

**Biatain Soft-Hold**
**Biatain Soft-Hold dressing (Coloplast Ltd)**
- 10cm x 10cm square = £2.65, 10cm x 20cm rectangular = £4.03, 15cm x 15cm square = £4.41, 5cm x 7cm rectangular = £1.34

**Kendall Plus**
**Kendall Foam Plus dressing (H & R Healthcare Ltd)**
- 10cm x 10cm square = £1.47, 10cm x 20cm rectangular = £2.69, 15cm x 15cm square = £3.38, 20cm x 20cm square = £4.04, 5cm x 5cm square = £0.82, 7.5cm x 7.5cm square = £1.42, 8.5cm x 7.5cm rectangular (fenestrated) = £1.24

**Kerraheel**
**Kerraheel (Crawford Healthcare Ltd) dressing 12cm x 20cm heel = £4.72

**Lyofoam Max**
**Lyofoam Max dressing (Mohlykke Health Care Ltd)**
- 10cm x 10cm square = £1.15, 10cm x 20cm rectangular = £2.03, 15cm x 15cm square = £2.16, 15cm x 20cm rectangular = £2.73, 20cm x 20cm square = £4.01, 7.5cm x 8.5cm rectangular = £1.10

**PermaFoam**
**PermaFoam (Paul Hartmann Ltd)**
- Cavity dressing 10cm x 10cm = £2.06, dressing (non-adhesive) 10cm x 10cm square = £2.17, 10cm x 20cm rectangular = £3.72, 15cm x 15cm square = £4.12, 20cm x 20cm square = £6.28, 6cm diameter circular = £1.12, 8cm x 8cm square (fenestrated) = £1.28

**PolyMem**
**PolyMem dressing (Aspen Medical Europe Ltd)**
- 7cm x 7cm square = £1.73, 9cm x 9cm square = £2.19, finger/toe size 1 = £2.52, 2 = £2.52, 3 = £2.52

**PolyMem**
**PolyMem dressing (Aspen Medical Europe Ltd)**
- 10cm x 10cm square = £0.98, 10cm x 20cm rectangular = £3.04, 12.5cm x 12.5cm square = £3.37, 12.5cm x 12.5cm square = £4.14, 15cm x 15cm square = £4.90, 20cm x 20cm square = £5.75, 7.5cm x 7.5cm square = £0.79

**Advazorb**
**Advazorb (Advancis Medical) Heel dressing 17cm x 21cm = £4.78, dressing 10cm x 10cm square = £1.09, 10cm x 20cm rectangular = £3.12, 12.5cm x 12.5cm square = £3.12, 12.5cm x 12.5cm square = £3.37, 15cm x 15cm square = £4.14, 15cm x 15cm square = £4.90, 20cm x 20cm square = £5.75, 7.5cm x 7.5cm square = £0.71

**Allevyn Non-Adhesive**
**Allevyn dressing (non-adhesive)** (Smith & Nephew Healthcare Ltd)
- 10.5cm x 13.5cm heel (cup shaped) = £5.24, 10cm x 10cm square = £2.56, 10cm x 20cm rectangular = £4.12, 20cm x 20cm square = £6.88, 5cm x 5cm square = £1.29

**Askina Foam**
**Askina (B.Braun Medical Ltd) Foam Cavity dressing 2.4cm x 40cm = £2.51, Foam dressing 10cm x 10cm square = £2.25, 10cm x 20cm rectangular = £3.55, 20cm x 20cm square = £5.93, Heel dressing 12cm x 20cm = £4.80

**Biatain -iBu Non-Adhesive**
**Biatain-iBu Non-Adhesive dressing (Coloplast Ltd)**
- 10cm x 12cm rectangular = £3.40, 10cm x 22.5cm rectangular = £5.34, 15cm x 15cm square = £5.34, 20cm x 20cm square = £9.09, 5cm x 7cm rectangular = £1.76

**Transorvent**
**Transorvent dressing (adhesive)** (B.Braun Medical Ltd)
- 10cm x 10cm square = £2.02, 15cm x 15cm square = £3.71, 20cm x 20cm square = £5.92, 5cm x 7cm rectangular = £1.07

**UrgoAbsorb dressing (Urgo)**
- 10cm x 10cm = £2.38, 15cm x 15cm = £4.20, 6cm x 6cm = £1.21, 12cm x 19cm heel = £4.80

**Alginate dressings**
Non-woven or fibrous, non-occlusive, alginate dressings, made from calcium alginate, or calcium sodium alginate, derived from brown seaweed, form a soft gel in contact with wound exudate. Alginate dressings are highly absorbent and suitable for use on exuding wounds, and for the promotion of autolytic debridement of debris in very moist wounds. Alginate dressings also act as a haemostatic, but caution is needed because blood clots can cause the dressing to adhere to the wound surface. Alginate dressings should not be used if bleeding is heavy and extreme caution is needed if used for
tumours with friable tissue. Alginate sheets are suitable for use as a wound contact dressing for moderately to heavily exuding wounds and can be layered into deep wounds; alginate rope can be used in sinuses and cavity wounds to improve absorption of exudate and prevent maceration. If the dressing does not have an adhesive border or integral adhesive plastic film backing, a secondary dressing will be required.

**ActivHeal Alginite**
Calcium sodium alginate dressing

**ActivHeal Alginite dressing (Advanced Medical Solutions Ltd)** 10cm x 10cm= £1.15, 10cm x 20cm= £2.83, 5cm x 5cm= £0.59

**ActivHeal Aquafiber**
Non-woven, calcium sodium alginate dressing

**ActivHeal Aquafiber (Advanced Medical Solutions Ltd)** Rope dressing 2cm x 42cm= £1.81, dressing 10cm x 10cm= £1.48, 15cm x 15cm= £2.79, 5cm x 5cm= £0.62

**Alginate M**
Calcium alginate fibre, non-woven dressing

**Alginate M (Smith & Nephew Healthcare Ltd)** Rope dressing 2cm x 20cm= £2.65, dressing 10cm x 10cm= £1.96, 15cm x 20cm= £5.27, 5cm x 5cm= £0.95

**Algosteril**
Calcium alginate dressing

**Algosteril (Smith & Nephew Healthcare Ltd)** Rope dressing 2g= £3.89, dressing 10cm x 10cm= £2.15, 10cm x 20cm= £3.64, 5cm x 5cm= £0.94

**Algipan**
Alginate and carboxymethylcellulose dressing, highly absorbent, gelling dressing

**Algipan (Coloplast Ltd)** 10cm x 10cm= £2.37, 15cm x 15cm= £4.50, 4cm x 4cm= £2.79, 5cm x 5cm= £1.00

**Cutimed Alginate**
Calcium alginate sodium dressing

**Cutimed Alginate dressing (BSN medical Ltd)** 10cm x 10cm= £1.61, 10cm x 20cm= £3.02, 5cm x 5cm= £0.77

**Kaltostat**
Calcium alginate fibre, non-woven dressing

**Kaltostat dressing (Convatec Ltd)** 10cm x 20cm= £4.19, 15cm x 25cm= £7.20, 2g= £3.93, 5cm x 5cm= £0.98, 7.5cm x 12cm= £2.13

**Kendall**
Calcium alginate dressing

**Kendall Calcium Alginate (H & R Healthcare Ltd)** Rope dressing 30cm= £2.89, 61cm= £5.07, 91cm= £5.46, dressing 10cm x 10cm= £1.52, 10cm x 14cm= £2.45, 10cm x 20cm= £2.96, 15cm x 25cm= £5.25, 30cm x 61cm= £27.56, 5cm x 5cm= £0.72

**Kendall Plus**
Calcium alginate dressing

**Kendall (H & R Healthcare Ltd)** Foam Plus dressing 10cm x 10cm square= £1.47

**Melgisorb**
Calcium sodium alginate fibre, highly absorbent, gelling dressing, non-woven

**Melgisorb (Molynex Health Care Ltd)** Cavity dressing 2.2cm x 32cm= £3.55, dressing 10cm x 10cm= £1.88, 10cm x 20cm= £3.52, 5cm x 5cm= £0.90

**Sorbalgon**
Calcium alginate dressing

**Sorbalgon (Paul Hartmann Ltd)** T dressing 2s= £3.56, dressing 10cm x 10cm= £1.74, 5cm x 5cm= £0.83

**Sorban Flat**
Calcium alginate fibre, highly absorbent, flat non-woven pads

**Sorban Flat dressing (Aspen Medical Europe Ltd)** 10cm x 10cm= £1.72, 10cm x 20cm= £3.22, 5cm x 5cm= £0.82

**Sorban Plus**
Alginate dressing bonded to a secondary absorbent viscose pad

**Sorban Plus dressing (Aspen Medical Europe Ltd)** 10cm x 15cm= £3.12, 10cm x 20cm= £3.98, 15cm x 20cm= £5.53, 7.5cm x 10cm= £1.77

**Sorban Ribbon**
Alginate dressing bonded to a secondary absorbent viscose pad

**Sorban (Aspen Medical Europe Ltd)** Ribbon dressing 40cm= £2.06

**Sorban Surgical Packing**
Alginate dressing bonded to a secondary absorbent viscose pad

**Sorban (Aspen Medical Europe Ltd)** Packing dressing 2g= £3.50

**Suprasorb A**
Calcium alginate dressing

**Suprasorb A (Lohmann & Rauscher) alginate dressing 10cm x 10cm= £1.26, 5cm x 5cm= £0.64, cavity dressing 2g= £2.34

**Tegaderm Alginate**
Calcium alginate dressing

**Tegaderm Alginate dressing (3M Health Care Ltd)** 10cm x 10cm= £1.73, 2cm x 3.4cm= £2.89, 5cm x 5cm= £0.82

**Urgosorb**
Alginate and carboxymethylcellulose dressing without adhesive border

**Urgosorb (Urgo Ltd)** Pad dressing 10cm x 10cm= £2.17, 10cm x 20cm= £3.97, 5cm x 5cm= £0.90, Rope dressing 30cm= £2.84

**Capillary-acting dressings**

**Vacutex**
Low-adherent dressing consisting of two external polyester wound contact layers with central wicking polyester/cotton mix absorbent layer

**Vacutex dressing (Haddenham Healthcare Ltd)** 10cm x 10cm= £1.70, 10cm x 15cm= £2.29, 10cm x 20cm= £2.75, 5cm x 5cm= £0.96

**Odour absorbent dressings**
Dressings containing activated charcoal are used to absorb odour from wounds. The underlying cause of wound odour should be identified. Wound odour is most effectively reduced by debridement of slough, reduction in bacterial levels, and frequent dressing changes. Fungating wounds and chronic infected wounds produce high volumes of exudate which can reduce the effectiveness of odour absorbent dressings. Many odour absorbent dressings are intended for use in combination with other dressings; odour absorbent dressings with a suitable wound contact layer can be used as a primary dressing.

**Aquasorb**
Activated charcoal and non-woven viscose rayon dressing

**Aquasorb (Aquasorb Ltd)** 10cm x 10cm= £2.97, 10cm x 20cm= £5.73

**CarboFLEX**
Dressing in 5 layers: wound-facing absorbent layer containing alginate and hydrocolloid; water-resistant second layer; third layer containing activated charcoal; non-woven absorbent fourth layer; water-resistant backing layer

**CarboFLEX dressing (Convatec Ltd)** 10cm x 10cm= £3.30, 15cm x 20cm= £7.50, 8cm x 15cm oval= £3.96

**Carbopad VC**
Activated charcoal non-absorbent dressing

**Carbopad VC dressing (Synergy Health (UK) Ltd)** 10cm x 10cm= £1.62, 10cm x 20cm= £2.19

**Clinisorb Odour Control Dressings**
Activated charcoal cloth enclosed in viscose rayon with outer polyamide coating

**Clinisorb dressing (CliniMed Ltd)** 10cm x 10cm= £1.94, 10cm x 20cm= £2.58, 15cm x 25cm= £4.15

**Antimicrobial dressings**

Spreading infection at the wound site requires treatment with systemic antibacterials. For local wound infection, a topical antimicrobial dressing can be used to reduce the level of bacteria at the wound surface but will not eliminate a spreading infection. Some dressings are designed to release
the antimicrobial into the wound, others act upon the bacteria after absorption from the wound. The amount of exudate present and the level of infection should be taken into account when selecting an antimicrobial dressing. Medical grade honey has antimicrobial and anti-inflammatory properties. Dressings impregnated with iodine can be used to treat clinically infected wounds. Dressings containing silver should be used only when clinical signs or symptoms of infection are present. Dressings containing other antimicrobials such as polihexanide (polyhexamethylene biguanide) or dialky Lacarbatamoyl chloride are available for use on infected wounds. Although hypersensitivity is unlikely with chlorhexidine impregnated tulle dressing, the antibacterial efficacy of these dressings has not been established.

**Honey dressings**

Medical grade honey has antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Medical grade honey has osmotic properties, producing an environment that promotes autolytic debridement; it can help control wound malodour. Honey dressings should not be used on patients with extreme sensitivity to honey, bee stings or bee products. Patients with diabetes should be monitored for changes in blood-glucose concentrations during treatment with topical honey. Dressings should not be used on patients with extreme sensitivity to honey, bee stings or bee products. Patients with diabetes should be monitored for changes in blood-glucose concentrations during treatment with topical honey.

For *Activon Tulle*, where no size is stated by the prescriber the 5 cm size is to be supplied. *Medihoney*® Antimicrobial Wound Gel is not recommended for use in deep wounds or body cavities where removal of waxes may be difficult.

**Honey-based topical application**

*Activon Honey*
Medical grade manuka honey
*Activon* (Advancis Medical) Medical Grade Manuka Honey dressing= £2.77

*L-Mesitran SOFT ointment dressing*
Honey (medical grade) 40%
*L-Mesitran* (Aspen Medical Europe Ltd) SOFT ointment dressing= £3.62

*MANUKApli Honey*
Medical grade manuka honey
*MANNUKApli* (Manuka Medical Ltd) dressing= £5.90

*Medihoney Antimicrobial Medical Honey*
Medical grade, Leptospermum sp.
*Medihoney* (Derma Sciences Europe, Ltd) Antimicrobial Medical Honey dressing= £9.97

*Medihoney Antimicrobial Wound Gel*
Medical grade, Leptospermum sp. 80% in natural waxes and oils
*Medihoney* (Derma Sciences Europe, Ltd) Antimicrobial Wound Gel dressing= £4.05

*Melladerm Plus Honey*
Medical grade; Bulgarian (mountain flower) 45% in basis containing polyethylene glycol
*Melladerm* (SanoMed Manufacturing BV) Plus dressing= £8.50

*Sheet dressing* (Advancis Medical) 10cm x 10cm= £1.23, 10cm x 20cm= £2.38, 5cm x 5cm= £0.71

*Actilite Gauze dressing* (Advancis Medical) 10cm x 10cm= £2.25

**Algivon dressing**
Activon dressing (Advancis Medical) 10cm x 10cm= £4.25, 5cm x 5cm= £2.48

**Algivon Plus**
Reinforced calcium alginate dressing impregnated with medical grade manuka honey
Algivon Plus (Advancis Medical) Ribbon dressing 2.5cm x 20cm= £4.20, dressing 10cm x 10cm= £4.20, 5cm x 5cm= £2.45

**L-Mesitran Border**
Hydrogel, semi-permeable dressing impregnated with medical grade honey, with adhesive border
L-Mesitran (Aspen Medical Europe Ltd) Border sheet 10cm x 10cm square= £2.76

**L-Mesitran Hydro**
Hydrogel, semi-permeable dressing impregnated with medical grade honey, without adhesive border
L-Mesitran Hydro sheet (Aspen Medical Europe Ltd) 10cm x 10cm square= £2.65, 15cm x 20cm rectangular= £5.48

**L-Mesitran Net**
Hydrogel, non-adherent wound contact layer, without adhesive border
L-Mesitran Net sheet (Aspen Medical Europe Ltd) Net sheet 10cm x 10cm square= £2.55

**Medihoney Antimicrobial Honey Apinate**
Non-adherent calcium alginate dressing, impregnated with medical grade honey
Medihoney Antimicrobial Honey Apinate (Derma Sciences Europe, Ltd) dressing 10cm x 10cm square= £3.42, 5cm x 5cm square= £2.01, rope dressing 1.9cm x 30cm= £4.23

**Medihoney Antibacterial Honey Tulle**
Woven fabric impregnated with medical grade manuka honey
Medihoney (Derma Sciences Europe, Ltd) Tulle dressing 10cm x10cm= £3.00

**Medihoney Gel sheet**
Sodium alginate dressing impregnated with medical grade honey
Medihoney Gel Sheet dressing (Derma Sciences Europe, Ltd) 10cm x 10cm= £4.23, 5cm x 5cm= £1.76

**MelMax**
Acetate wound contact layer impregnated with buckwheat honey 75% in ointment basis

**Melladerm Plus Tulle**
Knitted viscose impregnated with medical grade honey (Bulgarian, mountain flower) 45% in a basis containing polyethylene glycol
Melladerm (SanoMed Manufacturing BV) Plus Tulle dressing 10cm x 10cm= £2.10

**Iodine dressings**
Cadexomer—iodine, like povidone–iodine, releases free iodine when exposed to wound exudate. The free iodine acts as an antiseptic on the wound surface, the cadexomer absorbs wound exudate and encourages de-sloughing. Two-component hydrogel dressings containing glucose oxidase and iodide ions generate a low level of free iodine in the presence of moisture and oxygen. Povidone–iodine fabric dressing is a knitted viscose dressing with povidone–iodine incorporated in a hydrophilic polyethylene glycol basis; this facilitates diffusion of the iodine into the wound and permits removal of the dressing by irrigation. The iodine has a wide spectrum of antimicrobial activity but it is rapidly deactivated by wound exudate. Systemic absorption of iodine may occur, particularly from large wounds or with prolonged use. *Iodoflex®* and *Iodosorb®* are used for the treatment of chronic exuding wounds; max. single application 50g, max. weekly application 150g; max. duration up to 3 months in any single course of treatment. They are contra-indicated in patients receiving lithium, in thyroid disorders, in pregnancy and breast feeding, and in children; they should be used with caution in patients with severe renal impairment or history of thyroid disorder.
**Iodozyme** is an antimicrobial dressing used for lightly to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding.

Oxyzyme is used for non-infected, dry to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding.

**Povidone-iodine Fabric Dressing** is used as a wound contact layer for abrasions and superficial burns. It is contra-indicated in patients with severe renal impairment and in women who are pregnant or breast-feeding; it should be used with caution in patients with thyroid disease and in children under 6 months.

**Iodoflex Paste**

Iodine 0.9% as cadexomer–iodine in a paste basis with gauze backing.

Iodoflex paste (Smith & Nephew Healthcare Ltd) dressing 5g = £4.23, 10g = £8.45, 17g = £13.39

**Iodosorb Ointment**

Iodine 0.9% as cadexomer–iodine in an ointment basis.

Iodosorb (Smith & Nephew Healthcare Ltd) ointment dressing= £9.25

**Iodosorb Powder**

Iodine 0.9% as cadexomer–iodine microbeads, 3-g sachet.

Iodosorb (Smith & Nephew Healthcare Ltd) powder dressing sachets= £1.98

**Povidone-iodine fabric dressing**

Inadine

(Drug Tariff specification 43). Knitted viscose primary dressing impregnated with povidone–iodine ointment 10%

**Inadine dressing** (Systagenix Wound Management Ltd) 5cm x 5cm= £0.33, 9.5cm x 9.5cm= £0.49

**Silver dressings**

Antimicrobial dressings containing silver should be used only when infection is suspected as a result of clinical signs or symptoms (see also notes above). Silver ions exert an antimicrobial effect in the presence of wound exude; the volume of wound exude as well as the presence of infection should be considered when selecting a silver-containing dressing. Silver-impregnated dressings should not be used routinely for the management of uncomplicated ulcers. It is recommended that these dressings should not be used on acute wounds as there is some evidence to suggest they delay wound healing. Dressings impregnated with silver sulfadiazine have broad antimicrobial activity; if silver sulfadiazine is applied to large areas, or used for prolonged periods, there is a risk of blood disorders and skin discoloration. The use of silver sulfadiazine-impregnated dressings is contra-indicated in neonates, in pregnancy, and in patients with significant renal or hepatic impairment, sensitivity to sulfonamides, or G6PD deficiency. Large amounts of silver sulfadiazine applied topically may interact with other drugs—see Appendix 1 (sulfonamides).

**Alginate dressings**

**Algise Ag**

Calcium alginate dressing, with silver.

Algise Ag dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm= £4.27, 10cm x 20cm= £7.85, 2g= £5.90, 5cm x 5cm= £1.71

**Askina Calgitrol Ag**

Calcium alginate and silver alginate dressing with poyurethane foam backing.

Askina Calgitrol Ag dressing (B.Braun Medical Ltd) 10cm x 10cm square= £3.29, 15cm x 15cm square= £6.37, 20cm x 20cm square= £14.86

**Askina Calgitrol Thin**

Calcium alginate and silver alginate matrix, for use with absorptive secondary dressings.

**Askina Calgitrol Thin dressing** (B.Braun Medical Ltd) 10cm x 10cm square= £4.19, 15cm x 15cm square= £9.41, 20cm x 20cm square= £16.62, 5cm x 5cm square= £2.02

**Melgisor Ag**

Alginate and carboxymethylcellulose dressing, with ionic silver.

Melgisor Ag (Molynex Health Care Ltd) Cavity dressing 3cm x 4cm= £4.61, dressing 10cm x 10cm= £3.69, 15cm x 15cm= £7.82, 5cm x 5cm= £1.85

**Silvercel**

Alginate and carboxymethylcellulose dressing impregnated with silver.

Silvercel dressing (Systagenix Wound Management Ltd) 10cm x 20cm rectangular= £7.74, 11cm x 11cm square= £4.17, 2.5cm x 30.5cm rectangular= £4.49, 5cm x 5cm square= £1.69

**Silvercel Non-adherent**

Alginate and carboxymethylcellulose dressing with film wound contact layer, impregnated with silver.

Silvercel Non-Adherent (Systagenix Wound Management Ltd) cavity dressing 2.5cm x 30.5cm= £3.94, dressing 10cm x 20cm rectangular= £7.25, 11cm x 11cm square= £3.89, 5cm x 5cm square= £1.62

**Sorbsan Silver Flat**

Calcium alginate fibre, highly absorbent, flat non-woven pads, with silver.

Sorbsan Silver Flat dressing (Aspen Medical Europe Ltd) 10cm x 10cm= £4.00, 10cm x 20cm= £7.31, 5cm x 5cm= £1.58

**Sorbsan Silver Plus**

Calcium alginate dressing with absorbent backing, with silver.

Sorbsan Silver Plus dressing (Aspen Medical Europe Ltd) 10cm x 15cm= £5.60, 10cm x 20cm= £6.82, 15cm x 20cm= £9.15, 7.5cm x 10cm= £3.37

**Sorbsan Silver Ribbon**

With silver.

Sorbsan (Aspen Medical Europe Ltd) Silver Ribbon dressing 1g= £4.18

**Sorbsan Silver Surgical Packing**

With silver.

Sorbsan (Aspen Medical Europe Ltd) Silver Packing dressing 2g= £5.80

**Suprasorb A + Ag**

Calcium alginate dressing, with silver.

Suprasorb A + Ag (Lohmann & Rauscher) dressing 10cm x 10cm= £4.21, 10cm x 20cm= £7.78, 5cm x 5cm= £1.67, rope dressing 2g= £6.23

**Tegaderm Alginic Ag**

Calcium alginate and carboxymethylcellulose dressing, with silver.

Tegaderm Alginic Ag dressing (3M Health Care Ltd) 10cm x 10cm= £3.27, 3cm x 30cm= £3.73, 5cm x 5cm= £1.40

**Urgosorb Silver**

Alginate and carboxymethylcellulose dressing, impregnated with silver.

Urgosorb Silver (Urgo Ltd) Rope dressing 2.5cm x 30cm= £3.77, dressing 10cm x 10cm= £3.75, 10cm x 20cm= £7.06, 5cm x 5cm= £1.57

**Foam dressings**

**Acticoat Moisture Control**

Three layer polyurethane dressing consisting of a silver coated layer, a foam layer, and a waterproof layer.

Acticoat Moisture Control dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm square= £17.23, 10cm x 20cm rectangular= £33.58, 5cm x 5cm square= £7.37

**Allelyn Ag**

Silver sulfadiazine impregnated polyurethane foam film dressing with or without adhesive border.

Allelyn Ag (Smith & Nephew Healthcare Ltd) Adhesive dressing 10cm x 10cm square= £5.65, 12.5cm x 12.5cm square= £7.42, 17.5cm x 17.5cm square= £14.27, 17cm x 17cm sacral= £11.14, 22cm x 22cm sacral= £14.93, 7.5cm x 7.5cm square= £3.59, Heel Non-
Adhesive dressing 10.5cm × 13.5cm = £11.05, Non-Adhesive dressing 10cm × 10cm square = £6.31, 15cm × 15cm square = £11.95, 20cm × 20cm square = £17.51, 5cm × 5cm square = £3.35

Biatain Ag
Silver impregnated polyurethane foam film dressing, with or without adhesive border

Biatain Ag (Coloplast Ltd) cavity dressing 5cm × 8cm = £4.13, dressing 10cm × 10cm square = £8.29, 10cm × 20cm rectangular = £15.24, 12.5cm × 12.5cm square = £9.48, 15cm × 15cm square = £16.64, 18cm × 18cm square = £19.93, 1cm × 20cm heelp = £18.77, 20cm × 20cm square = £23.47, 23cm × 23cm sacral = £19.94, 5cm × 7cm rectangular = £3.41

PolyMem Silver
Silver impregnated polyurethane foam film dressing, with or without adhesive border

PolyMem Silver (Aspen Medical Europe Ltd) WIC dressing 8cm × 8cm = £7.10, dressing 10.8cm × 10.8cm square = £8.93, 12.7cm × 8.8cm oval = £5.64, 17cm × 19cm rectangular = £17.89, 5cm × 7.5cm oval = £2.29

UrgoCell Silver
Non-adherent, polyurethane foam film dressing with silver in wound contact layer

UrgoCell Silver dressing (Urgo Ltd) 10cm × 10cm = £6.05, 15cm × 20cm = £11.08, 6cm × 6cm = £4.40

Hydrocolloid dressings

Aquacel Ag
Soft non-woven pad containing hydrocolloid fibres, (silver impregnated)

Aquacel Ag (Convatec Ltd) Ribbon dressing 1cm × 45cm = £3.17, 2cm × 45cm = £4.84, dressing 10cm × 10cm square = £4.81, 15cm × 15cm square = £9.06, 20cm × 30cm rectangular = £22.48, 4cm × 10cm rectangular = £2.93, 4cm × 20cm rectangular = £3.82, 4cm × 30cm rectangular = £5.72

Physiostrip Ag
Non-adherent polyester fabric with hydrocolloid and silver sulfadiazine

Physiostrip (Coloplast Ltd) dressing 10cm × 10cm = £2.32

Low adherence dressing

Acticoat
Three-layer antimicrobial barrier dressing consisting of a polyester core between low adhesive silver-coated high density polyethylene mesh (for 3-day wear)

Acticoat dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square = £8.79, 10cm × 20cm rectangular = £13.75, 20cm × 40cm rectangular = £47.04, 5cm × 5cm square = £3.60

Acticoat 7
Five-layer antimicrobial barrier dressing consisting of a polyester core between low adhesive silver-coated high density polyethylene mesh (for 7-day wear)

Acticoat 7 dressing (Smith & Nephew Healthcare Ltd) 10cm × 12.5cm rectangular = £18.64, 15cm × 15cm square = £33.51, 5cm × 5cm square = £6.26

Acticoat Flex 3
Conformable antimicrobial barrier dressing consisting of a polyester core between low adhesive silver-coated high density polyethylene mesh (for 3-day wear)

Acticoat Flex 3 dressing (Smith & Nephew Healthcare Ltd) 10cm × 10cm square = £8.89, 10cm × 20cm rectangular = £13.90, 20cm × 40cm rectangular = £47.56, 5cm × 5cm square = £3.64

Acticoat Flex 7
Conformable antimicrobial barrier dressing consisting of a polyester core between low adhesive silver-coated high density polyethylene mesh (for 7-day wear)

Acticoat Flex 7 dressing (Smith & Nephew Healthcare Ltd) 10cm × 12.5cm rectangular = £18.85, 15cm × 15cm square = £33.89, 5cm × 5cm square = £6.33

Atrauman Ag
Non-adherent polyamide fabric impregnated with silver and neutral triglycerides

Atrauman Ag dressing (Paul Hartmann Ltd) 10cm × 10cm = £1.28, 10cm × 20cm = £2.51, 5cm × 5cm = £0.53

Soft polymer dressings

Allevyn Ag Gentle
Soft polymer wound contact dressing, with silver sulfadiazine impregnated polyurethane foam layer, with or without adhesive border

Allevyn Ag Gentle (Smith & Nephew Healthcare Ltd) Border dressing 10cm × 10cm = £6.53, 12.5cm × 12.5cm = £8.40, 17.5cm × 17.5cm = £16.00, 7.5cm × 7.5cm = £4.35, dressing 10cm × 10cm = £6.34, 10cm × 20cm = £10.48, 15cm × 15cm = £11.80, 20cm × 20cm = £17.48, 5cm × 5cm = £3.40

Mepilex Ag
Soft silicone wound contact dressing with polyurethane foam backing, with silver, with or without adhesive border

Mepilex (Molnlycke Health Care Ltd) Ag dressing 10cm × 10cm = £6.21, 10cm × 20cm = £10.24, 15cm × 15cm = £11.53, 20cm × 20cm = £17.03, 20cm × 50cm = £64.13, Border Ag dressing 10cm × 12.5cm = £6.25, 10cm × 20cm = £9.10, 10cm × 30cm = £13.68, 15cm × 17.5cm = £11.48, 17cm × 20cm = £14.87, 7.5cm × 7.5cm = £3.46, Border Sacrum Ag dressing 18cm × 18cm = £12.00, 20cm × 20cm = £14.59, 23cm × 23cm = £19.17, Heel Ag dressing 13cm × 20cm = £12.97, 15cm × 22cm = £14.53

Urgotol Silver
Non-adherent soft polymer wound contact dressing, with silver

Urgotol Silver dressing (Urgo Ltd) 10cm × 12cm = £3.64, 15cm × 20cm = £9.91

With charcoal

Actisorb Silver 220
Knitted fabric of activated charcoal, with one-way stretch, with silver residues, within spun-bonded nylon sleeve

Actisorb Silver 220 dressing (Sytagenix Wound Management Ltd) 10.5cm × 10.5cm = £2.60, 10.5cm × 19cm = £4.73, 6.5cm × 9.5cm = £1.66

Other antimicrobials

Cutimed Siltec Sorbact
Polyurethane foam dressing with acetate fabric coated with dialkylcarbamoyl chloride, with adhesive border

Cutimed Siltec Sorbact dressing (BSN medical Ltd) 12.5cm × 12.5cm = £6.62, 15cm × 15cm = £8.20, 17.5cm × 17.5cm = £11.47, 22.5cm × 22.5cm = £17.45, 7.5cm × 7.5cm = £2.58, 17.5cm × 17.5cm sacral = £8.29, 23cm × 23cm sacral = £12.46

Cutimed Sorbact
Low adherence acetate tissue impregnated with dialkylcarbamoyl chloride; dressing pad, swabs, round swabs or ribbon gauze, cotton

Cutimed Sorbact (BSN medical Ltd) Ribbon dressing 2cm × 50cm = £2.14, 5cm × 200cm = £9.16, Round swab 3cm = £3.39, dressing pad 10cm × 10cm = £5.65, 10cm × 20cm = £8.81, 7cm × 9cm = £3.61, swab 4cm × 6cm = £1.69, 7cm × 9cm = £2.82

Cutimed Sorbact Gel
Hydrogel dressing impregnated with dialkylcarbamoyl chloride

Cutimed Sorbact Gel dressing (BSN medical Ltd) 7.5cm × 15cm rectangular = £4.60, 7.5cm × 7.5cm square = £2.72

Cutimed Sorbact Hydroactive
Non-adhesive gel dressing with hydropolymer matrix and acetate fabric coated with dialkylcarbamoyl chloride

Cutimed Sorbact Hydroactive dressing (BSN medical Ltd) 14cm × 14cm = £5.51, 14cm × 24cm = £8.63, 19cm × 19cm = £10.38, 24cm × 24cm = £15.73, 7cm × 8.5cm = £3.78

Cutimed Sorbact Hydroactive B
Gel dressing with hydropolymer matrix and acetate fabric coated with dialkylcarbamoyl chloride, with adhesive border

Cutimed Sorbact Hydroactive B dressing (BSN medical Ltd) 10cm × 10cm = £7.38, 10cm × 20cm = £11.66, 15cm × 15cm = £13.70, 5cm × 6.5cm = £4.08

Flaminal Forte gel
Alginate with glucose oxidase and lactoperoxidase, for moderately to heavily exuding wounds

Flaminal Forte gel dressing (Flen Health UK Ltd) 15g = £7.87
Flaminal Hydro gel
Alginates with glucose oxidase and lactoperoxidase, for lightly to moderately exuding wounds
Flaminal Hydro gel dressing (Flan Health UK Ltd) 15g = £7.87

Kendall AMD
Foam dressing with polihexanide, without adhesive border
Kendall AMD Antimicrobial foam dressing (H & R Healthcare Ltd) 10cm x 10cm square= £4.71, 10cm x 20cm rectangular= £8.92, 15cm x 15cm square= £8.92, 20cm x 20cm square= £13.07, 5cm x 5cm square= £2.50, 8.8cm x 7.5cm rectangular (fenestrated)= £4.23

Kendall AMD Plus
Foam dressing with polihexanide, without adhesive border
Kendall AMD Antimicrobial Plus foam dressing (H & R Healthcare Ltd) 10cm x 10cm square= £4.94, 8.8cm x 7.5cm rectangular (fenestrated)= £4.43

Octenilen Wound gel
Wound gel, hydroxyethylcellulose and propylene glycol, with octenidine hydrochloride
Octenilen Wound Gel dressing (Schulke & Mayr UK Ltd) 20ml= £4.78, 250ml= £25.21

Prontosan Wound Gel
Hydrogel containing betaine surfactant and polihexanide
Prontosan (B.Braun Medical Ltd) Wound gel dressing= £6.55

Suprasorb X + PHMB
Biosynthetic cellulose fibre dressing with polihexanide
Suprasorb X + PHMB dressing (Lohmann & Rauscher) 14cm x 20cm rectangular= £11.93, 2cm x 21cm rope= £7.43, 5cm x 5cm square= £2.63, 9cm x 9cm square= £5.24

Telfa AMD
Low adherence absorbent perforated plastic film faced dressing with polihexanide
Telfa AMD dressing (H & R Healthcare Ltd) 10cm x 7.5cm= £0.18, 20cm x 7.5cm= £0.28

Telfa AMD Island
Low adherence dressing with adhesive border and absorbent pad, with polihexanide
Telfa AMD Island dressing (H & R Healthcare Ltd) 10cm x 12.5cm= £0.59, 10cm x 20cm= £0.86, 10cm x 25.5cm= £0.98, 10cm x 35cm= £1.22

Chlorhexidine gauze dressing
Bactigras
Fabric of lino weave, wet and warp threads of cotton and/or viscose yarn, impregnated with ointment containing chlorhexidine acetate
Bactigras gauze dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm= no price available, 5cm x 5cm= no price available

Irrigation fluids
Octenilen Wound irrigation solution
Aqueous solution containing glycerol, ethelyxylglycerin and octenidine hydrochloride
Octenilen irrigation solution 350ml bottles (Schulke & Mayr UK Ltd) bottle £4.60

Prontosan Wound Irrigation Solution
Aqueous solution containing betaine surfactant and polihexanide
Prontosan irrigation solution (B.Braun Medical Ltd) 350ml bottles= £4.90, 40ml unit dose= £14.57

Specialised dressings
Protease-modulating matrix dressings
Cadesorb Ointment
Cadesorb (Smith & Nephew Healthcare Ltd) ointment= £9.47

Catris
Catris dressing (Cranage Healthcare Ltd) sachets= £3.80

Promogran
Collagen and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing
Promogran dressing (Syntegens Wound Management Ltd) 123 square cm= £15.75, 28 square cm= £5.23

Promogran Prisma Matrix
Collagen, silver and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing
Promogran Prisma dressing (Syntegens Wound Management Ltd) 123 square cm= £18.12, 28 square cm= £6.36

UrgoStart
Soft adherent polymer matrix containing nano-oligosaccharide factor (NOSF), with polurethane foam film backing
UrgoStart dressing (Urgo Ltd) 10cm x 10cm= £6.26, 15cm x 20cm= £11.26, 6cm x 6cm= £4.53, 12cm x 19cm heel= £8.63

UrgoStart Contact
Non-adherent soft polymer wound contact dressing containing nano-oligosaccharide factor (NOSF)
UrgoStart (Urgo Ltd) Contact dressing 5cm x 7cm= £3.03

Silicone keloid dressings
Silicone gel and gel sheets are used to reduce or prevent hypertrophic and keloid scarring. They should not be used on open wounds. Application times should be increased gradually. Silicone sheets can be washed and reused.
Silicone gel
Bapscarcare Silicone gel
Bapscarcare (Espere Healthcare Ltd) gel= £17.12

Cilitech
Silicone gel
Cilitech (Su-Med International (UK) Ltd) gel= £50.00

Dermatix
Silicone gel
Dermatix gel (Meda Pharmaceuticals Ltd)= £60.53

Kelo-cote UV
Silicone gel with SPF 30 UV protection
Kelo-cote (Alliance Pharmaceuticals Ltd) UV gel= £17.88

Kelo-cote gel
Silicone gel
Kelo-cote (Alliance Pharmaceuticals Ltd) gel= £51.00

Kelo-cote spray
Silicone spray
Kelo-cote (Alliance Pharmaceuticals Ltd) spray= £51.00

Scarsil
Silicone gel
ScarSil (Jobskin Ltd) gel= £15.19

Silgel STC-SE
Silicone gel
Silgel (Nagar Ltd) STC-SE gel= £19.00

Silicone sheets
Advasil Conform
Self-adhesive silicone gel sheet with polyurethane film backing
Advasil Conform sheet (Advantis Medical) 10cm x 10cm square= £5.24, 15cm x 10cm rectangular= £3.24

Bapscarcare T
Self-adhesive silicone gel sheet
Bapscarcare T sheet (Espere Healthcare Ltd) 10cm x 15cm rectangular= £9.07, 5cm x 30cm rectangular= £9.07, 5cm x 7cm rectangular= £3.17

Cica-Care
Soft, self-adhesive, semi-occlusive silicone gel sheet with backing
Cica-Care sheet (Smith & Nephew Healthcare Ltd) 15cm x 12cm rectangular= £29.30, 6cm x 12cm rectangular= £15.03

Cilitech
Silicone gel sheet
Cilitech sheet (Su-Med International (UK) Ltd) 10cm x 10cm square= £7.50, 10cm x 20cm rectangular= £12.50, 15cm x 15cm square= £14.00

Dermatix
Self-adhesive silicone gel sheet (clear- or fabric-backed)
Dermatix (Meda Pharmaceuticals Ltd) Clear sheet 13cm × 13cm square= £15.79, 13cm × 25cm rectangular= £28.53, 20cm × 30cm rectangular= £51.97, 4cm × 13cm rectangular= £6.88, Fabric sheet 13cm × 13cm square= £15.79, 13cm × 25cm rectangular= £28.53, 20cm × 30cm rectangular= £51.97, 4cm × 13cm rectangular= £6.88

Mepiform
Self-adhesive silicone gel sheet with polyurethane film backing
Mepiform sheet (Molnlycke Health Care Ltd) 4cm × 31cm rectangular= £11.20, 5cm × 7cm rectangular= £3.54, 9cm × 18cm rectangular= £13.86

Scarf FX
Self-adhesive, transparent, silicone gel sheet
Scarf FX sheet (Jobskin Ltd) 10cm × 20cm rectangular= £16.00, 22.5cm × 14.5cm shaped= £12.00, 25.5cm × 30.5cm rectangular= £60.00, 3.75cm × 22.5cm rectangular= £12.00, 7.5cm diameter shaped= £8.50

Siligel
Silicone gel sheet
Siligel sheet (Nago Ltd) 10cm × 10cm square= £13.50, 10cm × 30cm rectangular= £31.50, 10cm × 5cm rectangular= £7.50, 15cm × 10cm rectangular= £19.50, 20cm × 20cm rectangular= £40.00, 25cm × 15cm shaped= £21.12, 30cm × 5cm rectangular= £19.50, 40cm × 40cm square= £144.00, 46cm × 8.5cm shaped= £39.46, 5.5cm diameter shaped= £4.00

Adjunct dressings and appliances
Surgical dressings
Surgical dressings are used to protect wounds, absorb drainage, and control wound edges. They are often combined with a primary dressing to secure them to the wound. Surgical dressings can be layered into the cavity is often more suitable.

Cotton

Absorbent Cotton, BP
Carded cotton fibres of not less than 10 mm average staple length, available in rolls and balls
Absorbent (Robert Bailey & Son Plc) cotton BP 1988

Absorbent Cotton, Hospital Quality
As for absorbent cotton but lower quality materials, shorter staple length etc.
Absorbent (Robert Bailey & Son Plc) cotton hospital quality

Gauze and cotton tissue

Gamgee Tissue (blue)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2
Gamgee (Robinson Healthcare) tissue blue label

Gamgee Tissue (pink)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2
Gamgee (Robinson Healthcare) tissue pink label DT

Gauze and tissue

Absorbent Cotton Gauze, BP 1988
Cotton fabric of plain weave, in rolls and as swabs (see below), usually Type 13 light, sterile
Absorbent (Robert Bailey & Son Plc) cotton BP 1988
Alvita (Alliance Healthcare (Distribution) Ltd) absorbent cotton BP 1988
Clini (CliniSupplies Ltd) absorbent cotton BP 1988
Vernaid (Synergy Health (UK) Ltd) absorbent cotton BP 1988

Absorbent Cotton and Viscose Ribbon Gauze, BP 1988
Woven fabric in ribbon form with fast selvedge edges, warp threads of cotton, weft threads of viscose or combined cotton and viscose yarn, sterile
Vernaid Fast Edge ribbon gauze sterile (Synergy Health (UK) Ltd) 1.25cm, 2.5cm

Lint

Absorbent Lint, BPC
Cotton cloth of plain weave with nap raised on one side from warp yarns
Absorbent (Robinson Healthcare) lint
Alvita (Alliance Healthcare (Distribution) Ltd) absorbent lint BPC
Clini (CliniSupplies Ltd) absorbent lint BPC

Pads

Drisorb
Absorbing Dressing Pads, Sterile
Drisorb (Synergy Health (UK) Ltd) dressing pad 10cm × 20cm= £0.17

PremierPad
Absorbing Dressing Pads, Sterile
PremierPad dressing pad (Shermon) 10cm × 20cm= £0.18, 20cm × 20cm= £0.25

XuPad
Absorbing Dressing Pads, Sterile
Xupad dressing pad (Richardson Healthcare Ltd) 10cm × 20cm= £0.17, 20cm × 20cm= £0.28, 20cm × 40cm= £0.40

Wound drainage pouches
Wound drainage pouches can be used in the management of wounds and fistulas with significant levels of exudate.

Biotrol Draina S
Wound drainage pouch
Biotrol Draina S wound drainage bag (B.Braun Medical Ltd) large (Transparent)= £98.03, medium (Transparent)= £79.71, mini (Transparent)= £79.95

Biotrol Draina S Vision
Wound drainage pouch
Draina S Vision (B.Braun Medical Ltd) 50 wound drainage bags= £103.84, 75 wound drainage bags= £109.70

Eakin Access window
For use with Eakin ® pouches
Eakin (Pelican Healthcare Ltd) access window large= £38.76

Eakin Wound pouch, bung closure
Wound pouch, bung closure
Eakin wound drainage bag with bung closure (Pelican Healthcare Ltd) large= £105.22, medium= £77.55, small= £55.38, and access window for horizontal wounds, extra large= £106.22, for horizontal wounds, extra large= £94.14, for vertical incision wounds, extra large= £94.14

Eakin Wound pouch, fold and tuck closure
Wound pouch, fold and tuck closure
Eakin wound drainage bag with fold and tuck closure (Pelican Healthcare Ltd) large= £94.14, medium= £71.99, small= £49.84, extra large= £83.07

Option Wound Manager
Wound drainage bag
Option wound manager bag (Oakmed Ltd) large= £162.58, medium= £136.41, small= £133.44, square= £142.34, extra small= £119.97

Option Wound Manager with access port
Wound drainage bag, with access port
Option wound manager bag with access port (Oakmed Ltd) large= £173.79, medium= £142.34, small= £139.37, square= £148.27, extra small= £131.18

Option Wound Manager, cut to fit
Wound drainage bag, cut to fit
Option wound manager bag (Oakmed Ltd) large= £85.47, medium= £81.61, small= £73.66

Welland Fistula bag
Wound drainage bag, cut-to-fit
Welland (Welland Medical Ltd) Fistula wound drainage bag= £84.29
Physical debridement pads

Debrisoft® is a pad that is used for the debridement of superficial wounds containing loose slough and debris, and for the removal of hyperkeratosis from the skin. Debrisoft® must be fully moistened with a wound cleansing solution before use and is not appropriate for use as a wound dressing.

Debrisoft Pad
Polyester fibres with bound edges and knitted outer surface coated with polycrylate
Debrisoft (Lohmann & Rauscher) pad 10cm × 10cm = £6.61

Complex adjunct therapies

Topical negative pressure therapy

Accessories
Renasys
Soft port and connector
Renasys (Smith & Nephew Healthcare Ltd) Soft Port = £11.38, connector for use with soft port = £3.34

V.A.C.
Drape, gel for canister, Sensa T.R.A.C. Pad
SensaT.R.A.C. (KCI Medical Ltd) pad = £11.04
T.R.A.C. (KCI Medical Ltd) connector = £3.16
V.A.C. (KCI Medical Ltd) drape = £9.46, gel strips = £3.79
Venturi
Gel patches, adhesive, and connector
Venturi (Talley Group Ltd) adhesive gel patch = £15.00, connector = £15.00

WoundASSIST gel strip
WoundASSIST (Huntleigh Healthcare Ltd) TNP gel strip = £3.37

Vacuum assisted closure products

Exsu-Fast kit 1
Dressing Kit
Exsu-Fast (Synergy Health (UK) Ltd) dressing kit 1 = £28.04

Exsu-Fast kit 2
Dressing Kit
Exsu-Fast (Synergy Health (UK) Ltd) dressing kit 2 = £35.83

Exsu-Fast kit 3
Dressing Kit
Exsu-Fast (Synergy Health (UK) Ltd) dressing kit 3 = £35.83

Exsu-Fast kit 4
Dressing Kit
Exsu-Fast (Synergy Health (UK) Ltd) dressing kit 4 = £28.04

V.A.C. GraniFoam
Polyurethane foam dressing (with adhesive drapes and pad connector); with or without silver
V.A.C. GraniFoam (KCI Medical Ltd) Bridge dressing kit = £32.29
Silver with SensaT.R.A.C dressing kit medium = £38.33, small = £31.05, dressing kit large = £31.94, medium = £27.53, small = £23.13

V.A.C. Simplace
Spiral-cut polyurethane foam dressings, vapour-permeable adhesive film dressings (with adhesive drapes and pad connector)
V.A.C. Simplace EX dressing kit (KCI Medical Ltd) medium = £30.82, small = £26.81

V.A.C. WhiteFoam
Polyvinyl alcohol foam dressing or dressing kit
V.A.C. WhiteFoam dressing (KCI Medical Ltd) large = £17.17, small = £16.72, kit large = £33.80, small = £26.11

Venturi
Wound sealing kit, flat drain; with or without channel drain
Venturi wound sealing kit with flat drain, (Talley Group Ltd) large = £17.50, standard = £15.00

WoundASSIST
Wound pack and channel drain
WoundASSIST TNP dressing pack (Huntleigh Healthcare Ltd) medium/large = £23.85, small/medium = £20.81, channel drain medium/large = £23.85, small/medium = £22.85, extra large = £34.05

Wound drainage collection devices

ActiV.A.C.
Canister with gel
ActiV.A.C (KCI Medical Ltd) canister with gel = £28.64
S-Canister
Canister kit
S-Canister (Smith & Nephew Healthcare Ltd) kit = £19.00

V.A.C Freedom
Canister with gel
V.A.C. (KCI Medical Ltd) Freedom Canister with gel = £29.08

Venturi
Canister kit with solidifier
Venturi (Talley Group Ltd) Compact canister kit = £12.50, canister kit = £12.50

WoundASSIST wound pack
Canister
WoundASSIST (Huntleigh Healthcare Ltd) TNP canister = £20.30

Wound care accessories

Dressing packs
The role of dressing packs is very limited. They are used to provide a clean or sterile working surface; some packs shown below include cotton wool balls, which are not recommended for use on wounds.

Multiple Pack Dressing No. 1
Contains absorbent cotton, absorbent cotton gauze type 13 light (sterile), open-wove bandages (banded)
Vernaid (Synergy Health (UK) Ltd) multiple pack dressing

Non-drug tariff specification sterile dressing packs

Dressit
Vitrex gloves, large apron, disposable bag, paper towel, softswabs, adsorbent pad, sterile field
Dressit sterile dressing pack (Richardson Healthcare Ltd) with medium/large gloves = £0.60, small/medium gloves = £0.60

Nurse It
Contains latex-free, powder-free nitrile gloves, sterile laminated paper sheet, large apron, non-woven swabs, paper towel, disposable bag, compartmented tray, disposable forceps, paper measuring tape
Nurse It sterile dressing pack (Medicareplus International Ltd) with medium/large gloves = £0.55, small/medium gloves = £0.55

Polyfield Nitrile Patient Pack
Contains powder-free nitrile gloves, laminate sheet, non-woven swabs, towel, polycrylene disposable bag, apron
Polyfield Nitrile Patient Pack (Shermond) with large gloves = £0.52, medium gloves = £0.52, small gloves = £0.52

Sterile Dressing Pack with Non-Woven Pads
Vernaid
Vernaid (Synergy Health (UK) Ltd) sterile dressing pack with non-woven pads

Sterile dressing packs
Vernaid
(Drug Tariff specification 10). Contains gauze and cotton tissue pad, gauze swabs, absorbent cotton wool balls, absorbent paper towel, water repellent inner wrapper
Vernaid (Synergy Health (UK) Ltd) sterile dressing pack

Woven and fabric swabs

Gauze Swab, PB 1988
Consists of absorbent cotton gauze type 13 light or absorbent cotton and viscose gauze type 1 folded into squares or rectangles of 8-ply with no cut edges exposed, sterile or non-sterile
Alvia gauze swab 8ply (Alliance Healthcare (Distribution) Ltd) non-sterile 10cm × 10cm, sterile 7.5cm × 7.5cm
CS (CliniSupplies Ltd) gauze swab 8ply non-sterile 10cm × 10cm
Appendix 4

**within non-woven viscose fabric folded sterile**

10 cm × 10 cm

**CliniMed**

- **(polymeric adhesive mass)**

**Non-sterile**

**Sofsorb non-woven fabric swab 4ply**

10 cm × 10 cm

**Softswab non-woven fabric swab 4ply**

10 cm × 10 cm

**Fileted non-woven Fabric Swab**

**Regal**

**Non-sterile**

**Surgical adhesive tapes**

- Adhesive tapes are useful for retaining dressings on joints or awkward body parts. These tapes, particularly those containing rubber, can cause irritant and allergic reactions in susceptible patients; synthetic adhesives have been developed to overcome this problem, but they, too, may sometimes be associated with reactions. Synthetic adhesive, or silicon adhesive, tapes can be used for patients with skin reactions to plasters and strapping containing rubber, or undergoing prolonged treatment.

- Adhesive tapes that are occlusive may cause skin maceration. Care is needed not to apply these tapes under tension, to avoid creating a tourniquet effect. If applied over joints they need to be orientated so that the area of maximum extensibility of the fabric is in the direction of movement of the limb.

**Occlusive adhesive tapes**

**Blenderm**

- (Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with a polymeric adhesive mass

**Blenderm tape**

(3M Health Care Ltd) 2.5cm= £1.78, 5cm= £3.39

**Sleek**

- (Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with an adhesive mass

**Leukoplast Sleek tape**

(3M medical Ltd) 2.5cm, 5cm, 7.5cm

**Permeable adhesive tapes**

**3M Kind Removal Silicone Tape**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

3M Micropore Silicone tape

(3M Health Care Ltd) 2.5cm= £3.61, 5cm= £6.53

**Chemifix**


**Chemifix tape**

(Medicareplus International Ltd) 10cm= £2.10, 2.5cm= £0.90, 5cm= £1.40

**Chemipore**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Chemipore tape**

(Medicareplus International Ltd) 1.25cm= £0.27, 2.5cm= £0.70, 5cm= £0.95

**Clinipore**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Clinipore tape**

(Medicareplus International Ltd) 1.25cm= £0.35, 2.5cm= £0.74, 5cm= £1.00

**Elastoplast**

- (Elastic Adhesive Tape, BP 1988). Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads, spread with adhesive mass containing zinc oxide

**Tensoplast**

(3M medical Ltd) elastic adhesive tape 2.5cm

**Hypafix**


**Hypafix tape**

(3M medical Ltd) 10cm= £4.80, 15cm= £7.11, 2.5cm= £1.73, 20cm= £9.43, 30cm= £13.63, 5cm= £2.75

**Insil**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

**Insil tape**

(Insight Medical Products Ltd) 2cm= £5.77, 4cm= £5.77

**Leukofix**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Leukofix tape**

(3M medical Ltd) 1.25cm= £0.57, 2.5cm= £0.92, 5cm= £1.61

**Leukopor**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Leukopor tape**

(3M medical Ltd) 1.25cm= £0.51, 2.5cm= £0.79, 5cm= £1.39

**Mediplast**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Mediplast tape**

(Neomedic Ltd) 1.25cm= £0.30, 2.5cm= £0.50

**Mediplast**

Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide

**Mediplast Zinc Oxide plaster**

(Neomedic Ltd) 1.25cm= £0.82, 2.5cm= £1.19, 5cm= £1.99, 7.5cm= £2.99

**Mefix**


**Mefix tape**

(3M medical Ltd) 10cm= £2.92, 15cm= £3.98, 2.5cm= £1.03, 20cm= £5.10, 30cm= £7.32, 5cm= £1.83

**Mepitac**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

**Mepitac tape**

(3M medical Ltd) 2cm= £7.01, 4cm= £7.01

**Micropore**

- (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass

www.getintopharma.com
Skin closure dressings

Skin closure strips are used as an alternative to sutures for closure of minor skin wounds and for additional suture support.

**Open-woven Bandage, Type 1 BP 1988**

Cotton cloth, plain weave, warp of cotton, weft of cotton, viscose, or combination, one continuous length

- **Omnifix tape** (Paul Hartmann Ltd) 10cm x 5m, 5.2cm x 5m, 5cm x 5m, 7.5cm x 5m
- **Vernaid white open woven bandage** (Synergy Health (UK) Ltd) 10cm x 5m, 5.2cm x 5m, 5cm x 5m, 7.5cm x 5m
- **White open woven bandage** (Robert Bailey & Son Plc) 10cm x 5m, 5.2cm x 5m, 5cm x 5m, 7.5cm x 5m

**Triangular Calico Bandage, BP 1980**

Unbleached calico right-angled triangle

- **Clini (Clinisupplies Ltd) triangular calico bandage BP 1980 90cm x 127cm**
- **Triangular (BSN medical Ltd) calico bandage 90cm x 127cm**

**Lightweight conforming bandages**

Lightweight conforming bandages are used for dressing retention, with the aim of keeping the dressing close to the wound without inhibiting movement or restricting blood flow. The elasticity of conforming-stretch bandages (also termed contour bandages) is greater than that of cotton conforming bandages.

**Acti-Wrap**

Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched (all)

**Acti-Wrap (cohesive/latex free) bandage** (L&R Medical UK Ltd) 10cm x 4m= £0.83, 6cm x 4m= £0.48, 8cm x 4m= £0.70

**Cotton Conforming Bandage, BP 1988**

Cotton fabric, plain weave, treated to impart some elasticity to warp and weft

**Easifix Crinx bandage** (BSN medical Ltd) 10cm x 3.5m= £1.06, 15cm x 3.5m= £1.45, 5cm x 3.5m= £0.70, 7.5cm x 3.5m= £0.86

**Easifix**

Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched (all)

**Easifix bandage** (BSN medical Ltd) 10cm x 4m= £0.52, 15cm x 4m= £0.89, 5cm x 4m= £0.36, 7.5cm x 4m= £0.44

**Easifix K**

Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched

**Easifix K bandage** (BSN medical Ltd) 10cm x 4m= £0.19, 15cm x 4m= £0.33, 2.5cm x 4m= £0.10, 5cm x 4m= £0.11, 7.5cm x 4m= £0.17

**Hospiform bandage**

Fabric, plain weave, warp of polyamide, weft of viscose

**Hospiform bandage** (Paul Hartmann Ltd) 10cm x 4m= £0.19, 12cm x 4m= £0.24, 6cm x 4m= £0.14, 8cm x 4m= £0.17

**K-Band**

Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched

**K-Band 50mm** (Urgo Ltd) 10cm x 4m= £0.29, 15cm x 4m= £0.50, 5cm x 4m= £0.21, 7cm x 4m= £0.26

**Knot Fix**

Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched

**Knot Fix bandage** (Robert Bailey & Son Plc) 10cm x 4m= £0.17, 15cm x 4m= £0.33, 5cm x 4m= £0.12, 7cm x 4m= £0.17

**Knot-Band**

Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4m stretched

**Knot-Band 50mm** (Clinisupplies Ltd) 10cm x 4m= £0.17, 15cm x 4m= £0.31, 5cm x 4m= £0.10, 7cm x 4m= £0.15

**Kontour bandage** (Easigrip Ltd) 10cm x 4m= £0.40, 15cm x 4m= £0.66, 5cm x 4m= £0.28, 7.5cm x 4m= £0.35

**Bandages**

Non-extensible bandages

Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive can be used for closure of minor skin wounds and for additional suture support.

**Micropore tape** (3M Health Care Ltd) 1.25cm= £0.62, 2.5cm= £0.92, 5cm= £1.63

**Omnifix**


**Omnifix tape** (Paul Hartmann Ltd) 10cm= £4.14, 15cm= £6.11, 5cm= £2.46

**OpSite Flexifix Gentle**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

**OpSite Flexifix Gentle tape** (Smith & Nephew Healthcare Ltd) 2.5cm= £0.60, 5cm= £1.87

**Primafix**


**Primafix tape** (Smith & Nephew Healthcare Ltd) 10cm= £2.40, 15cm= £3.54, 20cm= £4.36, 5cm= £1.63

**Scanpor**

(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988).

Backng of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Scanpor tape** (Bio-Diagnostics Ltd) 1.25cm= £0.56, 2.5cm= £0.92, 5cm= £1.76, 7.5cm= £2.58

**Silatape**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape

**Silatape** (Advancis Medical) 2cm= £5.64, 4cm= £5.64

**Strappal**

Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide

**Strappal adhesive tape** (BSN medical Ltd) 2.5cm= £1.42, 5cm= £2.41, 7.5cm= £3.62

**Transpore**

(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988).

Backng of paper-based or non-woven textile material spread with a polymeric adhesive mass

**Transpore tape** (3M Health Care Ltd) 2.5cm= £0.85, 5cm= £1.49

**Zinc Oxide Adhesive Tape, BP 1988**

Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide

**Fast Aid zinc oxide adhesive tape** (Robinson Healthcare) 1.25cm, 2.5cm, 5cm, 7.5cm

**Skin closure dressings**

Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive can be used for closure of minor skin wounds and for additional suture support.

**Skin closure strips, sterile**

**Leukostrip**

Drug Tariff specifies that these are specifically for personal administration by the prescriber

**Leukostrip** (Smith & Nephew Healthcare Ltd) skin closure strips 6.4mm x 76mm= £6.48

**Omnistrip**

Drug Tariff specifies that these are specifically for personal administration by the prescriber

**Omnistrip** (Paul Hartmann Ltd) skin closure strips sterile 6mm x 76mm= £24.68

**Steri-strip**

Drug Tariff specifies that these are specifically for personal administration by the prescriber

**Steri-strip** (3M Health Care Ltd) skin closure strips 6mm x 75mm= £8.03

**www.getintopharma.com**
Mollelast
Fabric plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)
Mollelast (Loehmann & Rauscher) bandage 4 cm × 4 m= £0.31

Peha-haft
Polyamide and Cellulose Contour Bandage, cohesive, latex-free
Peha-haft bandage (Paul Hartmann Ltd) 10 cm × 4 m= £0.78, 12 cm × 4 m= £0.92, 2.5 cm × 4 m= £0.75, 4 cm × 4 m= £0.48, 6 cm × 4 m= £0.57, 8 cm × 4 m= £0.68

PremierBand
Polyamide and Cellulose Contour Bandage
PremierBand bandage (Sherwood) 10 cm × 4 m= £0.17, 15 cm × 4 m= £0.25, 7.5 cm × 4 m= £0.14

Slinky
Fabric plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)
Slinky bandage (Mohlycke Health Care Ltd) 10 cm × 4 m= £0.72, 15 cm × 4 m= £0.65, 7.5 cm × 4 m= £0.60

Stayform
Fabric plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)
Stayform bandage (Robinson Healthcare) 10 cm × 4 m= £0.40, 15 cm × 4 m= £0.68, 8 cm × 4 m= £0.29, 7.5 cm × 4 m= £0.36

Tubular bandages and garments
Tubular bandages are available in different forms, according to the function required of them. Some are used under orthopaedic casts and some are suitable for protecting areas to which creams or ointments (other than those containing potent corticosteroids) have been applied. The conformability of the elasticated versions makes them particularly suitable for retaining dressings on difficult parts of the body or for soft tissue injury, but their use as the only means of applying pressure to an oedematous limb or to a varicose ulcer is not appropriate, since the pressure they exert is inadequate. Compression hosiery reduces the recurrence of venous leg ulcers and should be considered for use after wound healing. Silk clothing is available as an alternative to elasticated viscose stockinette garments, for use in the management of severe eczema and allergic skin conditions.

Elasticised Surgical Tubular Stockinette, Foam padded is used for relief of pressure and elimination of friction in relevant areas; porosity of foam lining allows normal water loss from skin surface.
For Elasticated Tubular Bandage, BP 1993, where no size stated by the prescriber, the 50 cm length should be supplied and width endorsed.
Non-elasticised Cotton Stockinette, Bleached, BP 1988 1 m lengths is used as basis (with wadding) for Plaster of Paris bandages etc.; 6 m length, compression bandage. For Non-elasticised Ribbed Cotton and Viscose Surgical Tubular Stockinette, BP 1988, the Drug Tariff specifies various combinations of sizes to provide sufficient material for part or full body coverage. It is used as protective dressings with tar-based and other steroid ointments.

Elasticated

Acti-Fast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage
Acti-Fast 2-way stretch stockinette (L&R Medical UK Ltd) 10.75 cm= £5.74, 17.5 cm= £1.85, 20 cm= £3.23, 3.5 cm= £0.56, 5 cm= £0.58, 7.5 cm= £0.78

Clinifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Clinifast stockinette (CliniSupplies Ltd) 10.75 cm= £6.04, 17.5 cm= £1.83, 3.5 cm= £0.56, 5 cm= £0.58, 7.5 cm= £0.77, clava 5-14 years= £6.75, 6 months-5 years= £5.85, cycle shorts large adult= £16.37, medium adult= £14.35, small adult= £12.59, gloves large adult= £5.03, child/small adult= £5.03, gloves medium adult= £5.03, child= £5.03, gloves small child= £5.03, leggins (Blue, Pink, White) 11-14 years= £11.88, 2-5 years= £2.90, 5-8 years= £10.69, 8-11 years= £11.88, mittens 2-8 years= £2.97, 8-14 years= £2.97, up to 24 months= £2.97, socks 8-14 years= £2.99, up to 8 years= £2.97, tights (Blue, Pink, White) 6-24 months= £7.13, vest long sleeve (Blue, Pink, White) 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 6-24 months= £7.13, 8-11 years= £11.88, vest short sleeve large adult= £16.37, medium adult= £14.35, small adult= £12.59

Comifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Comifast stockinette (Vernacare Ltd) 10.75 cm= £6.04, 17.5 cm= £1.83, 3.5 cm= £0.56, 5 cm= £0.58, 7.5 cm= £0.77

Comifast Easyswap
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Comifast Easyswap stockinette (Vernacare Ltd) clava 5-14 years= £6.75, 6 months-5 years= £5.85, leggins 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 8-11 years= £11.88, mittens 2-8 years= £2.97, 8-14 years= £2.97, up to 24 months= £2.97, socks 8-14 years= £2.97, up to 8 years= £2.97, tights 6-24 months= £7.13, vest long sleeve 11-14 years= £11.88, 2-5 years= £9.50, 5-8 years= £10.69, 6-24 months= £7.13, 8-11 years= £11.88

Comifast Multistretch
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Comifast Multistretch 2-way stretch stockinette (Vernacare Ltd) 10.75 cm= £6.45, 17.5 cm= £2.49, 3.5 cm= £0.61, 5 cm= £0.63, 7.5 cm= £0.83

Coverflex
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Coverflex stockinette (Paul Hartmann Ltd) 10.75 cm= £9.65, 17.5 cm= £2.54, 3.5 cm= £0.83, 5 cm= £0.87, 7.5 cm= £5.72

Easifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Easifast stockinette (Esasilk Ltd) 10.75 cm= £7.23, 17.5 cm= £1.91, 3.5 cm= £0.65, 5 cm= £0.69, 7.5 cm= £0.94

Elasticated Surgical Tubular Stockinette, Foam padded or Tupidap
(Drug Tariff specification 25). Fabric as for Elasticated Tubular Bandage with polyurethane foam lining.

Elasticated Tubular Bandage, BP 1993
(Drug Tariff specification 25). Fabric as for Elasticated Tubular Bandage with polyurethane foam lining; lengths 50 cm and 1 m

CLINigring bandage (CliniSupplies Ltd) 10 cm size F= £0.74, 12 cm size G= £0.77, 6.25 cm size B= £0.61, 6.75 cm size C= £0.65, 7.5 cm size D= £0.66, 8.75 cm size E= £0.74

Comifastigring bandage (Vernacare Ltd) 10 cm size F= £0.74, 12 cm size G= £0.77, 6.25 cm size B= £0.61, 6.75 cm size C= £0.65, 7.5 cm size D= £0.66, 8.75 cm size E= £0.74

Eseiban ESTS bandage (Esasilk Ltd) 10 cm size F= £1.80, 12 cm size G= £1.09, 6.25 cm size B= £0.87, 6.75 cm size C= £0.95, 7.5 cm size D= £0.98, 8.75 cm size E= £1.80

Tubigrip bandage (Mohlycke Health Care Ltd) 10 cm size F= £2.05, 12 cm size G= £2.37, 6.25 cm size B= £0.99, 6.75 cm size C= £1.89, 7.5 cm size D= £1.89, 8.75 cm size E= £2.05

easiGRIP bandage (Esasilk Ltd) 10 cm size F= £0.75, 12 cm size G= £0.78, 6.25 cm size B= £0.62, 6.75 cm size C= £0.66, 7.5 cm size D= £0.68, 8.75 cm size E= £0.75

Skinnies
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Skinnies Viscose stockinette (Dermacea Ltd) body suit (Blue, Ecru, Pink) 3-6 months= £16.97, 6-12 months= £19.11, up to 3 months= £16.97, clava (Blue, Ecru, Pink) 5-14 years= £8.11,
Support bandages

DreamSkin
Knitted silk fabric, hypoallergenic, sericin-free, with methacrylate copolymer and zinc-based antibacterial

Tubifast 2-way stretch
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes

CliniLite
Knitted fabric, viscose and elastomer yarn. Type

CliniPlus
Knitted fabric, viscose and elastomer yarn. Type

Support bandages
Light support bandages, which include the various forms of crepe bandage, are used in the prevention of oedema; they are also used to provide support for mild sprains and joints but their effectiveness has not been proven for this purpose. Since they have limited extensibility, they are able to provide light support without exerting undue pressure. For a warning against injudicious compression see Compression bandages.

Cotton Crepe Bandage
Light support bandage, 4.5 m stretched (all)

Hospicare C29 bandage (Paul Hartmann Ltd) 10cm x 4.5m £28.27, 15cm x 4.5m £34.27, 20cm x 4.5m £44.47, 25cm x 4.5m £53.67

Cotton Crepe Bandage, BP 1988
Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton and/or viscose threads; stretch bandage. 4.5 m stretched (both)

Elastocrepe bandage (BNF medical Ltd) 10cm x 4.5m, 7.5cm x 4.5m

www.getintopharma.com
**Flexocrepe bandage** (Robinson Healthcare) 10cm × 4.5m, 7.5cm × 4.5m

**Sterocrepe bandage** (Steroplast Healthcare Ltd) 10cm × 4.5m, 7.5cm × 4.5m

**Cotton Suspensory Bandage** (Drug Tariff). Type 1: cotton net bag with draw tapes and webbing waistband; small, medium, and large (all)

**Crepe Bandage, BP 1988**
Fabric, plain weave, warp of wool threads and crepe-twisted cotton threads, weft of cotton threads; stretch bandage; 4.5 m stretched

**Alvita crepe bandage** (Alliance Healthcare (Distribution) Ltd) 10cm × 4.5m, 15cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**CliniCrepe bandage** (CliniSupplies Ltd) 10cm × 4.5m, 15cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**Crepe bandage** (Robert Bailey & Son Pk) 10cm × 4.5m, 15cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**Propaz crepe bandage** (BSN medical Ltd) 10cm × 4.5m, 15cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**Vermaid crepe bandage** (Synergy Health (UK) Ltd) 10cm × 4.5m, 15cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**Elast Knitted fabric, viscose and elastomer yarn**. Type 2 (light support bandage)

**Elast (Molyl hype Healthcare Ltd) S bandage** 15cm × 12m= £5.64, bandage 10cm × 6m= £2.63, 10cm × 8m= £3.37, 15cm × 6m= £2.82

**Hospicrepe 233**
Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

**Hospicrepe 233 bandage** (Paul Hartmann Ltd) 10cm × 4.5m= £0.96, 15cm × 4.5m= £1.36, 5cm × 4.5m= £0.52, 7.5cm × 4.5m= £0.72

**Hospiline**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

**Hospiline bandage** (Paul Hartmann Ltd) 10cm × 4.5m= £0.63, 15cm × 4.5m= £0.92, 5cm × 4.5m= £0.37, 7.5cm × 4.5m= £0.52

**K-Lite**
Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

**K-Lite (Urgo Ltd) Long bandage** 10cm × 5.25m= £1.16, bandage 10cm × 4.5m= £1.02, 15cm × 4.5m= £1.47, 5cm × 4.5m= £0.56, 7cm × 4.5m= £0.78

**K-Plus**
Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

**K-Plus (Urgo Ltd) Long bandage** 10cm × 10.25m= £2.67, bandage 10cm × 8.7m= £2.31

**Knit-Firm**
Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

**Knit-Firm bandage** (Mallipledge Healthcare) 10cm × 4.5m= £0.66, 15cm × 4.5m= £0.96, 5cm × 4.5m= £0.36, 7cm × 4.5m= £0.51

**L3**
Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

**L3 (Smith & Nephew Healthcare Ltd) bandage** 10cm × 8.6m= £2.26

**Neosport**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

**Neosport bandage** (Neomedic Ltd) 10cm × 4.5m= £0.91, 15cm × 4.5m= £1.12, 5cm × 4.5m= £0.54, 7.5cm × 4.5m= £0.73

**PremierBand**
Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

**PremierBand bandage** (Sherwood) 10cm × 4.5m= £0.79, 15cm × 4.5m= £1.18, 5cm × 4.5m= £0.45, 7.5cm × 4.5m= £0.63

**Profore #2**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

**Profore #2 (Smith & Nephew Healthcare Ltd) bandage** 10cm × 4.5m= £1.39, latex free bandage 10cm × 4.5m= £1.47

**Profore #3**
Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

**Profore #3 (Smith & Nephew Healthcare Ltd) bandage** 10cm × 8.7m= £4.38

**Setocrepe**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

**Setocrepe (Molyl hype Healthcare Ltd) bandage** 10cm × 4.5m= £1.21

**Softcrepe**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

**Softcrepe bandage** (BSN medical Ltd) 10cm × 4.5m= £1.27, 15cm × 4.5m= £1.85, 5cm × 4.5m= £0.71, 7.5cm × 4.5m= £1.00

**Adhesive bandages**
Elastic adhesive bandages are used to provide compression in the treatment of varicose veins and for the support of injured joints; they should no longer be used for the support of fractured ribs and clavicles. They have also been used with zinc paste bandage in the treatment of venous ulcers, but they can cause skin reactions in susceptible patients and may not produce sufficient pressures for healing (significantly lower than those provided by other compression bandages).

**Elastic Adhesive Bandage, BP 1993**
Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads spread with adhesive mass containing zinc oxide. 4.5 m stretched

**Tensoplast bandage** (BSN medical Ltd) 10cm × 4.5m, 5cm × 4.5m, 7.5cm × 4.5m

**Cohesive bandages**
Cohesive bandages adhere to themselves, but not to the skin, and are useful for providing support for sports use where ordinary stretch bandages might become displaced and adhesive bandages are inappropriate. Care is needed in their application, however, since the loss of ability for movement between turns of the bandage to equalise local areas of high tension carries the potential for creating a tourniquet effect. Cohesive bandages can be used to support sprained joints and as an outer layer for multi-layer compression bandaging; they should not be used if arterial disease is suspected.

**Cohesive extensible bandages**

**Coban**
Bandage

**Coban (3M Health Care Ltd) self-adherant bandage** 10cm × 6m= £2.95

**K Press**
Bandage

**K Press bandage** (Urgo Ltd) 10cm × 6.5m= £2.96, 10cm × 7.5m= £3.45, 12cm × 7.5m= £4.34, 8cm × 7.5cm= £3.25

**Profore #4**
Bandage

**Profore #4 (Smith & Nephew Healthcare Ltd) bandage** 10cm × 2.5m= £3.33, latex free bandage 10cm × 2.5m= £3.62

**Ultra Fast**
Bandage

**Ultra (Robinson Healthcare) Fast cohesive bandage** 10cm × 6.3m= £2.59

**Compression bandages**
High compression products are used to provide the high compression needed for the management of gross varices, post-thrombotic venous insufficiency, venous leg ulcers, and gross oedema in average-sized limbs. Their use calls for an expert knowledge of the elastic properties of the products and experience in the technique of providing careful
graduated compression. Incorrect application can lead to uneven and inadequate pressures or to hazardous levels of pressure. In particular, injudicious use of compression in limbs with arterial disease has been reported to cause severe skin and tissue necrosis (in some instances calling for amputation). Doppler testing is required before treatment with compression. Oral pentoxifylline p. 254 can be used as adjunct therapy if a chronic venous leg ulcer does not respond to compression bandaging [unlicensed indication].

**High compression bandages**

**High Compression Bandage**
- Cotton, viscose, nylon, and Lycra® extensible bandage, 3 m (unstretched)
- K Three (Urgo Ltd) bandage 10cm × 3m= £2.87
- SurePress (Convatec Ltd) bandage 10cm × 3m= £3.71

**PEC High Compression Bandages**
- Polyamide, elastane, and cotton compression (high) extensible bandage, 3.5 m unstretched
- Setopress (Molnlycke Health Care Ltd) bandage 10cm × 3.5m= £3.58

**VEC High Compression Bandages**
- Viscose, elastane, and cotton compression (high) extensible bandage, 3 m unstretched (both)
- Tensopress bandage (BSN medical Ltd) 10cm × 3m= £3.54, 7.5cm × 3m= £2.75

**Short stretch compression bandages**

**Actico Bandage**
- Actico Bandage (L&R Medical UK Ltd) 10cm × 6m= £3.43, 12cm × 6m= £4.38, 4cm × 6m= £2.46, 6cm × 6m= £2.88, 8cm × 6m= £3.31

**Comprilan Bandage**
- Comprilan bandage (BSN medical Ltd) 10cm × 5m= £3.46, 12cm × 5m= £4.22, 6cm × 5m= £2.74, 8cm × 5m= £3.22

**Rosidal K Bandage**
- Rosidal K Bandage (Lohmann & Rauscher) 10cm × 10m= £6.17, 10cm × 5m= £3.55, 12cm × 5m= £4.30, 6cm × 5m= £2.72, 8cm × 5m= £3.25

**Sub-compression wadding bandage**

**Cellona Undercast Padding**
- Padding
- Cellona Undercast padding bandage (Lohmann & Rauscher) 10cm × 2.75m= £0.48, 15cm × 2.75m= £0.62, 5cm × 2.75m= £0.32, 7.5cm × 2.75m= £0.39

**Flexi-Ban Padding**
- Flexi-Ban (L&R Medical UK Ltd) bandage 10cm × 3.5m= £0.51

**K Tech Reduced Padding**
- K Tech Reduced bandage 10cm × (Urgo Ltd) 6m= £4.79, 7.3m= £5.23

**K-Soft Padding**
- K-Soft (Urgo Ltd) Long bandage 10cm × 4.5m= £0.58, bandage 10cm × 3.5m= £0.46

**K-Tech (K Tech in DMD) Padding**
- K-Tech (K Tech in DMD) Reduced bandage 10cm × 7.3m= £5.23, bandage 10cm × 5m= £3.99, 10cm × 6m= £4.79, 12cm × 6m= £6.04, 12cm × 7.3m= £6.60, 8cm × 6m= £4.52, 8cm × 7.3m= £4.93

**Ortho-Band Plus Padding**
- Ortho-Band (Millp ledgeHealthcare) Plus bandage 10cm × 3.5m= £0.37

**Profore #1 Padding**
- Profore #1 (Smith & Nephew Healthcare Ltd) bandage 10cm × 3.5m= £0.72, latex free bandage 10cm × 3.5m= £0.78

**Softex Padding**
Graduated compression hosiery

**Class 1 Light Support**
Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Class 2 Light Support**
Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Class 2 Medium Support**
Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Class 3 Strong Support**
Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Knee caps**
Class 2 Medium Support
Kneecaps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Class 3 Strong Support**
Kneecaps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Lymphoedema garments**
Lymphoedema compression garments are used to maintain limb shape and prevent additional fluid retention. Either flat-bed or circular knitting methods are used in the manufacture of elasticated compression garments. Seamless, circular-knitted garments (in standard sizes) can be used to prevent swelling if the lymphoedema is well controlled and if the limb is in good shape and without skin folds. Flat-knitted garments (usually made-to-measure) with a seam, provide greater rigidity and stiffness to maintain reduction of lymphoedema following treatment with compression bandages. A standard range of light, medium, or high compression garments are available, as well as low compression (12–16 mmHg) arm sleeves, made-to-measure garments up to compression 90 mmHg, and accessories—see Drug Tariff for details. Note there are different compression values for lymphoedema garments and graduated compression hosiery, see Compression hosiery and garments above.

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**Compression hosiery and garments**

£11.35, multi-layer compression bandage kit (8cm) 18cm–25cm ankle circumference=£7.77, 25cm–32cm ankle circumference=£8.45, multi-layer compression bandage kit size 0 short 18cm–25cm ankle circumference=£6.95, with UrgoStart multi-layer compression bandage kit 18cm–25cm ankle circumference=£10.27, 25cm–32cm ankle circumference=£10.95

**Medicated bandages**
Zinc Paste Bandage has been used with compression bandaging for the treatment of venous leg ulcers. However, paste bandages are associated with hypersensitivity reactions and should be used with caution. Zinc paste bandages are also used with coal tar or ichthammol in chronic lichenified skin conditions such as chronic eczema (ichthammol often being preferred since its action is considered to be milder). They are also used with calamine in milder eczematous skin conditions.

Zipzoc® can be used under appropriate compression bandages or hosiery in chronic venous insufficiency.

**Zinc Paste Bandage, BP 1993**
Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide; requires additional bandaging
Excipients: may include cetostearyl alcohol, hydroxybenzoates

**Viscopaste (Evolan Pharma AB) PB 7 bandage** 7.5cm × 6m= £3.74

**Zinc Paste and Ichtammol Bandage, BP 1993**
Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide and ichthammol; requires additional bandaging
Excipients: may include cetostearyl alcohol

**Ichthammol**
(Evolan Pharma AB) bandage 7.5cm × 6m= £3.78

**Zipzoc**
Sterile rayon stocking impregnated with ointment containing zinc oxide 20%

**Zipzoc (Evolan Pharma AB) stockings**= £34.70

**Compression hosiery and garments**

Compression (elastic) hosiery is used to treat conditions associated with chronic venous insufficiency, to prevent recurrence of thrombosis, or to reduce the risk of further venous ulceration after treatment with compression bandaging. Doppler testing to confirm arterial insufficiency is required before recommending the use of compression hosiery.

Before elastic hosiery can be dispensed, the quantity (single or pair), article (including accessories), and compression class must be specified by the prescriber. There are different compression values for graduated compression hosiery and lymphoedema garments (see table below). All dispensed elastic hosiery articles must state on the packaging that they conform with Drug Tariff technical specification No. 40, for further details see Drug Tariff.

**Graduated Compression hosiery, Class 1 Light Support** is used for superficial or early varices, varicosis during pregnancy.

**Graduated Compression hosiery, Class 2 Medium Support** is used for varices of medium severity, ulcer treatment and prophylaxis, mild oedema, varicosis during pregnancy.

**Graduated Compression hosiery, Class 3 Strong Support** is used for gross varices, post thrombotic venous insufficiency, gross oedema, ulcer treatment and prophylaxis.

**Compression values for hosiery and lymphoedema garments**

**Class 1:** Compression hosiery (British standard) 14–17 mmHg, lymphoedema garments (European classification) 18–21 mmHg; **Class 2** Compression hosiery (British standard) 18–24 mmHg, lymphoedema garments (European classification) 23–32 mmHg; **Class 3** Compression hosiery (British standard) 25–35 mmHg, lymphoedema garments (European classification) 34–46 mmHg; **Class 4** Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 49–70 mmHg; **Class 4 super** Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 60–90 mmHg.
Dental Practitioners’ Formulary

List of Dental Preparations

The following list has been approved by the appropriate Secretaries of State, and the preparations therein may be prescribed by dental practitioners on form FP10D (GP14 in Scotland, WP10D in Wales).

Licensed sugar-free versions, where available, are preferred.
Licensed alcohol-free mouthwashes, where available, are preferred.

Aciclovir Tablets, BP
Aciclovir Cream, BP
Aciclovir Oral Suspension, BP, 200 mg/5 mL
Aciclovir Tablets, BP, 200 mg
Amoxicillin Capsules, BP
Amoxicillin Oral Powder, DPF
Amoxicillin Oral Suspension, BP
Artificial Saliva Gel, DPF
Artificial Saliva Oral Spray, DPF
Artificial Saliva Pastilles, DPF
Artificial Saliva Protective Spray, DPF
Artificial Saliva Substitutes as listed below (to be prescribed only for indications approved by ACBS (patients suffering from dry mouth as a result of having or, having undergone, radiotherapy or sicca syndrome):
BioXtra Gel Mouthspray
BioXtra Moisturising Gel
Glansosane
Salvez
Artificial Saliva Substitute Spray, DPF
Aspirin Tablets, Dispensable, BP
Azithromycin Capsules, 250 mg, DPF
Azithromycin Oral Suspension, 200 mg/5 mL, DPF
Azithromycin Tablets, 250 mg, DPF
Azithromycin Tablets, 500 mg, DPF
Beclometasone Pressurised Inhalation, BP, 50 micrograms/metered inhalation, CFC-free, as:
Clenil Modulite
Benzydamine Mouthwash, BP 0.15%
Benzydamine Oromucosal Spray, BP 0.15%
Betamethasone Soluble Tablets, 500 micrograms, DPF
Carbamazepine Tablets, BP
Cefalexin Capsules, BP
Cefalexin Oral Suspension, BP
Cefalexin Tablets, BP
Cefradine Capsules, BP
Cetirizine Tablets, BP, 10 mg
Chlorhexidine Gluconate Gel, BP
Chlorhexidine Mouthwash, BP
Chlorhexidine Oral Spray, DPF
Chlorpheniramine Oral Solution, BP
Chlorpheniramine Tablets, BP
Choline Salicylate Dental Gel, BP
Clarithromycin Oral Suspension, 125 mg/5 mL, DPF
Clarithromycin Oral Suspension, 250 mg/5 mL, DPF
Clarithromycin Tablets, BP
Clindamycin Capsules, BP
Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
Co-amoxiclav Oral Suspension, BP, 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL
Co-amoxiclav Oral Suspension, BP, 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL
Diazepam Oral Solution, BP, 2 mg/5 mL
Diazepam Tablets, BP
Diclofenac Sodium Tablets, Gastro-resistant, BP
Dihydromocodeine Tablets, BP, 30 mg
Doxycline Tablets, Dispersible, BP
Doxycycline Capsules, BP, 100 mg
Doxycycline Tablets, 20 mg, DPF
Ephedrine Nasal Drops, BP
Erythromycin Ethyl Succinate Oral Suspension, BP
Erythromycin Ethyl Succinate Tablets, BP
Erythromycin Stearate Tablets, BP
Erythromycin Tablets, Gastro-resistant, BP
Fluconazole Capsules, 50 mg, DPF
Fluconazole Oral Suspension, 50 mg/5 mL, DPF
Hydrocortisone Cream, BP, 1%
Hydrocortisone Oromucosal Tablets, BP
Hydrogen Peroxide Mouthwash, BP, 6%
Ibuprofen Oral Suspension, BP, sugar-free
Ibuprofen Tablets, BP
Lansoprazole Capsules, Gastro-resistant, BP
Lidocaine Ointment, BP, 5%
Lidocaine Spray 10%, DPF
Loratadine Syrup, 5 mg/5 mL, DPF
Loratadine Tablets, BP, 10 mg
Menthol and Eucalyptus Inhalation, BP 1980
Metronidazole Oral Suspension, BP
Metronidazole Tablets, BP
Miconazole Cream, BP
Miconazole Oromucosal Gel, BP
Miconazole and Hydrocortisone Cream, BP
Miconazole and Hydrocortisone Ointment, BP
Nystatin Oral Suspension, BP
Omeprazole Capsules, Gastro-resistant, BP
Oxytetracycline Tablets, BP
Paracetamol Oral Suspension, BP
Paracetamol Tablets, BP
Paracetamol Tablets, Soluble, BP
Phenoxymethylpenicillin Oral Solution, BP
Phenoxymethylpenicillin Tablets, BP
Promethazine Hydrochloride Tablets, BP
Promethazine Oral Solution, BP
Saliva Stimulating Tablets, DPF
Sodium Chloride Mouthwash, Compound, BP
Sodium Fluoride Mouthwash, BP
Sodium Fluoride Oral Drops, BP
Sodium Fluoride Tablets, BP
Sodium Fluoride Toothpaste 0.619%, DPF
Sodium Fluoride Toothpaste 1.1%, DPF
Sodium Fusidate Ointment, BP
Temazepam Oral Solution, BP
Temazepam Tablets, BP
Tetracycline Tablets, BP

Preparations in this list which are not included in the BP or BPC are described under Details of DPF preparations.

For details of preparations that can be prescribed, see individual entries under the relevant drug monographs throughout the BNF publications.

Details of DPF preparations

Preparations on the List of Dental Preparations which are specified as DPF are described as follows in the DPF. Although brand names have sometimes been included for identification purposes preparations on the list should be prescribed by non-proprietary name.

Amoxicillin Oral Powder
amoxicillin (as trihydrate) 3 g sachet
Artificial Saliva Gel
(proprietary product: Biotene Oralbalance), lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis.

Artificial Saliva Oral Spray
(proprietary product: Xerotin) consists of water, sorbitol, carmellose (carboxymethylcellulose), potassium chloride, sodium chloride, potassium phosphate, magnesium chloride, calcium chloride and other ingredients, pH neutral.

Artificial Saliva Pastilles
(proprietary product: Salivix), consists of acacia, malic acid, and other ingredients.

Artificial Saliva Protective Spray
(proprietary product: Aquoral) consists of oxidised glycerol triesters, silicon dioxide, flavouring agents, aspartame.

Artificial Saliva Substitute Spray
(proprietary product: AS Saliva Orthana Spray) consists of mucin, methylparaben, benzalkonium chloride, EDTA, xylitol, peppermint oil, spearmint oil, mineral salts.

Azithromycin Capsules
azithromycin 250 mg.

Azithromycin Oral Suspension 200 mg/5 mL.
azithromycin 200 mg/5 mL when reconstituted with water.

Azithromycin Tablets
azithromycin 250 mg and 500 mg.

Betamethasone Soluble Tablets 500 micrograms.
betamethasone (as sodium phosphate) 500 micrograms.

Chlorhexidine Oral Spray
(proprietary product: Corsodyl Oral Spray), chlorhexidine gluconate 0.2%.

Clarithromycin Oral Suspension 125 mg/5 mL.
clarithromycin 125 mg/5 mL when reconstituted with water.

Clarithromycin Oral Suspension 250 mg/5 mL.
clarithromycin 250 mg/5 mL when reconstituted with water.

Doxycycline Tablets 20 mg.
(proprietary product: Periostat), doxycycline (as hyclate) 20 mg.

Fluconazole Capsules 50 mg.
fluconazole 50 mg.

Fluconazole Oral Suspension 50 mg/5 mL.
(proprietary product: Diflucan), fluconazole 50 mg/5 mL when reconstituted with water.

Lidocaine Spray 10%.
(proprietary product: Xylocaine Spray), lidocaine 10% supplying 10 mg lidocaine/spray.

Loratadine Syrup 5 mg/5 mL.
loratadine 5 mg/5 mL.

Saliva Stimulating Tablets
(proprietary product: SST), citric acid, malic acid and other ingredients in a sorbitol base.

Sodium Fluoride Toothpaste 0.619%.
(proprietary product: Duraphat ‘2800 ppm’ Toothpaste), sodium fluoride 0.619%.

Sodium Fluoride Toothpaste 1.1%.
(proprietary product: Duraphat ‘5000 ppm’ Toothpaste), sodium fluoride 1.1%.
Nurse Prescribers’ Formulary (NPF)

Nurse Prescribers’ Formulary for Community Practitioners

List of preparations approved by the Secretary of State which may be prescribed on form FP10P (form HS21(N) in Northern Ireland, form GP10(N) in Scotland, forms WP10CN and WP10PN in Wales) by Nurses for National Health Service patients.

Community practitioners who have completed the necessary training may only prescribe items appearing in the nurse prescribers’ list set out below. Community Practitioner Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Medicinal Preparations

Preparations on this list which are not included in the BP or BPC are described under Details of NPF preparations. Preparations on this list which are not included in the BP or BPC are described under Details of NPF preparations.

Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Emollient Bath and Shower Preparations as listed below:

- Aqueous Cream, BP
- Balneum® (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
- Balneum Plus® Bath Oil (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
- Cetiraben® emollient Bath Additive
- Dermal® Bath Emollient
- Doublebase® Emollient Bath Additive
- Doublebase® Emollient Shower Gel
- Doublebase® Emollient Wash Gel
- Hydromol® Bath and Shower Emollient
- Oiatum® Emollient
- Oiatum® Gel
- Oiatum® Junior Bath Additive
- Zerolatum® Emollient Medicinal Bath Oil
- Folic Acid Tablets 400 micrograms, BP
- Glycerol Suppositories, BP
- Ibuprofen Oral Suspension, BP (except for indications and doses that are prescription-only)
- Ibuprofen Tablets, BP (except for indications and doses that are prescription-only)
- Ispaghula Husk Granules, BP
- Ispaghula Husk Granules, Effervescent, BP
- Ispaghula Husk Oral Powder, BP
- Lactulose Solution, BP
- Lidocaine Ointment, BP
- Lidocaine and Chlorhexidine Gel, BP
- Macrogol Oral Liquid, Compound, NPF
- Macrogol Oral Powder, Compound, NPF
- Macrogol Oral Powder, Compound, Half-strength, NPF
- Magnesium Hydroxide Mixture, BP
- Magnesium Sulfate Paste, BP
- Malathion aqueous lotions containing at least 0.5% of both of which are available as
- Mebendazole Tablets, NPF
- Mebendazole Tablets, BP
- Miconazole Oromucosal Gel, BP
- Mouthwash Solution-tablets, NPF
- Nicotine Inhalation Cartridge for Oromucosal Use, NPF
- Nicotine Lozenge, NPF
- Nicotine Medicated Chewing Gum, NPF
- Nicotine Nasal Spray, NPF
- Nicotine Oral Spray, NPF
- Nicotine Sublingual Tablets, NPF
- Nicotine Transdermal Patches, NPF
- Nystatin Oral Suspension, BP
- Olive Oil Ear Drops, BP
- Paracetamol Oral Suspension, BP (includes 120 mg/5 mL and 250 mg/5 mL strengths—both of which are available as sugar-free formulations)

www.getintopharma.com
Paracetamol Tablets, BP (max. 96 tablets; max. pack size 32 tables)
Paracetamol Tablets, Soluble, BP (includes 120-mg and 500-mg tablets; max. 96 tablets; max. pack size 32 tablets)
Permethrin Cream, NPF
Phosphates Enema, BP
Povidone–Iodine Solution, BP
Senna Oral Solution, NPF
Senna Tablets, BP
Senna and Ispaghula Granules, NPF
Sodium Chloride Solution, Sterile, BP
Sodium Citrate Compound Enema, NPF
Sodium Picosulphate Capsules, NPF
Sodium Picosulphate Elixir, NPF
Spermicidal contraceptives as listed below:
- Gygel® Contraceptive Jelly
- Sterculia Granules, NPF
- Sterculia and Frangula Granules, NPF
- Titanium Ointment, BP
- Water for Injections, BP
- Zinc and Castor Oil Ointment, BP
- Zinc Oxide and Dimeticone Spray, NPF
- Zinc Oxide Impregnated Medicated Bandage, NPF
- Zinc Oxide Impregnated Medicated Stocking, NPF
- Zinc Paste Bandage, BP 1993
- Zinc Paste and Ichthammol Bandage, BP 1993

**Appliances and Reagents (including Wound Management Products)**

Community Practitioner Nurse Prescribers in England, Wales and Northern Ireland can prescribe any appliance or reagent in the relevant Drug Tariff. In the Scottish Drug Tariff, Appliances and Reagents which may not be prescribed by Nurses are annotated N.

**Appliances** (including Contraceptive Devices) as listed in Part I of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 3 (Appliances) and Part 2 (Dressing) of the Scottish Drug Tariff). (Where it is not appropriate for nurse prescribers in family planning clinics to prescribe contraceptive devices using form FP10(P) (forms WP10CN and WP10PN in Wales), they may prescribe using the same system as doctors in the clinic.)

**Incontinence Appliances** as listed in Part IXB of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 5 of the Scottish Drug Tariff).

**Stoma Appliances and Associated Products** as listed in Part IX of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 6 of the Scottish Drug Tariff).

**Chemical Reagents** as listed in Part IX of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 9 of the Scottish Drug Tariff).

The Drug Tariffs can be accessed online at:
- National Health Service Drug Tariff for England and Wales: [www.ppa.org.uk/ppa/edt_intro.htm](http://www.ppa.org.uk/ppa/edt_intro.htm)
- Health and Personal Social Services for Northern Ireland Drug Tariff: [www.hscbusiness.hscni.net/services/2034.htm](http://www.hscbusiness.hscni.net/services/2034.htm)

**Details of NPF preparations**

Preparations on the Nurse Prescribers’ Formulary which are not included in the BP or BPC are described as follows in the Nurse Prescribers’ Formulary. Although brand names have sometimes been included for identification purposes, it is recommended that non-proprietary names should be used for prescribing medicinal preparations in the NPF except where a non-proprietary name is not available.

**Arachis Oil Enema**

arachis oil 100%

**Catheter Maintenance Solution, Sodium Chloride**

(proprietary products: OptiFlo S; Uro-Tainer Sodium Chloride; Ureflex-S), sodium chloride 0.9%

**Catheter Maintenance Solution, ‘Solution G’**

(proprietary products: OptiFlo G; Uro-Tainer Suby G; Ureflex G), citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%

**Catheter Maintenance Solution, ‘Solution R’**

(proprietary products: OptiFlo R; Uro-Tainer Solution R; Ureflex R), citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%

**Chlorhexidine gluconate alcoholic solutions**

(proprietary products: ChloraPrep, Hydrex Solution; Hydrex spray), chlorhexidine gluconate in alcoholic solution

**Chlorhexidine gluconate aqueous solutions**

(proprietary product: Unisept), chlorhexidine gluconate in aqueous solution

**Co-danthramer Capsules**

(co-danthramer 25/200 (dantron 25 mg, poloxamer 188’ 200 mg)

**Co-danthramer Capsules, Strong**

(co-danthramer 37.5/200 (dantron 37.5 mg, poloxamer 188’ 500 mg)

**Co-danthramer Oral Suspension**

(proprietary product: Codalax), co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer 188’ 200 mg/5 mL)

**Co-danthramer Oral Suspension, Strong**

(proprietary product: Codalax Forte), co-danthramer 75/1000 in 5 mL (dantron 75 mg, poloxamer 188’ 1 g/5 mL)

**Co-danthrusate Oral Suspension**

(proprietary product: Normax), co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/5 mL)

**Dimeticone barrier creams**

(proprietary products Conotrane Cream, dimeticone 350’ 22%; Siopel Barrier Cream, dimeticone 1000’ 10%), dimeticone 10–22%

**Dimeticone Lotion**

(proprietary product: Hedrin), dimeticone 4%

**Docusate Enema**

(proprietary product: Norgalax Micro-enema), docusate sodium 120 mg in 10 g

**Liquid and White Soft Paraffin Ointment**

liquid paraffin 50%, white soft paraffin 50%

**Macrogol Oral Liquid, Compound**

(proprietary product: Movicol Liquid), macrogol 3350’ (polyethylene glycol 3350’ 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/25 mL)

**Macrogol Oral Powder, Compound**

(proprietary products: Laxido Orange, Molaxole, Movicol), macrogol 3350’ (polyethylene glycol 3350’ 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet; (amount of potassium chloride varies according to strength of Movicol® as follows: plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet; chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K⁺ 5.4 mmol/litre)

**Macrogol Oral Powder, Compound, Half-strength**

(proprietary product: Movicol-Half), macrogol 3350’ (polyethylene glycol 3350’ 6.563 g, sodium bicarbonate 89.3 g, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet)
Malathion aqueous lotions (proprietary products: Derbac-M Liquid), malathion 0.5% in an aqueous basis

Mebendazole Oral Suspension
(proprietary product: Vermox), mebendazole 100 mg/5 mL.

Mebendazole Tablets
(proprietary products: Ovex, Vermox), mebendazole 100 mg (can be supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg)

Mouthwash Solution-tablets consist of tablets which may contain antimicrobial, colouring and flavouring agents in a suitable soluble effervescence basis to make a mouthwash

Nicotine Inhalation Cartridge for Oromucosal Use
(proprietary products: NicAssist Inhalator, Nicorette Inhalator), nicotine 15 mg (for use with inhalation mouthpiece; to be prescribed as either a starter pack (6 cartridges with inhalator device and holder) or refill pack (42 cartridges with inhalator device)

Nicotine Lozenge
nicotine (as bitartrate) 1 mg or 2 mg (proprietary product: Nicorette Mint Lozenge, Nicotinell Mint Lozenge), or nicotine (as resinate) 1.5 mg, 2 mg, or 4 mg (proprietary product: NiQuitin Lozenges, NiQuitin Minis, NiQuitin Pre-quit)

Nicotine Medicated Chewing Gum
(proprietary products: NicAssist Gum, Nicorette Gum, Nicotinell Gum, NiQuitin Gum), nicotine 2 mg or 4 mg

Nicotine Nasal Spray
(proprietary product: NicAssist Nasal Spray, Nicorette Nasal Spray), nicotine 500 micrograms/metered spray

Nicotine Oral Spray
(proprietary product: Nicorette Quickmist), nicotine 1 mg/metered spray

Nicotine Sublingual Tablets
(proprietary product: NicAssist Microtab, Nicorette Microtab), nicotine (as a cyclodextrin complex) 2 mg (to be prescribed as either a starter pack (2 x 15-tablet discs with dispenser) or refill pack (7 x 15-tablet discs))

Nicotine Transdermal Patches releasing in each 16 hours, nicotine approx. 5 mg, 10 mg, or 15 mg (proprietary products: Boots NicAssist Patch, Nicorette Patch), or releasing in each 16 hours approx. 10 mg, 15 mg, or 25 mg (proprietary products: NicAssist Translucent Patch, Nicorette Invisi Patch), or releasing in each 24 hours nicotine approx. 7 mg, 14 mg, or 21 mg (proprietary products: Nicopatch, Nicotinell TTS, NiQuitin, NiQuitin Clear) (prescriber should specify the brand to be dispensed)

Permethrin Cream
(proprietary product: Lyclear Dermal Cream), permethrin 5%

Senna Oral Solution
(proprietary product: Senokot Syrup), sennosides 7.5 mg/5 mL.

Senna and Ispaghula Granules
(proprietary product: Manevac Granules), senna fruit 12.4%, ispaghula 54.2%

Sodium Citrate Compound Enema
(proprietary products: Micolette Micro-enema; Micralax Micro-enema; Relaxit Micro-enema), sodium citrate 450 mg with glycerol, sorbitol and an anionic surfactant

Sodium Picosulfate Capsules
(proprietary products: Dulcolax Perles), sodium picosulfate 2.5 mg
Non-medical prescribing

Overview
A range of non-medical healthcare professionals can prescribe medicines for patients as either Independent or Supplementary Prescribers. Independent prescribers are practitioners responsible and accountable for the assessment of patients with previously undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Supplementary prescribing is a partnership between an independent prescriber (a doctor or a dentist) and a supplementary prescriber to implement an agreed Clinical Management Plan for an individual patient with that patient’s agreement.

Independent and Supplementary Prescribers are identified by an annotation next to their name in the relevant professional register.


For information on the supply and administration of medicines to groups of patients using Patient Group Directions see Guidance on prescribing p. 1.

In order to protect patient safety, the initial prescribing and supply of medicines prescribed should normally remain separate functions performed by separate healthcare professionals.

Nurses
Nurse Independent Prescribers (formerly known as Extended Formulary Nurse Prescribers) are able to prescribe any medicine for any medical condition. Unlicensed medicines are excluded from the Nurse Prescribing Formulary in Scotland.

Nurse Independent Prescribers are able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine hydrochloride p. 456, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Nurse Independent Prescribers must work within their own level of professional competence and expertise.

The Nurse Prescribers’ Formulary (NPF) p. 1617 for Community Practitioners provides information on prescribing.

Pharmacists
Pharmacist Independent Prescribers can prescribe any medicine for any medical condition. This includes unlicensed medicines, subject to accepted clinical good practice.

They are also able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine hydrochloride p. 456, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Pharmacist Independent Prescribers must work within their own level of professional competence and expertise.

Physiotherapists
Physiotherapist Independent Prescribers can prescribe any medicine for any medical condition. This includes "off-label" medicines subject to accepted clinical good practice. They are also allowed to prescribe the following Controlled Drugs: oral or injectable morphine p. 463, transdermal fentanyl p. 458 and oral diazepam p. 343, dihydrocodeine tartrate p. 456, lorazepam p. 339, oxycodone hydrochloride p. 466 or temazepam p. 488.

Physiotherapist Independent Prescribers must work within their own level of professional competence and expertise.

Therapeutic radiographers
Therapeutic Radiographer Independent Prescribers can prescribe any medicine for any medical condition. This includes "off-label" medicines subject to accepted clinical good practice. Therapeutic Radiographer Independent Prescribers must work within their own level of professional competence and expertise.

Optometrists
Optometrist Independent Prescribers can prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye, except Controlled Drugs or medicines for parenteral administration. Optometrist Independent Prescribers must work within their own level of professional competence and expertise.

Podiatrists
Podiatrist Independent Prescribers can prescribe any medicine for any medical condition. This includes "off-label" medicines subject to accepted clinical good practice. They are also allowed to prescribe the following Controlled Drugs for oral administration: diazepam p. 343, dihydrocodeine tartrate p. 456, lorazepam p. 339 and temazepam p. 488.

Podiatrist Independent Prescribers must work within their own level of professional competence and expertise.

Further Information
For further details about the different types of prescribers, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).
Index of manufacturers

The following is an alphabetical list of manufacturers and other companies referenced in the BNF, with their medicines information or general contact details. For information on ‘special-order’ manufacturers and specialist importing companies see ‘Special-order manufacturers’.

3M Health Care Ltd, Tel: 01509 61611
A S Pharma Ltd, Tel: 01264 332712, info@ccmed.co.uk
A Menarini Farmaceutica Internazionale SRL, Tel: 0800 0858678, menarinig@medinformation.co.uk
A1 Pharmaceuticals, Tel: 01708 528900, enquiries@alp1.co.uk
Abbott Healthcare Products Ltd, Tel: 0800 1701177, ukabbottnutrition@abbott.com
AbbVie Ltd, Tel: 01628 561092, ukmedinfo@abbvie.com
Accord Healthcare Ltd, Tel: 021 385257, medinfo@accord-healthcare.co.uk
Actavis UK Ltd, Tel: 02171 385257, medinfo@actavis.co.uk
Actelion Pharmaceuticals UK Ltd, Tel: 02089 937088, enquiries@actelion.com
A1con Eye Care Ltd, Tel: 0345 2669363, medical.department@1alcon.com
Acon Pharma UK Ltd, Tel: 0800 6891992, medicalinformation@aklonpharma.com
Astellas Pharma Ltd, Tel: 0800 7835018, info@gb.astellas.com
AstraZeneca UK Ltd, Tel: 0800 7830033, medicalinformation@astrazeneca.com
Atlantic Pharma Ltd, Tel: 0845 5191609, enquiries@atlanticpharma.co.uk
Afnahs Pharma UK Ltd, Tel: 0279 406759, pservices@diamondpharmaservices.com
Aunden McKenzie (Pharma Division) Ltd, Tel: 02171 385257, Medinfo@accord-healthcare.co.uk
Aurobindo Pharma Ltd, Tel: 0208 8458811, medinfo@aurobindo.com
Aylesbury Medical Centre, Tel: 01626 746501
Ayre Medical Ltd, Tel: 01784 477167, medicalinformation@ayremedicals.com
ALK-Abello Ltd, Tel: 0198 9037940, info@uk.alk-abello.co.uk
Allergan Ltd, Tel: 01628 494026, UK, Medinfo@allergan.com
Allergy Therapeutics (UK) Ltd, Tel: 01903 844700, marketingsupport@allergytherapeutics.com
Alliance Pharmaceuticals Ltd, Tel: 0249 466966, medinfo@alliancepharma.co.uk
Almirall Ltd, Tel: 0800 0087399, almirall@professionalinformation.co.uk
Almus Pharmaceuticals Ltd, Tel: 0800 9179783, med.info@almus.co.uk
Altacor Ltd, Tel: 01189 026766, info@altacorpharma.com
Ambe Ltd, Tel: 01732 760900, info@ambemedical.com
Amgen Ltd, Tel: 01223 436441, gbinfo林@amgen.com
Amicus Therapeutics UK Ltd, Tel: 01753 888567
AMO UK Ltd, Tel: 01344 864042, rcc@its.jnj.com
Amryt Pharma, Tel: 01604 549952, medinfo@amrytpharma.com
AOP Orphan Pharmaceuticals AG, Tel: 0211 2624119, anne.wiorrall-hickmann@aoporpham.com
Aristo Pharma Ltd, Tel: 01483 920754, medinfo@aristo-pharma.co.uk
Arjun Products Ltd, Tel: 0800 0157806, info@arjunproducts.co.uk
Ascot Laboratories Ltd, Tel: 01923 711971, specials@ascotpharma.com
Aspar Pharmaceuticals Ltd, Tel: 020 82059846, info@aspar.co.uk
Astra Zeneca Healthcare Ltd, Tel: 0800 00731176, medicalinformation@astrella.co.uk
Atlantic Pharma Ltd, Tel: 0845 5191609, enquiries@atlanticpharma.co.uk
Afnahs Pharma UK Ltd, Tel: 0279 406759, pservices@diamondpharmaservices.com
Aunden McKenzie (Pharma Division) Ltd, Tel: 02171 385257, Medinfo@accord-healthcare.co.uk
Aurobindo Pharma Ltd, Tel: 0208 8458811, medinfo@aurobindo.com
AVIMES International Ltd, Tel: 0845-6805496, info@avimes.com
B. Braun Medical Ltd, Tel: 0114 2259000, info.bmuk@bbr.aum
B. Braun Melsungen AG, Tel: 049 3641 5195330, medinfo@biolitecpharma.com
B. Braun Medical Ltd, Tel: 0114 2259000, info.bmuk@bbr.aum
Bayer PLC, Tel: 0181 2063000, medicalinformation@bayer.co.uk
BBI Healthcare Ltd, Tel: 01656 868930, info@bbeihealthcare.com
Beacon Pharmaceuticals Ltd, Tel: 01233 506574, medicalinformation@beaconpharma.com
Beiersdorf UK Ltd, Tel: 0121 329 8800
Bell, Sons & Co (Drugists) Ltd, Tel: 0151 4222100, Med-info@bell-healthcare.com
Besins Healthcare (UK) Ltd, Tel: 01748 828849, medicalinformationuk@besins.com
BHR Pharmaceuticals Ltd, Tel: 02476 377210, bhrmedinfo@bhrpharmaceuticals.com
BIAL Pharma UK Ltd, Tel: 01753 916010, medinfo@bial.com
Bio Medicines, Tel: +44 61 5303193, info@siliconbio.com
Bio Products Laboratory Ltd, Tel: 020 89572622, medinfo@bpl.co.uk
Bio-Diagnostics Ltd, Tel: 01684 592262, enquiries@bio-diagnostics.co.uk
Biogen Idec Ltd, Tel: 0800 0087401, MedinfokUK@biogen.com
Biologics Ltd, Tel: +44 3641 5195330, medinfo@biolitecpharma.com
Biokin Biologicals Ltd, Tel: 0845 0177003, medinfomue@biomtns.com
Bio-Tech Pharmacal Inc, Tel: +1 304 3451199, customerservice@bio-tech-pharma.com
Biotest (UK) Ltd, Tel: 0121 7448444, medicinesinformation.ub@biotest.com
Blumont Pharma Ltd, Tel: 01476 978568
B.O.C. Medical, Tel: 0800 136603, healthcare.home-uk@boc.com
Boehringer Ingelheim Ltd, Tel: 01344 742579, medinfo@bhr.boehringer-ingelheim.com
Boston Healthcare Ltd, Tel: 01908 363499, medinfo@bostonhealthcare.co.uk
Brancaster Pharma Ltd, Tel: 01737 243407, safety@brancasterpharma.com
Bray Group Ltd, Tel: 01367 240736, info@bray-healthcare.com
Bristol Laboratories Ltd, Tel: 01442 200922, info@briallab.co.uk
Bristol-Myers Squibb Pharmaceuticals Ltd, Tel: 0800 7311736, medicalinformation@bms.com
Britannia Pharmaceuticals Ltd, Tel: 01483 920763, enquiries@medinformation.co.uk
Brown & Burk UK Ltd, Tel: 0208 5778200, bpbukq@bbukldt.com
BSN Medical Ltd, Tel: 01482 670100, orders.uk@bsnmedical.com
BTG International Ltd, Tel: +1 877 6269989, medical.services@btgplc.com
C D Medical Ltd, Tel: 01942 813933
Cambridge Healthcare Supplies Ltd, Tel: 01908 363434, medinfo@cambridge-healthcare.co.uk
Cambridge Sensors Ltd, Tel: 0800 0883920, info@micorodts.com
CareFusion UK Ltd, Tel: 0800 0437546, carefusion@professionalinformation.co.uk
Carniopharm GmbH, Tel: 01748 828812, carinopharm@professionalinformation.co.uk
Casen Recordati S.L., Tel: +34 91 3517964, info@casenrecordati.com
CD Pharma Srl, Tel: +39 02 43980539, info@cdpharma.com
Celgene Ltd, Tel: 08488 000045, medinfo.uk@ire.celgene.com
Canelle Medical UK Ltd, Tel: 0870 1923283, chanelle@medinformation.co.uk
Charles S. Bullen Stomacare Ltd, Tel: 0800 888501
Chattem (U.K.) Ltd, Tel: 01784 477167, info@chemidex.co.uk
Chemidex Pharma Ltd, Tel: 01784 477167, info@chemidex.co.uk
Cheplapharm Arzneimittel GmbH, Tel: 0800 1450314, cheplapharm@redlinepv.co.uk
Chiesi Ltd, Tel: 0161 4855555, medinfo.uk@chiesi.com
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</tr>
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<td>Chugai Pharma UK Ltd</td>
<td>020 89875600</td>
<td><a href="mailto:medinfo@chugai-pharm.co.uk">medinfo@chugai-pharm.co.uk</a></td>
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<td>0800 0281454</td>
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<td>01279 414969</td>
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<td>01748 828375</td>
<td><a href="mailto:medicalinfo@clinigenegroup.com">medicalinfo@clinigenegroup.com</a></td>
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<td>0808 1596017</td>
<td><a href="mailto:info@clinicalmed.co.uk">info@clinicalmed.co.uk</a></td>
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<td>Clinisupplies Ltd</td>
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<td>020 37511888</td>
<td><a href="mailto:drugssafety@consilienthealth.com">drugssafety@consilienthealth.com</a></td>
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<td><a href="mailto:info@contura.co.uk">info@contura.co.uk</a></td>
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<td><a href="mailto:wound.webcare@convatec.com">wound.webcare@convatec.com</a></td>
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<td>Creopharma Ltd</td>
<td>01484 007870</td>
<td><a href="mailto:medinfo@creopharma.com">medinfo@creopharma.com</a></td>
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<td><a href="mailto:info@crescentpharma.com">info@crescentpharma.com</a></td>
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<td>01444 447405</td>
<td><a href="mailto:medinfo@cslbehring.com">medinfo@cslbehring.com</a></td>
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<td>01634 766228</td>
<td><a href="mailto:orders@cubicpharmacy.co.uk">orders@cubicpharmacy.co.uk</a></td>
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<td>08000 028512</td>
<td><a href="mailto:medinfo@daichisankyo.co.uk">medinfo@daichisankyo.co.uk</a></td>
</tr>
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<td>Dendron Ltd</td>
<td>01923 229251</td>
<td><a href="mailto:info@dendron.co.uk">info@dendron.co.uk</a></td>
</tr>
<tr>
<td>Dentsply Ltd</td>
<td>0345 1935193</td>
<td><a href="mailto:sales@dentsplysirona.com">sales@dentsplysirona.com</a></td>
</tr>
<tr>
<td>Derma Laboratories Ltd</td>
<td>01462 458866</td>
<td><a href="mailto:medicalinfo@derma-laboratories.co.uk">medicalinfo@derma-laboratories.co.uk</a></td>
</tr>
<tr>
<td>Dermaplex Ltd</td>
<td>01562 884898</td>
<td><a href="mailto:info@dermaplex.co.uk">info@dermaplex.co.uk</a></td>
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<td>Dermatology Leeds Ltd</td>
<td>01427 231148</td>
<td><a href="mailto:info@dermatology-leeds.co.uk">info@dermatology-leeds.co.uk</a></td>
</tr>
<tr>
<td>Dermatics Ltd</td>
<td>01480 462910</td>
<td><a href="mailto:info@dermatics.co.uk">info@dermatics.co.uk</a></td>
</tr>
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<td>Desitin Pharma Ltd</td>
<td>01908 488817</td>
<td><a href="mailto:medinfo@desitin.co.uk">medinfo@desitin.co.uk</a></td>
</tr>
<tr>
<td>Dexcel-Pharma Ltd</td>
<td>01748 828784</td>
<td><a href="mailto:Dexcel@EU.ProPharmaGroup.com">Dexcel@EU.ProPharmaGroup.com</a></td>
</tr>
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<td>DHP Healthcare Ltd</td>
<td>01908 363437</td>
<td><a href="mailto:dphhealthcare@redinpix.co.uk">dphhealthcare@redinpix.co.uk</a></td>
</tr>
<tr>
<td>Diabetes Healthcare</td>
<td>01748 827266</td>
<td><a href="mailto:medinfo@diabeteshealthcare.co.uk">medinfo@diabeteshealthcare.co.uk</a></td>
</tr>
<tr>
<td>Dompé UK Ltd</td>
<td>+39 02 583831</td>
<td>info@dompé.com</td>
</tr>
<tr>
<td>Dr Reddy's Laboratories (UK) Ltd</td>
<td>01748 828873</td>
<td>DrReddy@g朝廷information.co.uk</td>
</tr>
<tr>
<td>Dr Schär Ltd (UK)</td>
<td>0800 1615838</td>
<td>foodservice.iq@dschär.com</td>
</tr>
<tr>
<td>Dr. Falk Pharma UK Ltd</td>
<td>01628 536616</td>
<td><a href="mailto:office@dfalkpharma.co.uk">office@dfalkpharma.co.uk</a></td>
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<td><a href="mailto:products@durbin.co.uk">products@durbin.co.uk</a></td>
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<td>0115 9787841</td>
<td><a href="mailto:info@sallis.co.uk">info@sallis.co.uk</a></td>
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<td><a href="mailto:info@easigrip.co.uk">info@easigrip.co.uk</a></td>
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<td>0116 2897162</td>
<td><a href="mailto:info@egen-europe.co.uk">info@egen-europe.co.uk</a></td>
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<tr>
<td>EcoLab Healthcare Division</td>
<td>0113 2322480</td>
<td><a href="mailto:info@healthcare.ecolab.co.uk">info@healthcare.ecolab.co.uk</a></td>
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<td>Eisai Ltd</td>
<td>0845 6761400</td>
<td><a href="mailto:EisMedInfo@elisal.com">EisMedInfo@elisal.com</a></td>
</tr>
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<td><a href="mailto:ukmedinfo@lilly.com">ukmedinfo@lilly.com</a></td>
</tr>
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<td>0800 0698421</td>
<td><a href="mailto:info@endoventures.co.uk">info@endoventures.co.uk</a></td>
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<td>Ennogen Healthcare Ltd</td>
<td>01322 692290</td>
<td><a href="mailto:info@ennogen.co.uk">info@ennogen.co.uk</a></td>
</tr>
<tr>
<td>Ennogen Pharma Ltd</td>
<td>01322 692290</td>
<td><a href="mailto:info@ennogen.co.uk">info@ennogen.co.uk</a></td>
</tr>
<tr>
<td>Entra Health Systems</td>
<td>+1 619 6846232</td>
<td><a href="mailto:info@entrahealthsystems.co.uk">info@entrahealthsystems.co.uk</a></td>
</tr>
<tr>
<td>Espère Healthcare Ltd</td>
<td>01462 346100</td>
<td><a href="mailto:info@esperethealth.co.uk">info@esperethealth.co.uk</a></td>
</tr>
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<td>Essential Pharmaceuticals Ltd</td>
<td>01784 477167</td>
<td><a href="mailto:info@essentialpharmaceuticals.com">info@essentialpharmaceuticals.com</a></td>
</tr>
<tr>
<td>Essential-Healthcare Ltd</td>
<td>01277 286199</td>
<td><a href="mailto:info@essential-healthcare.co.uk">info@essential-healthcare.co.uk</a></td>
</tr>
<tr>
<td>Ethicon Ltd</td>
<td>+1 877 3844266</td>
<td><a href="mailto:customersupport@ethicon.com">customersupport@ethicon.com</a></td>
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<td>Ethypharm UK Ltd</td>
<td>01277 266600</td>
<td><a href="mailto:info@ethypharm.co.uk">info@ethypharm.co.uk</a></td>
</tr>
<tr>
<td>Eumedica Pharmaceuticals</td>
<td>+32 44 488089</td>
<td><a href="mailto:info@eumedica.co.uk">info@eumedica.co.uk</a></td>
</tr>
<tr>
<td>Eurocet International bv</td>
<td>+31 35 5288377</td>
<td><a href="mailto:info@eurocet.nl">info@eurocet.nl</a></td>
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<td>EUSA Pharma Ltd</td>
<td>0330 5001155</td>
<td><a href="mailto:medicalinformation-uk@eusapharma.com">medicalinformation-uk@eusapharma.com</a></td>
</tr>
<tr>
<td>Evolan Pharma AB</td>
<td>+46 8 54496030</td>
<td><a href="mailto:info@evolan.se">info@evolan.se</a></td>
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<td>Farla Medical Ltd</td>
<td>0345 1935193</td>
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<td>Farmigea S.p.A.</td>
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<td>01384 233230</td>
<td><a href="mailto:admin@fatespecialfoods.com">admin@fatespecialfoods.com</a></td>
</tr>
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<td>Fentons Pharmaceuticals Ltd</td>
<td>0207 4338595</td>
<td><a href="mailto:mail@fentn-drugs.co.uk">mail@fentn-drugs.co.uk</a></td>
</tr>
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<td>Ferndale Healthcare Ltd</td>
<td>01452 441122</td>
<td><a href="mailto:info@ferndalepharma.co.uk">info@ferndalepharma.co.uk</a></td>
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<td>Ferring Pharmaceuticals Ltd</td>
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<td><a href="mailto:medical.uk@ferring.com">medical.uk@ferring.com</a></td>
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<td>0161 4804602</td>
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<td>Flynn Pharma Ltd</td>
<td>01438 727822</td>
<td><a href="mailto:medinfo@flynnpharma.com">medinfo@flynnpharma.com</a></td>
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<tr>
<td>Fontus Health Ltd</td>
<td>0212 6614615</td>
<td><a href="mailto:Medinfo@fontushealth.com">Medinfo@fontushealth.com</a></td>
</tr>
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<td>Ford Medical Associates Ltd</td>
<td>01233 633224</td>
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<td>Forest Laboratories UK Ltd</td>
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<td>01923 208950</td>
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<td>028 38334974</td>
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<td>Galpharm International Ltd</td>
<td>01226 704743</td>
<td><a href="mailto:customerservice@galpharm.co.uk">customerservice@galpharm.co.uk</a></td>
</tr>
<tr>
<td>Gepro Pharmacia GmbH</td>
<td>+43 354 53000</td>
<td><a href="mailto:pharmacia@gepro.com">pharmacia@gepro.com</a></td>
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<tr>
<td>Gedeon Richter (UK) Ltd</td>
<td>0207 6048806</td>
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<td><a href="mailto:info@genesis-pharm.com">info@genesis-pharm.com</a></td>
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<td><a href="mailto:thomtonross@medinformation.co.uk">thomtonross@medinformation.co.uk</a></td>
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<td><a href="mailto:customer.relations@gsk.com">customer.relations@gsk.com</a></td>
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</tr>
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<td>Glenwood GmbH</td>
<td>049 89 18935363</td>
<td><a href="mailto:info@gluenwood.de">info@gluenwood.de</a></td>
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<td>GlucoRx Ltd</td>
<td>01483 755133</td>
<td><a href="mailto:info@glucorx.co.uk">info@glucorx.co.uk</a></td>
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<td><a href="mailto:medinfo.uk@grifols.com">medinfo.uk@grifols.com</a></td>
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<td><a href="mailto:medicalinformation@grunenthal.com">medicalinformation@grunenthal.com</a></td>
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<td>01482 631606</td>
<td><a href="mailto:customerservices@hrhealthcare.co.uk">customerservices@hrhealthcare.co.uk</a></td>
</tr>
<tr>
<td>Haddenham Healthcare Ltd</td>
<td>01844 208842</td>
<td><a href="mailto:sales@hadhealth.com">sales@hadhealth.com</a></td>
</tr>
<tr>
<td>Hameln Pharmaceuticals Ltd</td>
<td>01452 621661</td>
<td><a href="mailto:drugsafety@hameln.co.uk">drugsafety@hameln.co.uk</a></td>
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<td>HBS Healthcare Ltd</td>
<td>01480 279481</td>
<td><a href="mailto:info@hbshomecare.com">info@hbshomecare.com</a></td>
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<td>Health+Plus Ltd</td>
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<td><a href="mailto:info@henning-am.de">info@henning-am.de</a></td>
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</tr>
</tbody>
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Transdermal Ltd, Tel: 0148 3920749, transdermal.mi@primevigilance.com
TRB Chemidica (UK) Ltd, Tel: 0845 3307556, info@trbchemedica.co.uk
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Veriton Pharma Ltd, Tel: 01932 690325, centralmedicalinformation@veritonpharma.com
Vertex Pharmaceuticals (UK) Ltd, Tel: 01923 437672, vertexmedicalinfo@VRTX.com
Vifor Pharma UK Ltd, Tel: 01276 853633, medicalinfo_UK@viforpharma.com
ViiV Healthcare UK Ltd, Tel: 020 83806200
Visufarma UK Ltd, Tel: 0113 4680661, UKMedicalInformation@Visufarma.com
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Warner Chilcott UK Ltd, Tel: 01271 385257, Medinfo@accord-healthcare.com
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Welland Medical Ltd, Tel: 01293 615455, info@wellandmedical.com
Wellfoods Ltd, Tel: 01226 382877, salesforce@fostersbakery.co.uk
Williams Medical Supplies Ltd, Tel: 01685 846666, medicalservices@wms.co.uk
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Wyvern Medical Ltd, Tel: 01264 332172, info@wyvernmedical.co.uk
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Unlicensed medicines are available from ‘special-order’ manufacturers and specialist-importing companies; the MHRA maintains a register of these companies at tinyurl.com/cdsleke.

Licensed hospital manufacturing units also manufacture ‘special-order’ products as unlicensed medicines, the principal NHS units are listed below. A database (Pro-File; www.pro-file.nhs.uk) provides information on medicines manufactured in the NHS; access is restricted to NHS pharmacy staff.

The Association of Pharmaceutical Specials Manufacturers may also be able to provide further information about commercial companies (www.apsm-uk.com).

The MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by use of a licensed medicine.

As well as being available direct from the hospital manufacturer(s) concerned, many NHS-manufactured Specials may be bought from the Oxford Pharmacy Store, owned and operated by Oxford Health NHS Foundation Trust.

England

London

Barts and the London NHS Trust
Mr J. A. Rickard, Head of Barts Health Pharmaceuticals Barts Health NHS Trust The Royal London Hospital Pathology and Pharmacy Building 80 Newark St Whitechapel London E1 2ES (020) 3246 0394 (order/enquiry) barts.pharmaceuticals@bartshealth.nhs.uk

Guy’s and St. Thomas’ NHS Foundation Trust
Mr P. Forsey, Associate Chief Pharmacist Guy’s and St. Thomas’ NHS Foundation Trust Guy’s Hospital Pharmacy Department Great Maze Pond London SE1 9RT (020) 7188 4992 (order) (020) 7188 5003 (enquiry) Fax: (020) 7188 5013 paul.forsey@gstt.nhs.uk

Moorfields Pharmaceuticals
Mr T. Record, Technical Director Moorfields Pharmaceuticals 25 Provost St London N1 7NH (020) 7684 9090 (order/enquiry) Fax: (020) 7502 2332

London North West Healthcare NHS Trust
Mr K. Wong, London North West Healthcare NHS Trust Northwick Park Hospital Watford Rd Harrow Middlesex HA1 3UJ (020) 8869 2295 (order) (020) 8869 2204/2223 (enquiry) kwong@nhs.net

Royal Free London NHS Foundation Trust
Mr J. Singh, Principal Pharmacist Technical Services Royal Free Hospital Pharmacy Technical Services Pond St Hampstead London NW3 2QG (020) 7830 2424 (order) (020) 7830 2282 (enquiry) Fax: (020) 7794 1875 r.f.specials@nhs.net jasdeep.singh1@nhs.net

St George’s Healthcare NHS Trust
Mr V. Kumar, Assistant Chief Pharmacist St George’s Hospital Technical Services Blackshaw Rd Tooting London SW17 0DT (020) 8725 1770/1768 Fax: (020) 8725 3947 vinodh.kumar@stgeorges.nhs.uk

University College Hospital NHS Foundation Trust
Mr T. Murphy, Production Manager University College Hospital 235 Euston Rd London NW1 2BU (020) 7380 9723 (order) (020) 7380 9472 (enquiry) Fax: (020) 7380 9726 tony.murphy@uclh.nhs.uk

Midlands and Eastern

Barking, Havering and Redbridge University Trust
Mr N. Fisher, Senior Principal Pharmacist Queen’s Hospital Pharmacy Department Romford Essex RM7 0AG (01708) 435 463 (order) (01708) 435 042 (enquiry) neil.fisher@bhrhospitals.nhs.uk

Burton Hospitals NHS Foundation Trust
Mr D. Raynor, Head of Pharmacy Manufacturing Unit Burton Hospitals NHS Foundation Trust Pharmacy Manufacturing Unit Belvedere Rd Burton-on-Trent DE13 0RB (01283) 511 511 ext: 5275 (order/enquiry) Fax: (01283) 593 036 david-raynor@burtonft.nhs.uk

Colchester Hospital University NHS Foundation Trust
Mr S. Pullen, Pharmacy Production Manager Colchester General Hospital Main Pharmacy Turner Rd Colchester Essex CO4 9JU (01206) 742 007 (order) (01206) 744 208 (enquiry) Fax: (01206) 841 249 pharmacy.stores@colchesterhospital.nhs.uk (order) psu.enquiries@colchesterhospital.nhs.uk (enquiry)

Ipswich Hospital NHS Trust
Dr J. Harwood, Production Manager Ipswich Hospital NHS Trust Pharmacy Manufacturing Unit Heath Rd Ipswich, IP4 5PD (01473) 703 410 (order) (01473) 703 403 (enquiry) Fax: (01473) 703 609 john.harwood@ipswichhospital.nhs.uk

Nottingham University Hospitals NHS Trust
Mr J. Graham, Senior Pharmacist, Production Nottingham University Hospitals NHS Trust Pharmacy Production Units Queens Medical Centre Campus Nottingham NG7 2UH (0115) 924 9924 ext: 66521 (enquiry/order) Fax: (0115) 970 9780 jeff.graham@nuh.nhs.uk

University Hospital of North Staffordshire NHS Trust
Ms K. Ferguson, Chief Technician University Hospital of North Staffordshire NHS Trust Pharmacy Technical Services City General Site Stoke-on-Trent ST4 6GQ (01782) 674 568 (order) (01782) 674 568 (enquiry) Fax: (01782) 674 575 caroline.ferguson@uhnhs.nhs.uk

North East

The Newcastle upon Tyne Hospitals NHS Foundation Trust
Mr Y. Hunter-Blair, Production Manager Royal Victoria Infirmary Newcastle Specials Pharmacy Production Unit Queen Victoria Rd Newcastle-upon-Tyne NE1 4LP (0191) 282 0395 (order) (0191) 282 0389 (enquiry) Fax: (0191) 282 0469 yan.hunter-blair@nuth.nhs.uk

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North West
Preston Pharmaceuticals
Ms A. Bolch, Deputy Chief Pharmacist (PMU)
Preston Pharmaceuticals
Royal Preston Hospital
Fulwood
Preston
PR2 9HT
(01772) 523 617 (order)
(01772) 522 593 (enquiry)
Fax: (01772) 523 645
angela.bolch@lthtr.nhs.uk

Stockport Pharmaceuticals
Mr A. Singleton, Head of Production
Stepping Hill Hospital
Stockport NHS Foundation Trust
Stockport
SK2 7JE
(0161) 419 5666 (order)
(0161) 419 5657 (enquiry)
Fax: (0161) 419 5426
andrew.singleton@stockport.nhs.uk

South
Portsmouth Hospitals NHS Trust
Mr R. Lucas, Product Development Manager
Portsmouth Hospitals NHS Trust
Pharmacy Manufacturing Unit
Unit D2, Railway Triangle Industrial Estate
Walton Road
Farlington
Portsmouth
PO6 1TF
(02392) 389 078 (order)
(02392) 316 312 (enquiry)
Fax: (02392) 316 316
robert.lucas@porthosp.nhs.uk

South East
East Sussex Healthcare NHS Trust
Mr P. Keen, Business Manager
Eastbourne District General Hospital
East Sussex Hospitals NHS Trust
Eastbourne Pharmaceuticals
Kings Drive
Eastbourne
BN21 2UD
(01323) 414 906 (order)
(01323) 417 400 ext: 3076 (enquiry)
Fax: (01323) 414 931
paul.keen@esht.nhs.uk

South West
Torbay Pharmaceuticals
Mr Leon Rudd, Commercial Strategy Director
Torbay and South Devon Healthcare NHS Foundation Trust
Torbay Pharmaceuticals
Wilkins Drive
Paignton
TQ4 7FG
(01803) 664 707
Fax: (01803) 664 354
leon.rudd@nhs.net

Yorkshire
Calderdale and Huddersfield NHS Foundation Trust
Dr B. Grewal, Managing Director
Calderdale and Huddersfield NHS Foundation Trust
Huddersfield Pharmacy Specials
Gate 2 - Acre Mills, School St West
Huddersfield
HD3 3ET
(01484) 355 388 (order/enquiry)
info.bps@cht.nhs.uk

Northern Ireland
Victoria Pharmaceuticals
Mr S. Cameron, Production Manager - Pharmacy
Victoria Pharmaceuticals
Royal Hospitals
Plenum Building
Grosvenor Road
Belfast
BT12 6BA
(028) 9063 0070 (order/enquiry)
Fax: (028) 9063 5282 (order/enquiry)
samuel.cameron@belfasttrust.hscni.net

Scotland
NHS Greater Glasgow and Clyde
Ms K. Pollock, Acting Production Manager
Pharmacy Production Unit
University Place
Glasgow
G12 8TA
(0141) 451 5820 (order)
(0141) 451 5822 (enquiry)
Fax: (0141) 334 9137
pharmacyproductionunit@ggc.scot.nhs.uk

Tayside Pharmaceuticals
Mr S. Bath, Production Manager
Ninewells Hospital
Tayside Pharmaceuticals
Dundee
DD1 9SY
(01382) 632 052 (order)
(01382) 632 273 (enquiry)
Fax: (01382) 632 060
sbath@nhs.net

Wales
Cardiff and Vale University Health Board
Mr P. Spark, Principal Pharmacist (Production)
Cardiff and Vale University Health Board
20 Fieldway
Cardiff
CF14 4HY
(029) 2074 8120
Fax: (029) 2074 8130
paul.spark@wales.nhs.uk

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# REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in BNF or [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) for guidance. Do not be put off reporting because some details are not known.

## PATIENT DETAILS
- **Patient Initials:**
- **Sex:** M / F
- **Is the patient pregnant?** Y / N
- **Ethnicity:**
- **Age (at time of reaction):**
- **Weight (kg):**
- **Identification number (e.g. Practice or Hospital Ref):**

## SUSPECTED DRUG(S)/VACCINE(S)

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
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<tbody>
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## SUSPECTED REACTION(S)

Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

<table>
<thead>
<tr>
<th>Outcome</th>
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<tbody>
<tr>
<td>Recovered [ ]</td>
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<tr>
<td>Recovering [ ]</td>
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<tr>
<td>Continuing [ ]</td>
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<tr>
<td>Other [ ]</td>
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</tbody>
</table>

- **Date reaction(s) started:**
- **Date reaction(s) stopped:**

Do you consider the reactions to be serious?  
[ ] Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- [ ] Patient died due to reaction
- [ ] Involved or prolonged inpatient hospitalisation
- [ ] Life threatening
- [ ] Involved persistent or significant disability or incapacity
- [ ] Congenital abnormality
- [ ] Medically significant; please give details: __________________________

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

- [ ] Mild
- [ ] Unpleasant, but did not affect everyday activities
- [ ] Bad enough to affect everyday activities

[www.getintopharma.com](http://www.getintopharma.com)
It's easy to report online: www.mhra.gov.uk/yellowcard

**OTHER DRUG(S) (including self-medication and complementary remedies)**

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
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**Additional relevant information** e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

---

Please list any medicines obtained from the internet:

**REPORTER DETAILS**

Name and Professional Address:

__________________________________________________________

Postcode: ___________________ Tel No: ___________________

Email: _______________________

Speciality: ___________________

Signature: ___________________ Date: ___________________

**CLINICIAN (if not the reporter)**

Name and Professional Address:

__________________________________________________________

Postcode: ___________________ Tel No: ___________________

Email: _______________________

Speciality: ___________________

Date: _______________________

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin Drug Safety Update at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in BNF or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

**PATIENT DETAILS**

- **Patient initials:**
- **Sex:** M/F
- **Is the patient pregnant?** Y/N
- **Ethnicity:**
- **Age (at time of reaction):**
- **Weight (kg):**
- **Identification number (e.g. Practice or Hospital Ref):**

**SUSPECTED DRUG(S)/VACCINE(S)**

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
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</tbody>
</table>

**SUSPECTED REACTION(S)**

Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

- **Outcome**
  - Recovered
  - Recovering
  - Continuing
  - Other

- **Date reaction(s) started:**
- **Date reaction(s) stopped:**

- **Do you consider the reactions to be serious?** Yes/No

- **If yes, please indicate why the reaction is considered to be serious (please tick all that apply):**
  - Patient died due to reaction
  - Involved or prolonged inpatient hospitalisation
  - Life threatening
  - Involved persistent or significant disability or incapacity
  - Congenital abnormality
  - Medically significant; please give details: ________________________________

- **If the reactions were not serious according to the categories above, how bad was the suspected reaction?**
  - **Mild**
  - Unpleasant, but did not affect everyday activities
  - Bad enough to affect everyday activities

www.getintopharma.com
It's easy to report online: www.mhra.gov.uk/yellowcard

OTHER DRUG(S) (including self-medication and complementary remedies)
Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No
If yes, please give the following information if known:

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
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</tbody>
</table>

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS
Name and Professional Address:

__________________________

Postcode: ___________ Tel No: ___________
Email: ___________
Speciality: ___________
Signature: ___________ Date: ___________

CLINICIAN (if not the reporter)
Name and Professional Address:

__________________________

Postcode: ___________ Tel No: ___________
Email: ___________
Speciality: ___________
Date: ___________

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Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
Adult Advanced Life Support Algorithm

Resuscitation Council (UK) 2015
Adult Advanced Life Support

Unresponsive and not breathing normally

Call resuscitation team

CPR 30:2
Attach defibrillator/monitor
Minimise interruptions

Assess rhythm

Shockable (VF/Pulseless VT)

1 Shock
Minimise interruptions

Immediately resume CPR for 2 min
Minimise interruptions

Return of spontaneous circulation

Immediate post cardiac arrest treatment
- Use ABCDE approach
- Aim for SpO₂ of 94-96%
- Aim for normal PaCO₂
- 12-lead ECG
- Treat precipitating cause
- Targeted temperature management

Non-shockable (PEA/Asystole)

Immediately resume CPR for 2 min
Minimise interruptions

During CPR
- Ensure high quality chest compressions
- Minimise interruptions to compressions
- Give oxygen
- Use waveform capnography
- Continuous compressions when advanced airway in place
- Vascular access (intravenous or intraosseous)
- Give adrenaline every 3-5 min
- Give amiodarone after 3 shocks

Treat Reversible Causes
- Hypoxia
- Hypovolaemia
- Hypo-hyperkalaemia/metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tension pneumothorax
- Tamponade – cardiac
- Toxins

Consider
- Ultrasound imaging
- Mechanical chest compressions to facilitate transfer/treatment
- Coronary angiography and percutaneous coronary intervention
- Extracorporeal CPR

Reproduced with the kind permission of the Resuscitation Council (UK) from Resuscitation Guidelines, 2015

www.getintopharma.com
Medical emergencies in the community

Overview
Drug treatment outlined below is intended for use by appropriately qualified healthcare professionals. Only drugs that are used for immediate relief are shown; advice on supporting care is not given. Where the patient’s condition requires investigation and further treatment, the patient should be transferred to hospital promptly.

Acute coronary syndromes

- **ANGINA: UNSTABLE**
  - Aspirin dispersible tablets p. 121 (75 mg, 300 mg)
    - By Mouth (dispersed in water or chewed)
    - Adult: 300 mg
  - **PLUS**
  - **EITHER**
    - Glyceril trinitrate aerosol spray p. 218
      - (400 micrograms/metered dose)
      - Sublingually
      - Adult: 1–2 sprays, repeated as required
  - **OR**
    - Glyceril trinitrate tablets (300 micrograms, 500 micrograms, 600 micrograms)
      - Sublingually
      - Adult: 0.3–1 mg, repeated as required
  - **MYOCARDIAL INFARCTION: NON-ST-SEGMENT ELEVATION**
  - Treat as for Angina: unstable
  - **MYOCARDIAL INFARCTION: ST-SEGMENT ELEVATION**
  - Aspirin dispersible tablets (75 mg, 300 mg)
    - By Mouth (dispersed in water or chewed)
    - Adult: 300 mg
  - Glyceril trinitrate aerosol spray (400 micrograms/metered dose)
    - Sublingually
    - Adult: 1–2 sprays, repeated as required
  - **OR**
    - Glyceril trinitrate tablets (300 micrograms, 500 micrograms, 600 micrograms)
      - Sublingually
      - Adult: 0.3–1 mg, repeated as required

Airways disease, obstructive

- **ASTHMA: ACUTE**
  - Regard each emergency consultation as being for severe acute asthma until shown otherwise; failure to respond adequately at any time requires immediate transfer to hospital
  - **EITHER**
    - Salbutamol aerosol inhaler p. 252
      - (100 micrograms/metered inhalation)
      - By Aerosol Inhalation Via Large-Volume Spacer
      - (And a Close-Fitting Face Mask If Child Under 3 Years)
      - Adult and child: 2–10 puffs each inhaled separately, repeated every 10–20 minutes or as necessary
  - **OR**
    - Salbutamol nebuliser solution (1 mg/mL, 2 mg/mL)
      - By Inhalation of Nebulised Solution (Via Oxygen-Driven Nebuliser If Available)
      - Child 4 years and below: 2.5 mg every 20–30 minutes or as necessary
      - Child 5-11 years: 2.5–5 mg every 20–30 minutes or as necessary
      - Child 12-17 years: 5 mg every 20–30 minutes or as necessary
      - Adult: 5 mg every 20–30 minutes or as necessary
  - **OR**
    - Terbutaline sulfate nebuliser solution p. 255 (2.5 mg/mL)
      - By Inhalation of Nebulised Solution (Via Oxygen-Driven Nebuliser If Available)
      - Child 4 years and below: 5 mg every 20–30 minutes or as necessary
      - Child 5-11 years: 5–10 mg every 20–30 minutes or as necessary
      - Child 12-17 years: 10 mg every 20–30 minutes or as necessary
      - Adult: 10 mg every 20–30 minutes or as necessary
  - **PLUS** (In all cases)
  - **EITHER**
    - Prednisolone tablets p. 678 (or prednisolone soluble tablets) (5 mg)
      - By Mouth
      - Child 11 years and below: 1–2 mg/kg (max. 40 mg) once daily for up to 3 days or longer if necessary; if child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily
      - Child 12-17 years: 40–50 mg once daily for at least 5 days
      - Adult: 40–50 mg once daily for at least 5 days
  - **OR**
    - Hydrocortisone p. 676 (preferably as sodium succinate)
      - By Intravenous Injection
      - Child 17 years and below: 4 mg/kg (max. 100 mg) every 6 hours until conversion to oral prednisolone is possible; alternative dose if weight unavailable:
        - Child 1 year and below: 25 mg
        - Child 2-4 years: 50 mg
        - Child 5-17 years: 100 mg
        - Adult: 100 mg every 6 hours until conversion to oral prednisolone is possible
  - High-flow oxygen should be given if available (via face mask in children)
  - Monitor response 15 to 30 minutes after nebulisation; if any signs of acute asthma persist, arrange hospital admission.
  - While awaiting ambulance, repeat nebulised beta₂ agonist (as above) and give with

www.getintopharma.com
Ipratropium bromide nebuliser solution p. 246
(250 micrograms/mL)
BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
▷ Child 11 years and below: 250 micrograms, repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary
▷ Child 12-17 years: 500 micrograms every 4–6 hours as necessary
▷ Adult: 500 micrograms every 4–6 hours as necessary
▷ CROUP
Dexamethasone oral solution p. 675 (2 mg/5 mL)
BY MOUTH
▷ Child 1 month-2 years: 150 micrograms/kg as a single dose

Anaphylaxis
▷ ANAPHYLAXIS
Adrenaline/epinephrine injection p. 222 (1 mg/mL (1 in 1000))
BY INTRAMUSCULAR INJECTION
▷ Child 5 years and below: 150 micrograms (0.15 mL), repeated every 5 minutes if necessary
▷ Child 6-11 years: 300 micrograms (0.3 mL), repeated every 5 minutes if necessary
▷ Child 12-17 years: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary
▷ Adult: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary
High-flow oxygen and intravenous fluids should be given as soon as available.
Chlorphenamine maleate injection p. 283
BY INTRAVENOUS OR INTRAMUSCULAR INJECTION
May help counter histamine-mediated vasodilation and bronchoconstriction.
Hydrocortisone (preferably as sodium succinate)
BY INTRAVENOUS INJECTION
Has delayed action but should be given to severely affected patients to prevent further deterioration.

Bacterial infection
▷ MENINGOCOCCAL DISEASE
Benzylenpenicillin sodium injection p. 547 (600 mg, 1.2 g)
BY INTRAMUSCULAR INJECTION (OR BY INTRAVENOUS INJECTION IF VENOUS ACCESS NOT AVAILABLE)
▷ Neonate: 300 mg
▷ Child 1 month-11 months: 300 mg
▷ Child 1-9 years: 600 mg
▷ Child 10-17 years: 1.2 g
▷ Adult: 1.2 g
NOTE A single dose should be given before urgent transfer to hospital, so long as this does not delay the transfer.
▷ OR if history of allergy to penicillin
Cefotaxime injection p. 527 (1 g)
BY INTRAVENOUS INJECTION (OR BY INTRAMUSCULAR INJECTION IF VENOUS ACCESS NOT AVAILABLE)
▷ Neonate: 50 mg/kg
▷ Child 1 month-11 years: 50 mg/kg (max. 1 g)
▷ Child 12-17 years: 1 g
▷ Adult: 1 g
NOTE A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer.
▷ OR if history of immediate hypersensitivity reaction (including anaphylaxis, angioedema, urticaria, or rash immediately after administration) to penicillin or to cephalosporins
Chloramphenicol injection p. 568 (1 g)
BY INTRAVENOUS INJECTION
▷ Child: 12.5–25 mg/kg
▷ Adult: 12.5–25 mg/kg
 NOTE A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer.
See also Central nervous system infections, antibacterial therapy p. 511.

Hypoglycaemia
▷ DIABETIC HYPOGLYCAEMIA
Glucose or sucrose
BY MOUTH
▷ Adult and child over 2 years: approx. 10–20 g (110–220 mL
Lucozade® Energy Original or 100–200 mL Coca-Cola®—both non-diet versions or 2–4 teaspoonfuls of sugar or 3–6 sugar lumps) repeated after 10–15 minutes if necessary
▷ OR if hypoglycaemia unresponsive or if oral route cannot be used
Glucagon injection p. 724 (1 mg/mL)
BY SUBCUTANEOUS OR INTRAMUSCULAR INJECTION
▷ Child body-weight up to 25 kg: 500 micrograms (0.5 mL)
▷ Child body-weight 25 kg and over: 1 mg (1 mL)
▷ Adult: 1 mg (1 mL)
▷ OR if hypoglycaemia prolonged or unresponsive to glucagon after 10 minutes
Glucose intravenous infusion p. 1041 (10%) BY INTRAVENOUS INJECTION INTO LARGE VEIN
▷ Child: 5 mL/kg (glucose 500 mg/kg)
Glucose intravenous infusion (20%) BY INTRAVENOUS INJECTION INTO LARGE VEIN
▷ Adult: 50 mL

Seizures
▷ CONVULSIVE (INCLUDING FEBRILE) SEIZURES LASTING LONGER THAN 5 MINUTES
▷ EITHER Diazepam rectal solution p. 343 (2 mg/mL, 4 mg/mL)
BY RECTUM
▷ Neonate: 1.25–2.5 mg, repeated once after 10–15 minutes if necessary
▷ Child 1 month-1 year: 5 mg, repeated once after 10–15 minutes if necessary
▷ Child 2-11 years: 5–10 mg, repeated once after 10–15 minutes if necessary
▷ Child 12-17 years: 10–20 mg, repeated once after 10–15 minutes if necessary
▷ Adult: 10–20 mg, repeated once after 10–15 minutes if necessary
▷ Elderly: 10 mg, repeated once after 10–15 minutes if necessary
▷ OR Midazolam oromucosal solution p. 340
BY BUCCAL ADMINISTRATION, REPEATED ONCE AFTER 10 MINUTES IF NECESSARY
▷ Neonate: 300 micrograms/kg [unlicensed]
▷ Child 1-2 months: 300 micrograms/kg (max. 2.5 mg) [unlicensed]
▷ Child 3 months-11 months: 2.5 mg
▷ Child 1-4 years: 5 mg
▷ Child 5-9 years: 7.5 mg
▷ Child 10-17 years: 10 mg
▷ Adult: 10 mg [unlicensed]
Approximate Conversions and Units

### Conversion of pounds to kilograms

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<thead>
<tr>
<th>lb</th>
<th>kg</th>
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<tbody>
<tr>
<td>1</td>
<td>0.45</td>
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<tr>
<td>2</td>
<td>0.91</td>
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<tr>
<td>3</td>
<td>1.36</td>
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<td>4</td>
<td>1.81</td>
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<td>5</td>
<td>2.27</td>
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<td>6</td>
<td>2.72</td>
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<tr>
<td>7</td>
<td>3.18</td>
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<tr>
<td>8</td>
<td>3.63</td>
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<td>9</td>
<td>4.08</td>
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<td>10</td>
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<td>11</td>
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<tr>
<td>13</td>
<td>5.90</td>
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<td>14</td>
<td>6.35</td>
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</table>

### Conversion of stones to kilograms

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<thead>
<tr>
<th>stones</th>
<th>kg</th>
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<tbody>
<tr>
<td>1</td>
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<td>2</td>
<td>12.70</td>
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<td>4</td>
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<td>14</td>
<td>88.90</td>
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<td>15</td>
<td>95.25</td>
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</table>

### Conversion from millilitres to fluid ounces

<table>
<thead>
<tr>
<th>mL</th>
<th>fl oz</th>
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<tbody>
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<td>1.8</td>
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<tr>
<td>100</td>
<td>3.5</td>
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<td>150</td>
<td>5.3</td>
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<td>200</td>
<td>7.0</td>
</tr>
<tr>
<td>500</td>
<td>17.6</td>
</tr>
<tr>
<td>1000</td>
<td>35.2</td>
</tr>
</tbody>
</table>

### Length

- 1 metre (m) = 1000 millimetres (mm)
- 1 centimetre (cm) = 10 mm
- 1 inch (in) = 25.4 mm
- 1 foot (ft) = 12 inches
- 12 inches = 304.8 mm

### Mass

- 1 kilogram (kg) = 1000 grams (g)
- 1 gram (g) = 1000 milligrams (mg)
- 1 milligram (mg) = 1000 micrograms
- 1 microgram = 1000 nanograms
- 1 nanogram = 1000 picograms

### Volume

- 1 litre = 1000 millilitres (mL)
- 1 millilitre (mL) = 1000 microlitres
- 1 pint = 568 mL

### Other units

- 1 kilocalorie (kcal) = 4186.8 joules (J)
- 1000 kilocalories (kcal) = 4.1868 megajoules (MJ)
- 1 megajoule (MJ) = 238.8 kilocalories (kcal)
- 1 millimetre of mercury (mmHg) = 133.3 pascals (Pa)
- 1 kilopascal (kPa) = 7.5 mmHg (pressure)

### Plasma-drug concentrations

Plasma-drug concentrations in BNF publications are expressed in mass units per litre (e.g. mg/litre). The approximate equivalent in terms of amount of substance units (e.g. micromol/litre) is given in brackets.

### Prescribing for children: weight, height, and gender

The table below shows the mean values for weight, height, and gender by age; these values have been derived from the UK-WHO growth charts 2009 and UK1990 standard centile charts, by extrapolating the 50th centile, and may be used to calculate doses in the absence of measurements. However, an individual’s weight and height might vary considerably from the values in the table and it is important to ensure that the value chosen is appropriate. In most cases the actual measurement should be obtained as soon as possible and the dose re-calculated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
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</thead>
<tbody>
<tr>
<td>Full-term neonate</td>
<td>3.5</td>
<td>51</td>
</tr>
<tr>
<td>1 month</td>
<td>4.3</td>
<td>55</td>
</tr>
<tr>
<td>2 months</td>
<td>5.4</td>
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<tr>
<td>3 months</td>
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<tr>
<td>4 months</td>
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<tr>
<td>6 months</td>
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<tr>
<td>1 year</td>
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<td>3 years</td>
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<td>5 years</td>
<td>18</td>
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<tr>
<td>7 years</td>
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<tr>
<td>10 years</td>
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<td>138</td>
</tr>
<tr>
<td>12 years</td>
<td>39</td>
<td>149</td>
</tr>
<tr>
<td>14 year old boy</td>
<td>49</td>
<td>163</td>
</tr>
<tr>
<td>14 year old girl</td>
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<td>159</td>
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<tr>
<td>Adult male</td>
<td>68</td>
<td>176</td>
</tr>
<tr>
<td>Adult female</td>
<td>58</td>
<td>164</td>
</tr>
</tbody>
</table>
Recommended wording of cautionary and advisory labels

For details including Welsh Language translation see p. 1588

1  Warning: This medicine may make you sleepy
2  Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol
3  Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines
4  Warning: Do not drink alcohol
5  Do not take indigestion remedies 2 hours before or after you take this medicine
6  Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
7  Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
8  Warning: Do not stop taking this medicine unless your doctor tells you to stop
9  Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop
10 Warning: Read the additional information given with this medicine
11 Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds
12 Do not take anything containing aspirin while taking this medicine
13 Dissolve or mix with water before taking
14 This medicine may colour your urine. This is harmless
15 Caution: flammable. Keep your body away from fire or flames after you have put on the medicine
16 Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening
17 Do not take more than... in 24 hours
18 Do not take more than... in 24 hours. Also, do not take more than... in any one week
19 Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol
20 Take with or just after food, or a meal
21 Take 30 to 60 minutes before food
22 Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
23 Suck or chew this medicine
24 Swallow this medicine whole. Do not chew or crush
25 Dissolve this medicine under your tongue
26 Take with a full glass of water
27 Spread thinly on the affected skin only
28 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
29 Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well
30 Contains aspirin. Do not take anything else containing aspirin while taking this medicine
32 www.getintopharma.com
Abbreviations and Symbols

Internationally recognised units and symbols are used in the BNF publications wherever possible.

ACBS Advisory Committee on Borderline Substances, see Borderline Substances
ACE Angiotensin-converting enzyme
ACD Attention deficit hyperactivity disorder
ADHD Acquired immunodeficiency syndrome
AIM approx. approximately
AV atrioventricular
AWMSG All Wales Medicines Strategy Group
BAN British Approved Name
BMI body mass index
BP British Pharmacopoeia 2013, unless otherwise stated
BPC British Pharmaceutical Codex 1973 and Supplement 1976, unless otherwise stated
BRCA breast cancer gene
CAPD Continuous ambulatory peritoneal dialysis
CDs preparation in Schedule 1 of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CDs preparation in Schedule 2 of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CDs preparation in Schedule 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CDs preparation in Schedule 4 (Part I) of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CDs preparation in Schedule 4 (Part II) of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CDs preparation in Schedule 5 of the Misuse of Drugs Regulations 2001 (and subsequent amendments), For regulations see Controlled drugs and drug dependence p. 8.
CHM Commission on Human Medicines
CHMP Committee for Medicinal Products for Human Use
c. = cent (one hundredth)
d. = deci (one tenth)
d. c. = deci cent (one hundredth)
DMARD Disease-modifying antirheumatic drug
DPP Dental Practitioners' Formulary
DT Drug Tariff price
e/d = enteric-coated (termed gastro-resistant in BP)
ECG electrocardiogram
EEG electro-encephalogram
eGFR estimated glomerular filtration rate, see Prescribing in renal impairment p. 19
f = film-coated
FSRH Faculty of Sexual and Reproductive Healthcare
G6PD glucose 6-phosphate dehydrogenase
GBP Glasgow Central Laboratory
GeV = ter in die (three times daily)
GFR = glomerular filtration rate
GIV = subcutaneously
HCT = haematocrit
HIV Human immunodeficiency virus
HRT Hormone replacement therapy
I/m = intramuscular
I/v = intravenous
INR international normalised ratio
IRP intravenous iron preparations
JCVI Joint Committee on Vaccination and Immunisation
K.V. = potassium
LDL-cholesterol low-density lipoprotein cholesterol
LMI = retail price
MAOI Monoamine-oxidase inhibitor
M/M = monthly
MHRRA Medicines and Healthcare products Regulatory Agency
MMD = modified-release
NCL no cautionary labels (prescription endorsement made by prescriber when recommended cautionary labels are not required)
NHS National Health Service
NICE National Institute for Health and Care Excellence
NPF Nurse Prescribers’ Formulary
NSAID Non-steroidal anti-inflammatory drug
NSKMS National Society for Kidney Medicine and Surgery
PCP recommendation only for community use, see Prescribing in general practice p. 1
PARP polyp (ADP-ribose) polymerase
PCE Public Health England (formerly Health Protection Agency
PMH prescription-only medicine, see Fig. 1 How to use BNF publications
PMS= trade mark
RiN Recommended International Non-proprietary Name
RSP respiratory syncytial virus
s/c sugar-coated
SLS Selected List Scheme
SMC Scottish Medicines Consortium
SPC Summary of Product Characteristics
SSRI Selective serotonin reuptake inhibitor
STEMI ST-segment elevation myocardial infarction
UK United Kingdom
UNITS for SI units see Prescribing writing p. 5
WHO World Health Organization

Latin abbreviations

Directions should be in English without abbreviation. However, Latin abbreviations have been used when prescribing.

The following is a list of appropriate abbreviations. It should be noted that the English version is not always an exact translation.

a. c. = ante cibum (before food)
b. d. = bis die (twice daily)
o. d. = omni die (every day)
o. m. = omni mane (every morning)
o. n. = omni nocte (every night)
p. c. = post cibum (after food)
p. r. n. = pro re nata (when required)
q. d. s. = quater die sumendum (to be taken four times daily)
q. q. h. = quaerat die quaque hora (every four hours)
stat = immediately
t. d. s. = ter die sumendum (to be taken three times daily)
t. i. d. = ter in die (three times daily)

E numbers

The following is a list of common E numbers and the inactive ingredients to which they correspond.

E102 Tartrazine
E104 Quinoline Yellow
E110 Sunset Yellow FCF
E123 Amaranth
E124 Ponceau 4R
E127 Erythrosine BS
E132 Indigo Carmine
E142 Green S
E171 Titanium Dioxide
E172 Iron oxides, iron hydroxides
E200 Sorbic Acid
E211 Sodium Benzoate
E223 Sodium Metabisulphite
E320 Butylated Hydroxyanisole
E321 Butylated Hydroxytoluene
E322 Lecithins
E420 Sorbitol
E421 Mannitol
E422 Glycerol
E901 Beeswax (white and yellow)
E1520 Propylene Glycol